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Topical review

Definition, diagnosis and treatment strategies for opioid-induced bowel dysfunction—Recommendations of the Nordic Working Group

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HIGHLIGHTS

- Opioid-induced bowel dysfunction and constipation (OIC) are underdiagnosed and undertreated.
- Pain management and quality of life in chronic pain patients is reduced by OIC.
- Conventional laxatives have limited effects on OIC and may cause adverse effects.
- Peripherally-acting opioid antagonists that do not enter the brain are effective against OIC without major adverse effects.
- An evidence-based practice guideline for OIC based on the GRADE-method is proposed.

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ABSTRACT

Background and aims: Opioid-induced bowel dysfunction (OIBD) is an increasing problem due to the common use of opioids for pain worldwide. It manifests with different symptoms, such as dry mouth, gastro-oesophageal reflux, vomiting, bloating, abdominal pain, anorexia, hard stools, constipation and incomplete evacuation. Opioid-induced constipation (OIC) is one of its many symptoms and probably the most prevalent. The current review describes the pathophysiology, clinical implications and treatment of OIBD.

Methods: The Nordic Working Group was formed to provide input for Scandinavian specialists in multiple, relevant areas. Seven main topics with associated statements were defined. The working plan provided a structured format for systematic reviews and included instructions on how to evaluate the level of evidence according to the GRADE guidelines. The quality of evidence supporting the different statements was rated as high, moderate or low. At a second meeting, the group discussed and voted on each section with recommendations (weak and strong) for the statements.

Results: The literature review supported the fact that opioid receptors are expressed throughout the gastrointestinal tract. When blocked by exogenous opioids, there are changes in motility, secretion and absorption of fluids, and sphincter function that are reflected in clinical symptoms. The group supported a recent consensus statement for OIC, which takes into account the change in bowel habits for at least one week rather than focusing on the frequency of bowel movements. Many patients with pain receive opioid therapy and concomitant constipation is associated with increased morbidity and utilization of healthcare resources. Opioid treatment for acute postoperative pain will prolong the postoperative ileus

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and should also be considered in this context. There are no available tools to assess OIBD, but many rating scales have been developed to assess constipation, and a few specifically address OIC. A clinical treatment strategy for OIBD/OIC was proposed and presented in a flowchart. First-line treatment of OIC is conventional laxatives, lifestyle changes, tapering the opioid dosage and alternative analgesics. Whilst opioid rotation may also improve symptoms, these remain unalleviated in a substantial proportion of patients. Should conventional treatment fail, mechanism-based treatment with opioid antagonists should be considered, and they show advantages over laxatives. It should not be overlooked that many reasons for constipation other than OIBD exist, which should be taken into consideration in the individual patient.
Conclusion and implications: It is the belief of this Nordic Working Group that increased awareness of adverse effects and OIBD, particularly OIC, will lead to better pain treatment in patients on opioid therapy. Subsequently, optimised therapy will improve quality of life and, from a socio-economic perspective, may also reduce costs associated with hospitalisation, sick leave and early retirement in these patients.

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1. Introduction and methods

This review summarizes the consensus recommendations of the multidisciplinary Nordic Working Group on the clinical care of patients with opioid-induced bowel dysfunction (OIBD) and particularly opioid-induced constipation (OIC). Opioid-induced bowel dysfunction is a pharmacologically induced condition, which manifests with different symptoms, such as dry mouth, gastro-oesophageal reflux, vomiting, bloating, abdominal pain, anorexia, hard stools, constipation and incomplete evacuation [1,2]. Opioid-induced constipation is one of the many symptoms of OIBD and probably the most prevalent and bothersome symptom. Since opioids affect the enteric nervous system throughout the gut, OIBD is the most appropriate term, although for practical and traditional reasons most studies have focused on OIC.

The aim of the current work was to evaluate the available literature on the definition, diagnosis and management of OIBD/OIC using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method (http://www.gradeworkinggroup.org/publications/JCE_series.htm) to aid Nordic healthcare personnel to expand their understanding of OIBD/OIC. The group was formed to provide multidisciplinary expert input for the report and included Scandinavian specialists in different relevant areas. Six members of the Nordic Working Group (AMD, PM, MS, HB, UK, JGH) formed the Steering Committee and, after an opening meeting, wrote the initial manuscript over a six-month period and proposed seven main topics with associated statements. The working plan provided a structured format for systematic reviews, and included instructions on how to evaluate the level of evidence and clinical implications according to

the GRADE guidelines, as adapted for "UpToDate" (http://www.uptodate.com/home/grading-tutorial). Evidence, where available, was ranked according to the GRADE method; in the absence or limited availability of literature, the Nordic Working Group decided if a recommendation would be included in the consensus report. The quality of evidence supporting the different statements was graded as (i) "high" if there was very low probability of further research completely changing the presented conclusions, (ii) "moderate" if further research may completely change the conclusions, (iii) "low" if further research is likely to change the presented conclusions completely. The term "very low" (iv) could be used if new research will most probably change the presented conclusions completely; however, the term was not used in the present work.

During a second meeting, after receiving instructions on how to grade both the level of evidence and strength of the recommendations, five members of the Steering Committee (MS excused) discussed and voted on each section; recommendations could be "weak", "strong" or "not applicable". The final manuscript was then reviewed critically and commented upon by specialists in pharmacology (LLC), nursing (MF) and general practice (LA) to ensure a multidisciplinary approach and general relevance and applicability of the conclusions.

Based on these evaluations, the Nordic Working Group created a clinical treatment strategy for OIBD/OIC in the advent of new medications specifically designed to treat the debilitating adverse effects of opioid treatment.

