Opioid-Induced Constipation and Bowel Dysfunction

A Clinical Guideline

Müller-Lissner, Stefan; Bassotti, Gabrio; Coffin, Benoit; Drewes, Asbjørn Mohr; Breivik, Harald; Eisenberg, Elon; Emmanuel, Anton; Laroche, Françoise; Meissner, Winfried; Morlion, Bart

Published in:
Pain Medicine

DOI (link to publication from Publisher):
10.1093/pm/pnw255

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

Pain Medicine 2017; 18: 1837–1863
doi: 10.1093/pm/pnw255

OXFORD

GENERAL SECTION

Review Article

Opioid-Induced Constipation and Bowel Dysfunction: A Clinical Guideline

Stefan Müller-Lissner, MD,[*] Gabrio Bassotti, MD,[†] Benoit Coffin, MD,[‡] Asbjørn Mohr Drewes, MD,[§] Harald Breivik, MD,[¶] Elon Eisenberg, MD,[‖] Anton Emmanuel, MD,[‖‖] Françoise Laroche, MD,[**] Winfried Meissner, MD,[††] and Bart Morlion, MD[‡‡]

[*]Department of Internal Medicine, Park-Klinik Weissensee, Berlin, Germany; [†]Gastroenterology and Hepatology Section, Department of Medicine, University of Perugia School of Medicine, Piazza Università, 1, Perugia, Italy; [‡]AP-HP Hôpital Louis Mourier, University Denis Diderot-Paris 7, INSERM U987, Paris, France; [§]Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark; [¶]Department of Pain Management and Research, University of Oslo, Rikshospitalet, Oslo, Norway; [‖]Institute of Pain Medicine, Rambam Health Care Campus, The Technion, Israel Institute of Technology, Haifa, Israel; [‖‖]GI Physiology Unit, University College Hospital, Queen Square, London, UK; [**]Saint-Antoine University Hospital, Paris, France; [††]Jena University Hospital, Jena, Germany; [‡‡]The Leuven Center for Algology and Pain Management, University of Leuven, KU Leuven, Leuven, Belgium

Funding sources: Funded by an unrestricted educational grant from Mundipharma International.

Disclosures and conflicts of interest: Stefan Müller-Lissner: consultancy for Mundipharma International, Develco, and Astra Zeneca; Gabrio Bassotti: consulting fees from Mundipharma International and lecturing fee from Shire Pharmaceutical for educational purposes; Benoit Coffin: no conflict of interest; Asbjørn Mohr Drewes: no conflict of interest; Harald Brevik: no conflict of interest; Elon Eisenberg: grant from Mundipharma International to study opioid-induced hyperalgesia; Anton Emmanuel: advisory board for NAPP, Shire, and Takeda; Francoise Laroche: consultancy for Mylan, Grünenthal, and Mundipharma International; Winfried Meissner: advisory boards for Menarini, Grünenthal, BioQPharma, Medicines Company, and Mundipharma International. No competing interests.

Correspondence to: Stefan Müller-Lissner, MD, Eisenacherstrasse 103D, 10781 Berlin, Germany. Tel: +49 30 21997504, Mobile: +49 151 12629359; Fax: +49 96 283605; E-mail: stefan@mueller-Lissner.de.

Abstract

Objective. To formulate timely evidence-based guidelines for the management of opioid-induced bowel dysfunction.

Setting. Constipation is a major untoward effect of opioids. Increasing prescription of opioids has correlated to increased incidence of opioid-induced constipation. However, the inhibitory effects of opioids are not confined to the colon, but also affect higher segments of the gastrointestinal tract, leading to the coining of the term "opioid-induced bowel dysfunction."

Methods. A literature search was conducted using Medline, EMBASE, and EMBASE Classic, and the Cochrane Central Register of Controlled Trials. Predefined search terms and inclusion/exclusion criteria were used to identify and categorize relevant papers. A series of statements were formulated and justified by a comment, then labeled with the degree of agreement and their level of evidence as judged by the Strength of Recommendation Taxonomy (SORT) system.

Results. From a list of 10,832 potentially relevant studies, 33 citations were identified for review. Screening the reference lists of the pertinent papers identified additional publications. Current definitions, prevalence, and mechanism of opioid-induced bowel dysfunction were reviewed, and a treatment algorithm and statements regarding patient management were developed to provide

guidance on clinical best practice in the management of patients with opioid-induced constipation and opioid-induced bowel dysfunction.