2. Mechanisms of opioid-induced bowel dysfunction

Delta- (δ-), kappa- (κ-) and mu- (μ-) opioid receptors have been identified in the gastrointestinal tract [3]. Whilst they are predominantly present in the enteric nervous system, their relative distribution varies with region and histological layers of the gut and, most importantly, between species [4,5]. In humans, μ-receptors are considered to be of greatest importance and have been identified in neuronal cells of submucosal and myenteric neurones and on mononuclear cells in lamina propria [5]. Whilst *endogenous* ligands influence normal regulation of gastrointestinal function, opioid receptors are also activated by *exogenous* opioids [5–7]. All opioid receptors belong to the G-protein-coupled receptor family. Opioid-induced intracellular signalling is complex and involves direct activation of K^+-channels (membrane hyperpolarization) and inhibition of Ca^{2+}-channels (decreased neurotransmitter release); it may also involve Na^+-channels [8]. The main effect, however, is probably decreased formation of cyclic adenosine monophosphate [9], which subsequently activates several target molecules and leads to decreased neuronal excitability with an overall inhibitory effect on the cells.

Opioid receptor activation in the gut has three main effects: (i) a change in gut motility, (ii) decreased gut secretion, and (iii) increased sphincter tone. Gut motility is controlled from the myenteric plexus via neurotransmitters released onto the smooth muscle cells [1,10]. Since opioid administration inhibits release of these neurotransmitters, it directly causes abnormal coordination of gut motility as reflected by increased tone and decreased propulsive activity. Results from *in vivo* human studies have confirmed that opioid administration causes oesophageal and gallbladder dysmotility, increased stomach tone [10–13], and delays in gastric emptying, oral-coecal transit and colonic transit [14–16].

Intestinal fluid secretion is essential for an ideal intestinal environment. In the gut, the submucosal plexus (influenced by opioid receptors) controls local secretory and absorptive activity of the epithelial cells [17,18]. Opioids inactivate chloride channels and decrease chloride transport from the enterocyte into the gut lumen and less water follows due to lower osmotic gradient [7,19]. This results in decreased gut secretion and absorption of water together with less gastric and pancreatico-biliary secretion [4,20,21]. Slowing of gut motility also allows more time for water absorption. The resultant decrease in faecal volume negatively affects motility since intrinsic reflexes that cause propulsive contractions depend on mechanoreceptor activation [4].

The knowledge on the opioid effect on human sphincters is limited, since only few studies have been carried out. Moreover, the influence on, for example, the lower oesophageal sphincter is still controversial. Nonetheless, results from most studies have shown opioid treatment to cause increased resting pressure but abnormal coordination that leads to symptoms, such as reflux and sphincter of Oddi spasms [22–24]. Opioid-induced dysfunction of anorectal function is especially relevant because contraction leads to excessive straining and incomplete evacuation. The importance of anal sphincter dysfunction has only been evaluated sparsely [16], but results from preclinical studies indicate that opioids inhibit the detection of stools and internal anal sphincter relaxation [25,26].

2.1. Statements according to GRADE

- Opioid receptors are expressed throughout the gastrointestinal tract and are involved in an array of cellular functions (high quality, strong recommendation)
- Opioids cause motility changes that instigate slowing of normal motility, segmentation, increased tone and dis-coordinated motility (moderate quality, strong recommendation)
- Opioids decrease gut fluid secretion, causing dry faeces and less propulsive motility (low quality, strong recommendation)
- Opioids increase sphincter tone, which may lead to symptoms, such as sphincter of Oddi spasms and defecation difficulties (moderate quality, strong recommendation).

3. Definition and diagnosis of opioid-induced constipation

No generally accepted definition of OIC exists; methods used to define OIC differ across disciplines and studies [27]. Nevertheless, the majority of definitions consider the history of current or recent opioid treatment combined with some of the symptoms used to define functional constipation according to the Rome III criteria [28], particularly infrequent, hard or lumpy stools, straining and incomplete evacuation [29]. Yet such definitions may overlook many patients suffering from constipation; their definitions of constipation after initiating opioid treatment are often subjective and based on bowel habits before treatment initiation [30]. Moreover, other conditions that cause or exacerbate constipation, such as metabolic and neurological conditions, mechanical colonic obstruction, non-opioid drugs and any underlying rectal evacuation disorder (more common than previously thought), should be excluded with reasonable certainty before diagnosing OIC [31].

A recently published consensus statement and proposed OIC definition by a multidisciplinary working group has taken into account the change in bowel habits from baseline recorded for at least one week as opposed to a specific number of bowel movements per week [32]. The group proposed that OIC is defined as a change from baseline bowel habits upon opioid treatment initiation characterized by any of the following symptoms:

- Reduced bowel movement frequency
- Development or worsening of straining to pass bowel movements
- A sense of incomplete rectal evacuation
- Harder stool consistency.

The need for future psychometric validation of this definition and the possibility of restricting it by requiring that two or more of

the aforementioned symptoms are present before OIC is diagnosed were acknowledged. This definition was supported by a systematic review in 2015 by Gaertner et al. [33] who analysed 47 publications relating to the definition of OIC. They concluded that a definition of OIC should include (a) objective measures such as stool frequency, (b) patient reported outcome measures, and (c) a change in these parameters since initiation of opioid therapy. The Rome Committee is also working on a definition of OIC for the forthcoming Rome IV criteria for functional gastrointestinal disorders.

Notably, some patients suffer from abdominal pain that worsen despite escalating doses of opioids [34]. This condition is labelled "narcotic bowel syndrome" and has many similarities with the opioid-induced hyperalgesia described in somatic tissues; it is characterized by allodynia and/or hyperalgesia that, paradoxically, is caused by opioid use and fails to improve despite increased dosing. The mechanism is centrally mediated and should be distinguished from OIBD where the pathophysiology is peripheral. For a review, please see Kurlander and Drossman [35].

3.1. Statement according to GRADE

- Opioid-induced constipation can be defined as a change from baseline bowel habits upon opioid treatment initiation, characterized by any of the following symptoms: reduced bowel movement frequency; development or worsening of straining to pass stool; a sense of incomplete rectal evacuation; and/or harder stool consistency (low quality, strong recommendation).

4. Epidemiology and cost of opioid-induced constipation

Opioid-induced constipation is an underdiagnosed, yet common and debilitating adverse effect of opioid treatment. Many patients with acute and chronic, moderate-to-severe pain receive opioid treatment [32]. In the US, more than 240 million opioid prescriptions are dispensed per year, the majority for non-cancer pain, such as back pain and other musculoskeletal causes [36]. In placebo trials, constipation occurs in 11% of patients, whereas the chronic constipation frequency ranges from 33 to 94% in non-cancer and cancer opioid-treated patients [37–42] (Table 1).

The frequency of OIC varies depending on the number and types of opioids used [38,39] and acute OIC also occurs when opioids are used to treat acute pain [11]. In the Patient Reports of Opioid-related Bothersome Effects (PROBE) survey of 322 patients with chronic pain in the US and EU, 33% stated that they had missed doses, decreased the dose of or stopped using opioid medication in order to relieve bowel-related side effects; 92% of patients subsequently experienced increased pain, 86% of whom reported that it reduced their Quality of Life (QoL) and daily activities [37,39].

In the non-interventional, Swedish UPPSIKT study that included patients treated with all types and administration forms of strong opioids during six months, 60–70% of the 197 OIC patients reported some degree of bothersome constipation each month. Moreover, approximately 12% of patient-months were categorized as months with severe problems due to OIC, 25% as moderate, 26% as mild and 37% as months with no constipation [43]. Clearly, OIC is uncomfortable, affects patient QoL and mortality and can prevent effective clinical management of pain.

Table 1
Prevalence of opioid-induced constipation (OIC) in chronic opioid users.

	OIC
Single opioid [37]	67%
Patients ± cancer [36,42]	33–70%
Non-cancer patients [39–41]	41–57%
Patients with cancer [40]	94%

Constipation may lead to colonic distension, ileus and perforation [44] and is associated with increased morbidity and increased utilization of healthcare resources [45,46]. Indeed, the economic burden of constipation is substantial in terms of both direct and indirect costs [47–49]. The direct costs include physician visits, hospitalisation, procedures and medications. Indirect costs include self-medication, lost earnings, restricted activity and costs of caregivers [48]. Hence, opioid use is expensive to society and costs vary with OIC severity [43]. Patients with severe constipation incur the highest total costs, i.e., 1525 EUR per patient-month, whereas patients with mild, moderate and no problems cost 1196 EUR, 1088 EUR, and 1034 EUR, respectively [43]. The indirect cost associated with sick leave is the largest cost item across all disease severity groups [43].

4.1. Statements according to GRADE

- Many patients with acute and chronic, moderate-to-severe pain receive opioid treatment (moderate quality, strong recommendation)
- The majority of opioids are prescribed for non-cancer pain (high quality, strong recommendation)
- Constipation may lead to colonic distension, ileus and perforation (moderate quality, strong recommendation)
- Constipation is associated with increased morbidity and utilization of healthcare resources (moderate quality, strong recommendation)
- The economic burden (direct and indirect costs) of constipation is high (moderate quality, strong recommendation).

5. Assessment tools for opioid-induced bowel dysfunction

The first step in diagnosing constipation is to clarify the patient complaints. Opioid-induced bowel dysfunction has a plethora of symptoms, many of which resemble other conditions. A set of definitive diagnostic criteria, therefore, would clearly aid clinicians in understanding the different mechanisms involved and initiating a treatment strategy to solve this problem.

Many rating scales for assessing constipation, each of which addresses a specific need, have been developed over the past 20 years. The high number of constipation scales highlights increasing awareness of this disorder, yet also suggests that individual scales are not sensitive enough to assess constipation in all patient types. A systematic search for assessment scales identified 16 studies focused on a selection of diverse symptoms of constipation. The scales were evaluated in different patient groups [50]. Table 2 shows the most common rating scales, all of which potentially can be used for OIC.

Whilst some of these scales are easy to use in daily clinical practice, particularly when the cause of constipation is known, others are time consuming and adapted primarily for research. Four different assessment scales have been used for OIC [51,52,55,58] (Table 2); probably the most straightforward is the Bowel Function Index (BFI). The three numerical scales of the BFI provide a single, easy, scoring method (ease of defecation + feeling of incomplete bowel evacuation + patient's personal judgment of constipation). Inclusion of these items in the BFI is supported by psychometric tests that demonstrate validity, reliability and responsiveness [50,58,62,63]. Recently, Argoff et al. [64] reviewed 5 validated assessments for constipation and concluded that BPI is the most practical and easy-to-use tool in clinical assessment of OIC. Permission from Mundipharma may be needed, however, to use the scale in clinical trials. Outcome measures were also evaluated in the systematic review from Gaertner et al. [33] as mentioned previously. They concluded that single surrogate measures such as

Table 2
An overview of the most common constipation assessment tools.