Conclusions. In recent years, more insight has been gained in the pathophysiology of this "entity"; new treatment approaches have been developed, but guidelines on clinical best practice are still lacking. Current knowledge is insufficient regarding management of the opioid side effects on the upper gastrointestinal tract, but recommendations can be derived from what we know at present.

Key Words. Opioids; Constipation; Opioid Antagonists; PAMORAs; Laxatives

Introduction

Pain, when not effectively treated and relieved, has detrimental effects on all aspects of a patient's quality of life (QoL) [1]. Opioids represent the cornerstone of pain treatment, being the most commonly prescribed medication to treat severe pain in the Western world [2]. Opioids are increasingly used for the treatment also of noncancer pain [3]. However, opioids are associated with side effects, which include sedation, physical dependence, respiratory depression, and gastrointestinal (GI)-related side effects [4]. These side effects can directly reduce patient QoL and increase medical service use, but may also be dose limiting, thus affecting pain control [5,6]. While tolerance develops to most side effects, GI side effects remain an ongoing problem for the majority of patients [5].

GI-related side effects are mediated through the binding of opioid agonists to μ-receptors located in the enteric nervous system, which causes increased nonpropulsive contractions and inhibition of water and electrolyte excretion, leading to delayed GI transit and hard, infrequent stools [4,7,8]. A less common side effect of opioids is narcotic bowel syndrome (NBS), characterized by a paradoxical increase in abdominal pain associated with continuous or increasing doses of opioids [9].

GI-related side effects, which include constipation, nausea, vomiting, dry mouth, gastro-oesophageal reflux, abdominal cramping, spasms, and bloating, are collectively known as opioid-induced bowel dysfunction (OIBD) [4,10]. Opioid-induced constipation (OIC) is the most frequently reported and persistent side effect in patients receiving opioids for analgesia [11]. This review aims to evaluate the current understanding of OIBD and provide timely evidence-based recommendations for the management of patients affected by this condition.

Methods

A search of the medical literature was conducted using Medline (1946–September 2014), EMBASE and EMBASE Classic (1947–September 2014), and The Cochrane Central Register of Controlled Trials.

Potentially relevant studies were identified using the terms listed in the *Appendix*. Using further search terms (also listed in the *Appendix*), the identified studies were categorized as relating to prevalence, epidemiology, mechanisms, nonpharmacological treatment, pharmacological treatment, and treatment with opioid antagonists.

In total, the search yielded 10,832 unique citations (Figure 1). For inclusion, all studies were required to be performed in a population of adults who were receiving opioids and who had a confirmed diagnosis of OIBD based on clinical symptoms, physician's opinion, or diagnostic criteria specified by study investigators. Studies identified within the treatment categories were also required to be randomized controlled trials (RCTs), comparing pharmacological or nonpharmacological therapies with a control measure. There was no minimum duration of therapy, but quantitative assessment of response to therapy was required. Results had to be supplemented by negative investigations (e.g., colonoscopy) where deemed necessary by the trial. Only publications in English were included in the analysis. Using the above inclusion and exclusion criteria, the identified citations were screened independently by two investigators for relevance by title and then abstract, which resulted in 124 and 52 citations, respectively. Full publications of the 52 citations were assessed, and, following discussion to resolve any disagreement, a final list of 33 citations was generated [12–44]. Screening the reference lists of the pertinent papers identified additional publications.

Statements were then formulated and justified by a comment. The statements were labeled with the degree of agreement (usually unanimous) and their level of evidence by the strength of recommendation taxonomy (SORT) system (level 1 = high; level 2 = moderate; level 3 = low) [45]. This corresponds to the classification by the GRADE system where the levels of evidence "low" and "very low" are pooled [46]. The strength of recommendation is given as "strong" or "weak" when applicable. Independent electronic voting was carried out after a joint meeting where all authors had the possibility to discuss the different sections and comment on each statement. The table showing the results can be found in the *Appendix*.