Acronym	Name	Studies	No. of items	Patient groups
CSS	Constipation Scoring System (Cleveland Clinic Score)	Agachan 1996 [51]	8	Chronic constipation and OIBD
CAS	Constipation Assessment Scale	McMillan 1989 [52]	8	OIBD
KESS	The Knowles–Eccersley–Scott symptom questionnaire	Knowles 2000 [53]	11	Chronic constipation
SBFQ	Subjective Bowel function Questionnaire	Griffenberg 1997 [54]	20	Chronic constipation
PAC-SYM	Patient Assessment of Constipation Symptoms	Frank 2001 [55]	36	OIBD
VSAQ	Visual Scale Analogue Questionnaire	Pamuk 2003 [56]	4	Chronic constipation
GQ	Garrigues Questionnaire	Garrigues 2004 [57]	21	Chronic constipation
BFI	Bowel Function Index	Rentz 2009 [58]	3	OIBD
CM	Rome III Constipation Questionnaire Module	Drossman 2006 [59], Drossman 2006 [60]		Irritable bowel syndrome, functional constipation
FICA	Faecal Incontinence and Constipation Assessment scale	Bharucha 2004 [61]	98	Bowel disorders

stool consistency should be avoided and replaced with a combined measure including (a) objective assessments such as the Bristol Stool Form Scale, (b) integrate patient reported outcome measures such as BFI and (c) assess the patients' burden of OIC.

Notably, there is no consensus as to which assessment tools should be used for the whole spectrum of OIBD, either in clinical practice or in research studies. Whilst standardized assessment scales are used in some studies [63–66], other intervention studies report primarily on spontaneous bowel movements and laxative use [67,68]. Questionnaires, such as the Gastrointestinal Symptom Rating Scale, are well validated, available in many languages and assess most relevant gastrointestinal symptoms [70]. Sensitivity to opioid-induced adverse effects, however, requires further investigation; such a questionnaire would require supplementary questions to increase its specificity for OIBD.

Physical examination is always important, for example, checking for palpable masses and anal sphincter tone in order to exclude faecal impaction. Other diagnostic investigations, such as colonoscopy, abdominal radiographs [71], colonic transit time studies [53] and anorectal physiology measurement may also be necessary to unravel the reasons behind constipation yet these tools are more expensive and not always easily accessible. An optimal diagnosis of OIBD essentially requires patient diaries, including information on bowel movements, stool consistency, pain, use of rescue laxatives and opioid medication.

5.1. Statements according to GRADE

- No consensus in the choice of assessment tools for OIBD or OIC exists (moderate quality, strong recommendation)
- The Bowel Function Index (BFI) is a valid, reliable and responsive tool to assess OIC (moderate quality, strong recommendation).

6. Opioid-induced constipation in postoperative settings

Postoperative pain will, like all acute pain conditions, inhibit gastrointestinal motility partly due to increased sympathetic excitation of the intestines. This "normal" postoperative gastrointestinal ileus resolves spontaneously once the pain and stress after the surgical trauma dissipate. Epidural analgesia with weak concentrations of a local anaesthetic drug infused into the thoracic and thoraco-lumbar epidural space dramatically reduces the time to first bowel movement after abdominal surgery [72–74]. This effect is partially antagonised by co-administration of morphine, but maintained if either a low concentration (2 μg/ml) or dose (20 μg/h) of fentanyl is co-administered with the local anaesthetic and adrenaline [75,76]. It is also well documented that opioid treatment for postoperative pain will prolong postoperative ileus [77] especially after abdominal surgery with intestinal resection/anastomosis [78].

Opioid-induced, postoperative constipation can be reduced by co-administering a peripherally-acting mu-opioid receptor antagonist (PAMORA) [1]. For example, the PAMORA alvimopan is reported to significantly reduce the time to first bowel movement after bowel surgery and is approved only for the prevention or shortening of the duration of postoperative ileus after bowel resection [78]. However, results from long-term safety studies have indicated that alvimopan may increase the risk of adverse cardiovascular events and so far alvimopan is available solely in the US and restricted for hospital use only. Interestingly, a six- to twelve-fold higher dose of alvimopan (12 mg/day) is required for the prevention/reversal of OIC after bowel surgery in opioid-naïve patients compared to that needed to reverse OIC in chronic pain patients on long-term opioid treatment (1–2 mg/day) [11,79].

6.1. Statements according to GRADE

- Opioid analgesic treatment for acute postoperative pain will prolong the postoperative ileus (moderate quality, strong recommendation)
- Opioid-induced constipation and bowel dysfunction, including post-operative ileus, can be reduced significantly by PAMORAs (moderate quality, weak recommendation).

7. Differential diagnosis of opioid induced bowel dysfunction

Other gastrointestinal disorders may present with the same symptoms as OIBD. Patients frequently experiencing chronic constipation or irritable bowel syndrome (IBS) with constipation for long periods of time are particularly susceptible to increased complaints upon initiation of opioid treatment. Gastroduodenal ulcerations induced by, for example, non-steroidal anti-inflammatory drugs (NSAIDs) with or without complications may underlie the nausea, pain or even vomiting in the case of pyloric stenosis [80]. Gastro-oesophageal reflux disease is also aggravated by NSAIDs, and predisposed patients may experience worsening of symptoms with increasing time spent in a recumbent position; it may also contribute to upper abdominal symptoms. In such cases, upper gastrointestinal endoscopy or even 4–8 weeks' treatment with a proton pump inhibitor is often indicated [81]. Intestinal obstruction due to tumours (primary or secondary) can mimic symptoms of severe constipation and should also be ruled out as a cause of new abdominal complaints, particularly in cases with a history of malignant disorders. Moreover, nausea may be caused by intracranial pathology, including central nervous system (CNS) tumours. Finally, clinicians should also be aware of the "narcotic bowel syndrome" which is an equivalent of opioid induced hyperalgesia in somatic diseases [34]. The syndrome is characterized by chronic or intermittent abdominal pain, which often increases in severity despite continued or escalating dosages of opioids, and treatment is opioid withdrawal.