Definition, Symptoms, and Assessment of OIC and OIBD

The Definition of OIC/OIBD Is Based on a Clinical Evaluation Relating to a Change in Bowel Habits During Opioid Therapy

Comment: Previously, the diagnosis was arbitrarily based on changes in bowel function temporally associated with intake of opioids. A recent working group

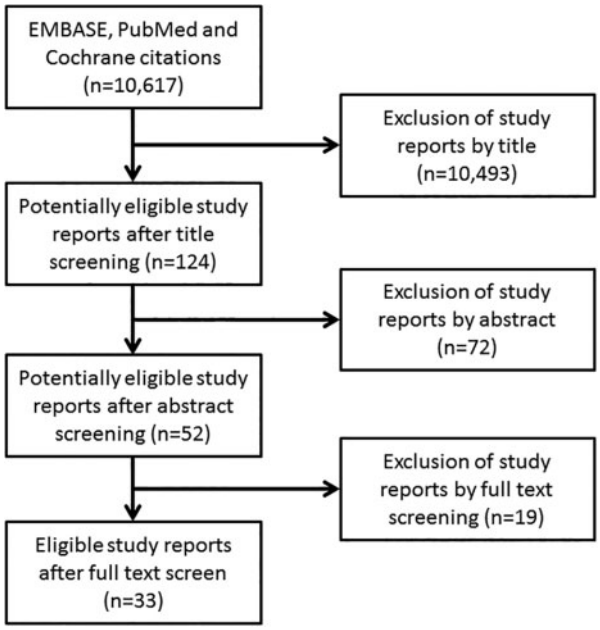

Figure 1 Flow diagram showing review of literature to identify clinical research papers relating to OIBD.

suggested that OIC was defined as follows: "A change when initiating opioid therapy from baseline bowel habits (over 7 days) that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency" [47]. A somewhat comparable definition was recently suggested based on a systematic literature review [48]. These definitions represent the first attempts to ensure a uniform diagnosis, and this definition is recommended for future studies to ensure a uniform terminology.

The Symptoms of OIC Are Related to the Colon, Whereas OIBD Manifests with Symptoms Throughout the GI Tract

Comment: Opioid receptors are present throughout the GI tract, and therefore symptoms should not be restricted to the colon [49]. OIBD is a distressing condition that manifests through a variety of different symptoms, including vomiting, dry mouth, abdominal pain, gastroesophageal reflux, and constipation [4]. Descriptive studies have demonstrated that patients undergoing opioid treatment also had prevalent complaints related to the upper gut [17,20,30]. However, most clinical studies looking into adverse effects of opioids and opioid antagonists have focused on OIC, and especially on the number of complete bowel movements that can be quantified. It should also be stressed that straining at stools can cause upper GI symptoms such as reflux, and it is therefore questionable as to whether OIC and OIBD can be distinguished in clinical settings.

OIBD symptoms are potentially difficult to localize and distinguish from each other due to the complex organization of the visceral sensory system; visceral afferents show diffuse termination over many segments of the spinal cord [50–52]. It is therefore plausible that colonic distension due to OIC may also be felt in the upper abdomen. Furthermore, mechanisms such as viscero-visceral hyperalgesia may play a role for symptom manifestations as afferents from somatic structures, and different visceral organs often terminate on the same neurons in the spinal cord [53–55]. As a consequence, it has been shown that the acidification of the esophagus may result in widespread changes in pain perception from remote organs, such as the rectum [56–58]. Although not investigated in detail, it seems plausible that opioid treatment also results in widespread symptoms in most patients.

Importantly, while the effect on pain may decrease during continuing opioid treatment, OIC tends to remain a clinical problem and is not subject to tolerance [59].

Subjective Reports of OIC Are Based on Validated Questionnaires, Whereas There Is No Consensus About Assessment of OIBD

Comment: In many studies, symptom assessments were based on self-made questionnaires. Questionnaires developed and validated to assess "normal" constipation, such as the Bristol Stool Form Scale, Patient Assessment of Constipation Scale, and the Knowles-Eccersley-Scott symptom scoring system, have also been used, although the sensitivity of these

questionnaires when used by opioid users has not been assessed [37,47,60]. Alongside the introduction of slow-release oxycodone/naloxone combinations designed to reduce OIC, a new and specific questionnaire was developed. This is termed the Bowel Function Index (BFI) and is a clinician-administered questionnaire to evaluate and assess OIC. The BFI has been validated against the Patient Assessment of Constipation Scale, bowel movements, and laxative use, with excellent correlation being found [61].

For OIBD, there is no valid assessment tool specifically designed to measure the burden of these symptoms. Instruments such as the Gastrointestinal Symptom Rating Scale are well validated for general GI symptoms and are available in many languages [62]. However, sensitivity to opioid-induced adverse events will require further investigation. The questionnaire will also require supplementary questions to increase its specificity for OIBD. Recently the use of several outcome variables based on objective measures (e.g., bowel movements), patient-reported assessment with questionnaires, and a global measure of burden such as life quality were suggested [48]. Future studies are, however, needed to explore the reliability and validity of these tools.