7.1. Statements according to GRADE

- Polypharmacy with medications, such as NSAIDs, may cause abdominal complaints that can be mistaken for OIBD (medium quality, strong recommendation)
- Abdominal disorders, including gastroduodenal ulcerations and the narcotic bowel syndrome, may mimic OIBD and patients should be investigated when in doubt (high quality, strong recommendation)
- Abdominal malignant disease may cause intestinal obstruction, which must be ruled out (medium quality, strong recommendation).

8. Non-pharmacological and pharmacological treatment of opioid-induced bowel dysfunction

8.1. Fibres, diet and exercise

The basic advice of clinicians to patients complaining of constipation, such as having a high fibre dietary content and ample daily intake of fluid volumes, has been difficult to prove efficacious [82] and has not been specifically evaluated in OIBD. The type of dietary fibre is likely to be important; ispaghula (psyllium) is commonly recommended because it is associated with fewer complaints of intestinal gas, as are probiotics [83]. Although physical exercise increases gastrointestinal motility in healthy subjects [84,85] and its usefulness in chronic constipation associated with IBS has not been well documented [86], and specific information on its efficacy in OIBD is lacking. Nevertheless, mild exercise should at least be recommended due to its positive influence on appetite and social activities, although many patients are treated with opioids because of back pain or other musculoskeletal disorders, which limit the possibility of recommending increased physical exercise.

8.1.1. Statements according to GRADE

- Soluble fibre, such as ispaghula, is effective in relieving constipation, including OIC (low quality, weak recommendation)
- Physical exercise is likely to be beneficial in reducing complaints of OIC (medium quality, weak recommendation).

8.2. Conventional laxatives

Treatment with conventional laxatives is commonly recommended in all opioid-treated patients [87]. Laxatives can be divided into different subgroups, including osmotic agents (magnesium, lactulose, polyethylene glycol), stimulant laxatives (bisacodyl, senna), and bulking agents (methylcellulose, psyllium). Combined treatment with osmotic laxatives and stimulant agents are often recommended despite anecdotal evidence for laxatives in this setting and no evidence when preferring one laxative agent over the other. Usually, oral laxative treatment is initiated, and enemas are used in many patients especially when constipation affects the most anal segments of colon.

The efficacy of laxatives in the treatment of functional constipation is still debatable [88,89]. As pointed out by Brenner and Chey in a recent review, most conventional laxatives are insufficient for treatment of OIBD [90], possibly because the key symptoms related to opioid receptor blockade in the gastrointestinal tract are not targeted by laxatives, which primarily affect the colon [1,91]. As a consequence of the current lack of randomized, controlled, double-blinded trials investigating the efficacy of conventional laxatives in OIC patients, no evidence exists to suggest which laxatives are beneficial. Results from a study in OIC patients, however, showed that when the choice of rescue laxative was left to the patients, approximately 80–90% preferred stimulant laxatives [92]. Furthermore, it has been shown that prophylactic administration of laxatives in opioid-naïve patients generally was effective in preventing OIC. In this Japanese study magnesium oxide and senna were mostly used; however, no apparent difference in efficacy between the laxatives was demonstrated [93].

Moreover, laxative treatment *per se* may cause side effects, such as bloating, abdominal distension, rumbling, flatulence and gastro-oesophageal reflux. Together with the possible lack of efficacy, this may explain why approximately one third of patients omit, reduce or even discontinue their opioid treatment to relieve adverse effects instead of taking laxatives [36]. Sugar and sugar alcohol metabolism by intestinal microbiota produces short chain carbonic acids and gas, which may lead to or worsen the abdominal distension in OIBD [94]. Many of the bothersome symptoms associated with OIC, therefore, may not be improved by treatment with laxatives. Indeed, large-scale studies report that most (81%) patients treated chronically with opioids suffer from OIC despite using laxatives [2]. However, since many patients do experience a sufficient effect with conventional laxatives, most of which are relatively cheap, conventional laxatives are still recommended as first-line treatment in OIC patients (see Fig. 1, Section 9).

8.2.1. Statements according to GRADE

- Laxatives are recommended as first-line treatment in OIC patients (low quality, strong recommendation)
- Recommendations often suggest combined treatment with stool softeners and stimulant agents (low quality, weak recommendation)
- Laxative treatment in OIBD may cause side effects *per se* (high quality, strong recommendation).

8.3. Opioid rotation and alternative opioids

An individual's responsiveness and sensitivity to opioids involves interplay between genetic, physiological, and pharmacokinetic and -dynamic factors; together these determine both the analgesic response and tolerance to a particular drug [95]. Opioids may have a direct local effect on opioid receptors in the gastrointestinal tract, and changing from oral to parenteral or transdermal administration may partially alleviate symptoms of OIC/OIBD. Results from two studies have indicated that transdermal administration of fentanyl administered is associated with a significantly lower rate of constipation than morphine administered orally [96,97], although a Cochrane review of its effects and side effects stated that constipation was reported inconsistently [98]. Hence, gut receptors invariably will be affected when opioids reach the systemic circulation and, from a mechanistic perspective, transdermal treatment may not be better than systemic administration.

Gastrointestinal function in OIBD patients may be improved by rotating one opioid with another, whilst maintaining analgesia [99–101]. The balance between cross-tolerance to analgesic response and adverse effects contribute to the relative success of any rotation. Opioid rotation is frequently used in clinical practice; however, few prospective, randomized trials that support opioid rotation for either efficacy or adverse effects exist.

The "new" opioid tapentadol, used for pain relief, is both a μ-opioid agonist and norepinephrine reuptake inhibitor; it exhibits weaker μ-receptor activity than pure opioid agonists [102] and may be associated with a lower incidence of constipation than other opioids [103,104]. When patients with lower back or osteoarthritis pain were treated with tapentadol, oxycodone or placebo, tapentadol was shown to cause less bowel function impairment than oxycodone, i.e., significantly fewer days without a bowel movement, softer stools, less straining, and improved constipation assessment scores [105]. The proportions of treatment days with no bowel

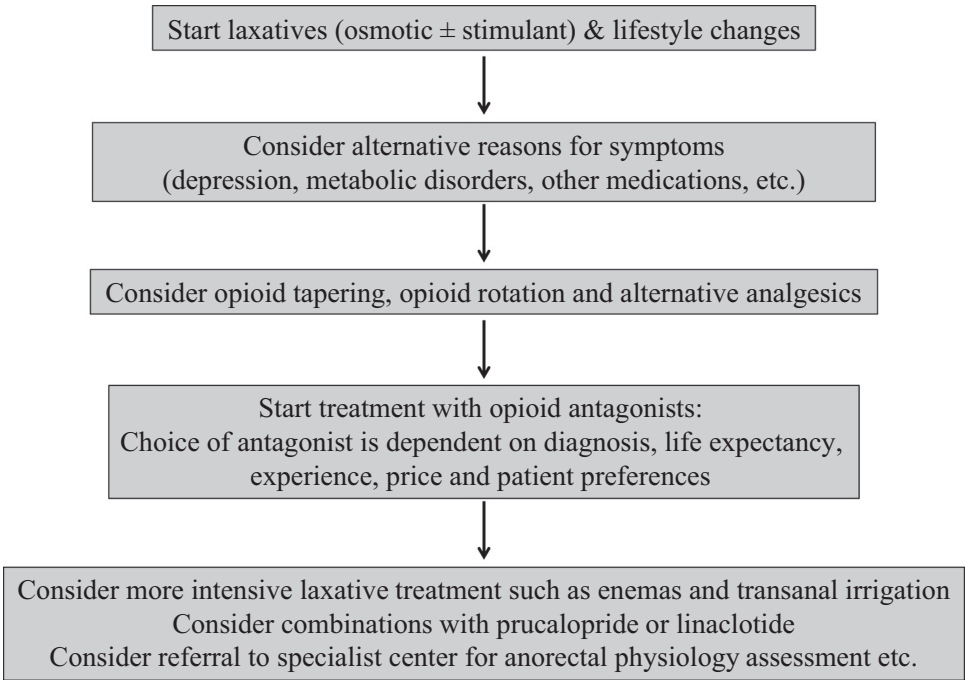

Fig. 1. Proposed algorithm for the treatment of opioid induced bowel dysfunction, especially constipation. The arrows indicate a failure of the first recommendation and thus continuation to next step. Treatment goals are to establish regular bowel function and eliminate upper gastrointestinal symptoms, improve quality of life and avoid complications, such as haemorrhoids, rectal prolapse and faecal impaction. As support for clinical evaluation questionnaires such as the Bowel Function Index may be used, where a score > 30 should lead to more intensive treatment.

movements or with incomplete bowel movements were similar among tapentadol- and placebo-treated patients. A recent systematic review in which prolonged-release oxycodone/naloxone were compared with extended-release tapentadol, however, favoured the oxycodone/naloxone combination regarding patient-reported constipation [106].

Daeninck and colleagues [107] reported on four cancer pain patients with OIBD who experienced an improvement in constipation and a reduction in laxative dose after opioid rotation to methadone. Results from another study demonstrated significant improvement in several morphine-related adverse effects, including constipation, in 52 cancer patients after rotation to methadone [108]. Moreover, a study of 189 consecutive patients who underwent methadone initiation/rotation showed improved constipation and nausea after the initiation/rotation [104]. These findings, however, must be confirmed in prospective studies with clearly defined endpoints and longer follow-up periods.

8.3.1. Statements according to GRADE

- Tapentadol causes less bowel function impairment than oxycodone (moderate quality, strong recommendation)
- Transdermal fentanyl is associated with a significantly lower rate of constipation than oral morphine (low quality, weak recommendation)
- Rotation from different opioids to methadone leads to reduced laxative doses and an improvement in constipation (low quality, weak recommendation).

8.4. Other treatments relevant for opioid-induced constipation

In patients suffering from OIBD, tapering the opioid to lowest possible dose or replacing it with other analgesics may be optional. Non-opioid analgesics are often insufficient in treating chronic pain, although guidelines recommend a basic regimen of paracetamol (acetaminophen) to reduce the required opioid dose [109,110]. Adjuvant analgesics, such as anti-epileptics (e.g., carbamazepine, gabapentin and pregabalin), are also recommended therapies for chronic pain, although mainly proven efficacious in specific conditions like neuropathic pain associated with diabetes mellitus or post-herpetic nerve injury [111]. In humans, a recent meta-analysis confirmed that at doses of 1200 mg daily or more, gabapentin was associated with pain reduction in significantly more patients than placebo, but the "number needed to treat" was as high as 6–8 for neuropathic pain and little documentation exists for other pain conditions [112]. Recently, morphine requirement in the 72-hour postoperative phase was investigated in patients randomized either to gabapentin or placebo, yet no difference in morphine consumption or in adequacy of pain relief was seen [113].

Various classes of antidepressants, often at low doses, are also used to treat neuropathic and other chronic conditions of pain and may reduce the opioid dose. A Cochrane review of the different antidepressant classes was optimistic in its support for using antidepressants to avoid opioid treatment [114]; in contrast, recent reviews of single antidepressants have shown little evidence for this [115,116]. Notably, the balance between adverse effects and analgesia often lead to other treatment alternatives.