Objective Assessment of OIBD Has Focused on Motility, but There Are Only a Few Human Studies on Opioid Effects on Secretion and Sphincter Function

Comment: Self-reported number of bowel movements and time to bowel movement may be used as objective measures of OIC. The feces can be quantified with semi-objective questionnaires such as the Bristol Stool Form scale [60]. When it comes to more physiological measurements, most studies have focused on motility disturbances where transit time was measured in different ways [63,64].

No methods are able to estimate the total flux of water in the human intestine. Fecal collection and measurement of water content is possible, but difficult to use in clinical practice. Secretion of water from the gut mucosa can be directly assessed from biopsies in an Ussing chamber [65]. It is also possible to quantify the amount of feces within the colon based on magnetic resonance scanning, but no such studies have yet been performed to address OIBD [66,67].

Sphincter tone has been shown to be increased following opioid treatment; however, there is only one study that has demonstrated a pressure increase of the human internal sphincter during opioid treatment [68,69]. Methods such as the Functional Lumen Imaging Probe and high-resolution manometry may increase our knowledge about anal sphincter function in the near future [70,71].

Prevalence

Data on Prevalence of OIC Differs Widely Based on the Definitions Used and Origin of the Studies, but Not on Gender

Comment: The prevalence of constipation was reported in 22–81% of patients [14,20]. Prevalence rates relate to the instrument used—in a study of 520 individuals, the prevalence was 59% according to the BFI, 67% using the Knowles–Eccersley–Scott symptom score, and 86% according to the clinician's opinion [37]. Prevalence of OIC is not related to gender (odds ratios = 1:1.25 male:female) [30].

The Type of Pure Opioid Drugs Does Not Influence the Prevalence of OIC Symptoms

Comment: One placebo-controlled study of opioids showed a 14% rate of constipation with placebo vs 39–48% for various forms of oxycodone and oxymorphone [72]. A review of different opioids showed no difference in rates of OIC between morphine, hydrocodone, and hydromorphone [73]. A recent approach to reduce OIC is through dual action drugs. One of these, tapentadol, is an opioid with classic μ-agonistic properties that also has simultaneous action as a noradrenaline reuptake inhibitor [74]. Hence, for an equianalgesic dose, less μ-agonism is required in opioid-naïve patients [75–77]. However, experienced pain specialists have seen withdrawal when patients have been switched from long-term treatment with potent opioids to an "equipotent" dose of tapentadol without first tapering the opioid.

Dose and Frequency of Opioids Influences Likelihood of OIC Symptoms

Comment: In one study, daily use of opioids led to reports of constipation in 81% of patients, whereas only 46% of patients using opioids two to three times per week reported constipation [20]. The study documented that daily opioid users tended to take more than one type of opioid.

Transdermal Preparations of Fentanyl and Buprenorphine May Be Associated with Lower Incidence of OIC than Oral Opioids

Comment: The rates of constipation reported for transdermal opioids are numerically lower than for oral opioids. In a nonrandomized, retrospective study, the rates of constipation were 3.7% for transdermal fentanyl, 6.1% for oxycodone controlled-release (CR), and 5.1% for morphine CR [78]. Similar findings, reproducing these extremely low incidences of OIC, were seen with fentanyl patch (5%) vs morphine (6%) [79]. A systematic review of 14 studies on buprenorphine showed lower rates of

constipation for buprenorphine than for morphine and similar rates to those reported for fentanyl. However, there were no direct comparisons of the two transdermal opioids [80]. Patch administration of buprenorphine does indeed cause constipation. A buprenorphine patch (median dose 10 ug/hour) caused constipation in 24% of 100 osteoarthritis patients compared with only 5% in the placebo-patch group [81]. The opioid, when released from the patch, will still reach the intestinal circulation and enteric nervous system and, therefore, may exert its inhibitory effect on motility. However, the more uniform blood opioid concentration provided by the patch, particularly in regards to reduced peaks in concentration, may be advantageous. It is also important to remember that caution must be taken when interpreting the prementioned data as there are no high-quality comparative trials between oral and transdermal opioids.

Duration of Opioid Therapy Influences the Impact of OIC Symptoms

Comment: A systematic review of 11 studies, including 2,877 patients with nonmalignant pain, identified that opioid treatment for more than six weeks significantly improved QoL and functional outcomes [82]. However, patients who had been taking opioid analgesia for more than six months and suffering OIC had a higher impact on their QoL, as well as impairment of in-work productivity and activities of daily living (in all comparisons), and greater work time was missed than for patients without OIBD [83]. Though this statement is based on an indirect comparison, we do know that opioid treatment for more than six weeks can improve QoL and that there is a difference in impact on QoL between patients with OIC and without OIC. As such, there needs to be a judgment made that balances the benefits of chronic opioid usage against the risks of intestinal symptoms.

Mechanisms of OIBD

Opioid Receptors Are Spread Throughout the GI Tract from the Mid-Esophagus to Rectum and Are Involved in a Variety of Cellular Functions

Comment: δ-, κ-, and μ-opioid receptors have been identified in the GI tract [84]. These receptors are predominantly found in the enteric nervous system, but their relative distribution varies within regions and histological layers of the gut and, most importantly, between species [85,86]. In rats, μ-receptors are widely distributed in the myenteric plexus, where they control motility, as well as in the submucosal plexus, where they mainly regulate ion and water transport [85–88]. The endogenous opioid ligands (e.g., enkephalins, endorphins, and dynorphins) have correspondingly been localized in the same regions [89]. In humans, the distribution of the different opioid receptors and subclasses is less thoroughly investigated, but μ-receptors in the enteric nervous system are thought to be of utmost importance [86].

Endogenous ligands play a role in normal regulation of GI function, but opioid receptors are also activated by exogenous opioids [86,90,91]. Opioid-induced intracellular signaling is complex, but leads to decreased neuronal excitability and less neurotransmitter release, resulting overall in an inhibitory effect on the cells. The main effect is thought to be decreased formation of cyclic adenosine monophosphate, a molecule involved in the activation of several target molecules that regulate cellular functions [92]. The effect opioids have on GI motility and secretion is further complicated by opioid receptor agonists' ability to influence both excitatory and inhibitory activity, as well as activating the interstitial cell of the Cajal–muscle network [84].

Opioid Agonists Administration Results in Slowing of Normal GI Motility, Segmentation, Increased Tone, and Uncoordinated Motility Reflected in, for Example, Increased Transit Times

Comment: Gut motility is mainly controlled by the myenteric plexus. This is dependent on neurotransmitters where acetylcholine activates the motor neurons in the longitudinal smooth muscles, whereas vasoactive intestinal peptide and nitric oxide control the inhibition of inhibitory motor neurons in the circular smooth muscles [49,93]. As opioid administration inhibits the release of the neurotransmitters, it directly results in an increase in tone and a decrease in the normal propulsive activity. μ-opioid receptors are likely of most importance as the effect of morphine on GI motility is absent in μ-receptor knockout mice [94]. Central effects of opioids on motility may play a role via sympathetic activation, but are likely to be of minor importance [95].

The results of the animal experiments were confirmed in vitro on isolated human gut strips [96]. Furthermore, in vivo human studies have confirmed that opioid administration leads to dysmotility of the esophagus and gallbladder and increase of tone in the stomach [93,97–99], as well as a delay in gastric emptying, oral-coecal transit, and colonic transit time [64,69,100].

Although confirmation is required in other species, a recent study in mice suggests that the effect of opioids on the gut, may vary between opioids [101]. Hence, opioids such as tapentadol, which have effects on the noradrenergic system, may preserve the analgesic effects with fewer adverse effects on the gut [102].

Opioids Result in Increased Absorption and Decreased Secretion of Fluids in the Gut, Leading to Dry Feces and Less Propulsive Motility

Comment: Opioids inhibit acetylcholine release, which can lead to a decrease in saliva production, resulting in the symptom of dry mouth. In the gut, the submucosal plexus controls local secretory and absorptive activity

[59,103]. Acetylcholine, along with serotonin and vasoactive intestinal peptide, is released from neurons activating intracellular mechanisms in mucosa cells and, subsequently, epithelial cell chloride channels. As chloride moves from the enterocyte cytoplasm into the gut lumen, water follows via an osmotic gradient [91,101,104].

Opioids bind to the secretomotor neurons in the submucosa and suppress neurotransmitter release, resulting in a decrease in chloride and water secretion [91]. In this way, gut secretion and absorption is affected together with gastric and pancreatico-biliary secretion [85,105,106].