Apart from changes in analgesic therapy, new treatment options are available for chronic idiopathic constipation and IBS with constipation and can potentially be used in special cases in patients with OIC. For example, lubiprostone specifically activates the ClC-2 chloride channels on the apical aspect of gastrointestinal epithelial cells to produce a net secretion into the gut lumen [117]. This softens the stools, stimulates motility and increases the number of spontaneous bowel movements. Lubiprostone was tested successfully in patients with chronic idiopathic constipation [118] and IBS with constipation [119] and recent randomized, placebo-controlled trials showed that it effectively relieves OIC and associated signs and symptoms, whilst being well tolerated in chronic, non-cancer pain patients [120,121]. Conversely, another smaller study showed no advantage of lubiprostone compared to the less expensive senna in postoperative orthopaedic surgery patients [122]. The drug has been approved for OIC in adults with chronic, non-cancer pain in the US since 2013, but not in Europe.

Linaclotide is a potent and selective guanylate cyclase C agonist, which induces secretion into the gut lumen, accelerates transit and reduces pain perception [123,124]. In large clinical trials, linaclotide improved abdominal and bowel symptoms in patients with chronic idiopathic constipation [125] and IBS with constipation [126]. Based on its mechanism of action, it is likely to be effective in OIC; currently a clinical trial programme is underway to assess this. Linaclotide is approved for chronic idiopathic constipation in the US and for IBS with constipation in the US and in Europe.

Prucalopride is a highly selective 5-HT_4 agonist with strong gastro-prokinetic effects [127,128]. Clinical data support its value in treating chronic idiopathic constipation, where it is safe and increases the number of bowel movements [129]. One Phase II trial has compared prucalopride with placebo in non-cancer pain patients with OIC; although several outcome variables were improved in the prucalopride group, some failed to reach statistical significance [130]. Prucalopride is currently approved in Europe for women with chronic constipation in whom laxative treatment has failed.

8.4.1. Statements according to GRADE

- Pregabalin and gabapentin may be effective alternative therapies for relieving neuropathic and other chronic pain conditions (moderate quality, strong recommendation)
- Antidepressants may be useful in treating neuropathic pain (moderate quality, weak recommendation)
- Lubiprostone can be tried for OIC (moderate quality, strong recommendation)
- Prucalopride can be tried for OIC (low quality, weak recommendation)
- Linaclotide can be tried for OIC (low quality, no recommendation).

8.5. Combination therapies: slow-release tablets with an opioid agonist and peripherally-restricted opioid antagonist (slow-release oxycodone and naloxone)

Naloxone is the classical opioid antagonist, which, when administered by parenteral injection, reverses all effects of opioid agonists and precipitates severe pain and withdrawal symptoms in chronic pain patients on long-term opioid treatment. Orally administered naloxone is well absorbed from the gastrointestinal tract and is subject to an extensive first pass metabolism. In a randomized clinical trial (RCT), however, the effect of either 2 mg or 4 mg of naloxone administered three times to nine patients with constipation on stable doses of opioids was evaluated [131]. All patients who received oral naloxone showed some improvement in bowel frequency, although the analgesic effect was reversed in three patients. Thus, when given orally in conventional tablets, naloxone might reach the systemic circulation and cause anti-analgesic and withdrawal effects. On the other hand, when naloxone is administered orally in a prolonged-release formulation, >97% is metabolised due to the hepatic first-pass mechanism, leaving only tiny amounts to reach the systemic circulation and CNS [132,133]. The effect of a combination of prolonged-release (or slow- or controlled-release) oxycodone/naloxone compared to prolonged-release oxycodone/placebo has been investigated in four RCTs in a total of 974 patients, and in which the primary outcome was the BFI scores [134–136]. A 2:1 ratio of oxycodone:naloxone was identified by the manufacturer to be the most suitable to ensure alleviation of constipation without risk for systemic effects [137]. Doses ranged between 40–120 mg for oxycodone and 10–60 mg for naloxone and trials lasted 4–12 weeks. Oxycodone/naloxone-treated patients experienced improved bowel function compared to those on oxycodone/placebo and no serious adverse effects were reported.

Ultra-low doses of naloxone may suppress some of the adverse effects of morphine, such as nausea, sedation, and itching [138,139]. Hence, improved pain control with intravenous morphine has been observed even with ultra-low doses of intravenous naloxone, which reduces opioid-induced hyperalgesia, allodynia and tolerance [140–142]. These surprising effects of ultra-low doses of naloxone may be explained by the hypothesis that μ-opioid receptor excitatory G-protein complexes are inhibited whilst the inhibitory G-protein receptors are left undisturbed [142].

For further information on these aspects of controlled- or slow-release oxycodone/naloxone, see Breivik and Werner [143] and Hesselbarth and colleagues [144].

8.5.1. Statements according to GRADE

- Naloxone, taken orally in doses sufficient to treat OIC, may cause withdrawal symptoms and reverse analgesia (moderate quality, strong recommendation)
- Slow-release naloxone–oxycodone is more efficacious than oxycodone in avoiding OIC (high quality, strong recommendation).

8.6. Peripherally-acting μ-opioid receptor antagonists

Opioid agonists cause OIBD, including OIC, primarily by binding to submucosal μ-opioid receptors in the gastrointestinal tract (see Section 2). Opioid antagonists that block only these peripheral opioid receptors should, therefore, reduce OIBD and OIC with no reduction in central opioid analgesia. In addition to naloxone administered in slow-release tablets, the effects of three PAMORAs (methylnaltrexone, naloxegol and alvimopan) have been evaluated in RCTs and are available in some countries. Alvimopan is described in the postoperative section and will be not be dealt with here.