The slowing of gut motility also allows more time for water absorption. A decrease in fecal volume has a negative effect on motility as the intrinsic reflexes that result in propulsive contractions are dependent on mechanoreceptor activation [85].

Opioids Increase Sphincter Tone, Which May Cause Symptoms Such as Sphincter of Oddi Spasms and Difficult Defecation

Comment: The effect of opioids on the lower esophageal sphincter in humans remains unclear. Most volunteer studies have shown an increase in resting pressure but an abnormal coordination [107,108]. In patients with reflux, morphine was shown to reduce the number of transient sphincter relaxations, but in some experiments there was an increased incidence of gastro-esophageal reflux [109,110]. However, many of the studies were flawed by methodological limitations. New devices, such as the functional lumen imaging probe (EndoFLIP), may clarify how opioids interfere with esophageal function [111].

The effect on the pylorus was investigated by Stacher et al. (1992), who documented increased tone, which will invariably worsen gastro-esophageal reflux [112].

Morphine administration results in sphincter of Oddi contractions, leading to a decreased emptying of pancreatic juice and bile, and therefore delayed digestion [113]. It has been observed that patients on opioid therapy may experience acute biliary pain attacks [114,115]. Opioid-induced sphincter of Oddi dysfunction has also been described in patients addicted to opioids, presenting findings such as pancreatobiliary pain and dilation of the bile duct [68].

The ileal brake has only been investigated in animal studies, where it was shown that endogenous opioids contribute to the stomach-to-caecum transit [116].

Opioid-induced dysfunction of the ano-rectal physiology is particularly relevant as sphincter dysfunction can result in straining, hemorrhoids, and/or incomplete evacuation, which are worsened by constipation. The significance of anal sphincter dysfunction in OIBD has only been sparsely assessed [69], but preclinical studies indicate that opioids not only inhibit relaxation of the internal anal sphincter, but also the detection of stool in the upper anal canal [117,118]. This is in line with a recent study of patients treated with opioid analgesics, where one-third of patients had feeling of anal blockage [30].

Opioid Antagonists Counteract the Effects of Opioids in the Human Gut on Motility, Fluid Transport, and Sphincter Function

Comment: Antagonism of μ-receptors has been shown to reverse the effect of opioids on gut motility in numerous animal studies [89,119,120]. In humans, opioid antagonists reversed the effect of opioids on the esophagus and stomach and increased gut motility in the intestine [64,110,121–125]. It should be noted that some studies found no effect of opioid antagonists (e.g., on motility in the stomach and small intestine), but this may be explained by methodological limitations [90,97]. Consistent with the physiological experiments, pilot clinical studies have shown that naloxone can improve chronic idiopathic gastric stasis, “normal” constipation, and chronic idiopathic pseudoobstruction [100,126–128].

Preclinical studies have shown that antagonists of δ-receptors reverse the effects of opioids on secretion [113]. However, there is a lack of human physiological studies; the effect of antagonists on secretion has not been addressed, although relief of evacuation problems due to dry feces is frequently reported [129].

Opioid antagonists were shown to eliminate the effect of opioids on sphincter function in preclinical studies [114]. In humans, the effect of morphine and pethidine on sphincter of Oddi contractions was also reduced by naloxone [130].

QoL

QoL Can Be Worse due to Side Effects of Opioids

Comment: Patients with moderate-to-severe pain who receive opioid analgesic treatment for their pain often experience a secondary burden due to the adverse effects of opioids (for example, OIC) [59,131].

Many of the adverse events associated with opioid analgesics may subside due to tolerance. However, the symptoms of OIC often persist for some time, resulting in a significant impact on patients’ QoL [59]. In patients taking opioids, constipation may be more distressing for the patient than the underlying pain. In a large international survey of patients treated with opioid therapies for six or more months, patients suffering from constipation were more likely to visit their physician, take time off

work, and feel that their work productivity and their capability of performing daily activities was impaired compared with those who did not experience constipation [83].

Assessment of QoL in Patients with OIC/OIBD Can Assist Therapeutic Choices

Comment: As reviewed recently, numerous assessment tools, both generic (such as SF-36/EQ5D, etc.) and constipation specific (such as PAC-QoL), are used to assist therapeutic choices and evaluate QoL in constipated patients in general, and in patients with OIC/OIBD in particular [132]. One special type of general QoL measure is the utility value, which is usually measured between 0 and 1, where perfect health is given a score of 1. A number of studies have shown a reduction in QoL as a result of constipation. A study of patients who were treated with opioid analgesics and had a severe noncurable disease and relatively short life expectancy used the EuroQoL five-dimension questionnaire (EQ-5D) to measure QoL. The EQ-5D score in patients without advanced illness who did not experience constipation was much higher (0.65) than the score for patients with constipation (0.31) [27]. In a study on QoL in patients with chronic functional constipation, a cost-effectiveness model that measured health outcomes by number of quality-adjusted life-years demonstrated a small 1% health benefit for one laxative over another [133].

Nonpharmacological Prevention and Treatment of OIC

Nonpharmacological Treatments of OIC Include Dietary Recommendations and Lifestyle Modifications

Comment: In patients with OIC, no study in the current literature has tested the efficacy of nonpharmacological treatments. In subjects with chronic idiopathic constipation, there is no evidence that increasing fluid intake, unless there is co-existent dehydration, is an effective treatment.

In nonopioid-induced constipation (i.e., chronic idiopathic constipation), increasing soluble dietary fiber, psyllium, or ispaghula may improve symptoms [134,135]. Finally, moderate-to-intense physical activity may improve moderate chronic idiopathic constipation [134]. With regard to OIC, standard daily fluid and fiber intakes should be recommended, although this is not evidence based. However, increases in physical activity might be difficult to obtain in patients with chronic pain requiring treatment with opioids.

If narcotic bowel syndrome is suspected to contribute to the symptoms, tapering or withdrawal of opioids should be tried and pain should be treated by alternative measures [136].

Pharmacological Prevention and Treatment of OIC/OIBD

The Choice of a Laxative to Treat OIC/OIBD Depends on the Perceived Efficacy and the Preference of the Patient; Indirect Evidence Favors Bisacodyl, Sodium Picosulfate, Macrogol (Polyethelene Glycol), and Sennosides as First Choice

Comment: Both bisacodyl (and its derivative sodium picosulfate) and sennosides stimulate secretion and are very potent prokinetics in the colon. Their prokinetic action may potentially also be active in the more oral segments of the gut [137–139]. Bisacodyl is used as the rescue laxative in most of the therapeutic trials for OIC, and the amount taken is considered a sensitive variable for the efficacy of the drug under investigation [32–34,43,140–142]. Macrogol and sugars, such as lactulose, act by binding water. Macrogol and lactulose proved to be significantly superior to placebo, macrogol being numerically better than lactulose (Table 1) [142].

When the choice of the rescue laxative was decided by OIC patients, in one study approximately 80–90% of patients preferred a "stimulant laxative" (bisacodyl or senna) [22], whereas in another study macrogol and sodium picosulfate were the preferred laxatives [147]. Hence, bisacodyl, sodium picosulfate, sennosides, and macrogol appear to have similar efficacy in OIC [147].

Preventive administration of laxatives to 720 adult Japanese patients treated with oral opioid analgesics for the first time was effective in preventing OIC (defined as a stool-free interval of $\geq$72 hours). The most frequently prescribed laxatives were magnesium oxide and senna. There were no apparent differences in the efficacy between laxatives [148].

Of importance is that many patients are not informed (or do not recall that they have been informed) about constipation and laxatives when opioids are prescribed. Hence, in a recent interview study at the pharmacy with patients having their first opioid prescription, only 28% remembered having received information about the risk of constipation and 13% were prescribed laxatives or instructed to request them [149].

Sugars and Sugar Alcohols Such as Lactulose, Lactose, and Sorbitol Should Not Be Used to Prevent or Treat OIC

Comment: Metabolism of sugars and sugar alcohols by the intestinal microbiota leads to short chain carbonic acids and gas. The ensuing abdominal distension may aggravate distension in OIBD [150,151]. Lactulose and polyethylene glycol were studied in a controlled trial that comprised of 308 critically ill patients with multiple organ failure and mechanical ventilation. Intestinal