Methylnaltrexone is a quaternary ammonium compound and thus an extremely polar compound, which does not readily cross biological membranes, such as the epithelial cells in the gut and endothelial cells in the blood–brain barrier. Thus, the compound does not gain access to the CNS and must be administered parenterally. The effects of methylnaltrexone have been investigated in five RCTs with different numbers and types of patients suffering from OIC. Treatment duration, and outcome measurements varied in the single studies (time to defecation, number of patients with drug-related bowel movements) [92,145–146]. Dosing schedules and administration routes of methylnaltrexone also differed. Doses of 0.15 mg/kg, 0.30 mg/kg or a fixed dose of 12 mg were administered daily or every second day, and by intravenous or subcutaneous injections. Results from all studies showed significantly better outcomes with methylnaltrexone compared with placebo. Secondary outcomes, such as decreased laxative use, were also reported. Generally, methylnaltrexone was well tolerated by all patients, but its high price and parenteral route of administration limits its use.

Naloxegol is a PEGylated derivative of the naloxone molecule; the PEGylation process prevents it from crossing the blood–brain barrier due to the increased size of the molecule, as well as reduced passive and active permeability. Results from two RCTs have shown that at a daily dose of 25 mg, naloxegol significantly increased the number of days per week with spontaneous and normal bowel movements (defecations) compared to that seen after administration of placebo. Pain intensity and opioid requirements were unchanged, and no withdrawal symptoms or serious cardiovascular events were observed [67,69]. Moreover, opioid-induced upper gastrointestinal dysfunctions improved (i.e., there was less regurgitation of stomach content, heartburn and nausea). It is an advantage that naloxegol can be used as an add-on to existing pain therapy, as many pain patients are on a stable and satisfactory analgesic regime, but suffer from OIBD symptoms [147]. Tack et al. [148] reported the outcome of two Phase 3 trials confirming the high efficacy of naloxegol in relieving OIC in patients with laxative-inadequate response. Naloxegol has been approved by the FDA in the US and the European Medicines Agency for the treatment

of laxative-resistant OIC, which includes cancer and non-cancer patients in Europe.

Three other PAMORAs are in development for the treatment of OIBD: bevenopran, TD-1211 and naldemedine [143].

8.6.1. Statements according to GRADE

- Methylnaltrexone blocks peripheral opioid receptors and can be used to reduce OIC (moderate quality, weak recommendation)
- Naloxegol blocks peripheral opioid receptors and can be used to reduce OIC (moderate quality, strong recommendation).

9. Conclusions and treatment practice advisory recommendations

Opioid-induced bowel dysfunction is an increasing problem due to the common use of opioids worldwide. In most countries, concurrent use of laxatives with opioids is recommended. Despite the use of conventional laxatives, however, a substantial portion of patients still suffers from OIBD, which causes a significant decrease in QoL [149]. Opioid antagonists with mechanism-based local effects on the gut are, therefore, a well-validated treatment option. Awareness of the problem is mandatory for the treating physician, and it is important to stress that constipation is only part of the plethora of OIBD symptoms, which can also be dominated by other symptoms, such as reflux and gas.

Fig. 1 summarizes a recommendation for OIBD and OIC treatment based on the current evidence outlined in this article. With regards to conventional laxatives, local traditions often guide treatment choice. Magnesium sulphate, bisacodyl, sodium picosulfate and macrogol are the most frequently used laxatives in Scandinavia and recommended as first-line medication. Lifestyle changes and alternative analgesics should always be considered. Tapering the opioid dosage, opioid rotation and dual action opioids like tapentadol may also improve OIBD. Should conventional treatment fail to alleviate symptoms, mechanism-based treatment with opioid antagonists should be considered, which shows advantages over conventional laxative use. As support for the clinical evaluation Argoff et al. [64] recently recommended that after evaluation of first-line interventions, a BFI score of >30 points should lead to prescription of PAMORAs. These treat OIC effectively and are also likely to treat other symptoms associated with opioid use, although this must still be demonstrated in experimental and clinical studies. In difficult cases, particularly in hospitalised patients, methylnaltrexone may be used as an initial "OIC test therapy" due to its parenteral administration and strong effect that may unmask the nature of the symptoms. Newer drugs, such as prucalopride, linaclotide or lubiprostone may also be tried in specific cases. It should not be overlooked that there are many other reasons for constipation than OIBD, which should also be taken into consideration in the diagnosis of an individual patient.

It is the belief of this Nordic Working Group that increased awareness of adverse effects associated with opioid therapy, particularly OIC and OIBD, will lead to better pain treatment in patients. Subsequently, optimised treatment will improve QoL and, from a socio-economic perspective, may also reduce costs associated with hospitalisation, sick leave and early retirement in patients suffering from pain.

Conflicts of interest

AMD has received financial support from Mundipharma, AstraZeneca, Shire, Almirall, Grünenthal and Pfizer. HB has received honoraria from Weifa, Mundipharma, AstraZeneca, Grünenthal and Pfizer. LA has no conflicts of interest. MS has served as an advisory board member and has been a speaker for AstraZeneca, Shire and Almirall. UEK has served as an advisory member and been on the speaker's bureau for AstraZeneca, Mundipharma and Takeda Nycomed. JH has no relevant disclosures. MS has served as an advisory board member and has been on the speaker's bureau for AstraZeneca, Shire and Almirall. HB has received honoraria from Weifa, Mundipharma, AstraZeneca, Grünenthal and Pfizer. LLC has received financial support from norpharma and has been participating in advisory boards for Grünenthal and teaching for Norpharma and AstraZeneca. MF and LA had no relevant disclosures.

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