Table 1 Controlled trials with laxatives in OIC

Trial design	Population	Intervention	Efficacy variable	Results	Reference
Randomized, double-blind, placebo-controlled crossover trial Duration: unclear	57 subjects from a methadone maintenance program with self-defined constipation	Lactulose 30 mL, macrogol (Polyethylene glycol 3350/electrolyte solution), placebo	Soft and loose stools per week	Baseline 1.57 soft and loose stools/week, placebo 4.74, lactulose 4.82, macrogol 5.81; difference between groups not significant	Freedman 1997 [143]
Randomized open trial Duration: 7 days	91 terminally ill patients with self-defined OIC	Senna 12–48 mg/day compared with lactulose 15–60 mL/day	Defecation-free interval 72-hour period	No significant difference was found between the 2 laxatives: Senna 0.9, lactulose 0.9	Agra 1998 [144]
Randomized, placebo-controlled double-blind trial Duration: 6 days	64 orthopedic surgery patients with self-perceived OIC and at least 1 additional symptom of Rome criteria	Lubiprostone 24 μg BID compared with senna ("2 capsules")	Change in bowel movement	ΔSBMs/day: lubiprostone -0.04, senna 0.32 ($P = 0.29$)	Marciniak 2014 [145]
Randomized, controlled double-blind trial Duration: 12 weeks	418 noncancer pain patients with fewer than 3 stools/week and at least 1 additional symptom of Rome criteria	Lubiprostone 24 μg BID compared with placebo	Change in SBM at week 8	ΔSBMs: Lubiprostone 3.3 SBMs/week, placebo 2.4 SBMs/week ($P < 0.005$)	Cryer 2014 [142]
Randomized, placebo-controlled double-blind trial Duration: 12 weeks	424 noncancer pain patients with fewer than 3 SBMs/week and at least 1 additional symptom of Rome criteria	Lubiprostone 24 μg BID compared with placebo BID	At least 1 SBM improvement in all weeks and at least 3 SBMs/week for ≥9 of the 12 weeks	Responder rate lubiprostone 27.1%, placebo 18.9% ($P = 0.03$)	Jamal 2015 [146]

(continued)

Table 1

Trial design	Population	Intervention	Efficacy variable	Results	Reference
Randomized, controlled double-blind trial Duration: 4 weeks	196 noncancer pain patients with "clearly OIC"	Prucalopride 2 mg, prucalopride 4 mg once daily compared with placebo	Proportion of patients with a mean increase of at least 1 SCBM per week from baseline	Prucalopride 2 mg 35.9%, prucalopride 4 mg 40.3%, placebo 23.4% Results with prucalopride were not significantly different compared with placebo	Sloots 2010 [140]

BID = twice daily; OIC = opioid-induced constipation; SBM = spontaneous bowel movement (i.e., not induced by additional laxative); SCBM = SBM perceived as complete.

Table 2 Controlled trials with naloxone for OIC

Trial design	Population	Intervention	Efficacy variable	Results	Reference
Randomized, placebo-controlled double-blind trial Duration: unclear	Nine patients with noncancer pain "with OIC"	Immediate release naloxone 2 mg, compared with naloxone 4 mg and placebo TID	Stool frequency and daily opioid usage	All naloxone-treated patients had some improvement in their bowel frequency; 1 patient also had complete reversal of analgesia, and 3 patients experienced reversal of analgesia	Liu 2002 [13]
Phase III, randomized, controlled parallel trial Duration: 12 weeks	322 patients with chronic noncancer pain "with OIC"	Prolonged-release oxycodone/naloxone compared with prolonged-release oxycodone/placebo	BFI at end of week 4	Improvement of BFI 26.9 compared with 9.4 points (naloxone compared with control) ($P < 0.001$)	Simpson 2008 [18]
Phase II, randomized, dose finding, placebo-controlled parallel trial Duration: 4 weeks	202 patients with chronic pain (2.5% with cancer pain) "with concomitant constipation"	Stable doses of oxycodone 40, 60 compared with 80 mg/day plus 10, 20, and 40 mg naloxone or placebo	BFI	Dose-dependent improvement of BFI by naloxone ($P < 0.05$)	Meissner 2009 [160]
Phase III, randomized, placebo-controlled parallel trial Duration: 4 weeks	265 patients with chronic noncancer pain with fewer than 3 SCBMs/week	Prolonged-release oxycodone 60–80 mg/day)/naloxone compared with same doses of prolonged-release oxycodone/placebo	BFI	BFI reduced by 26.5 compared with 10.8 points (naloxone vs control) ($P < 0.001$) and SBMs increased to 3 per week compared with 1 per week	Lowenstein 2009 [23]
Phase II, randomized, placebo-controlled parallel trial Duration: 4 weeks	185 patients with moderate-to-severe cancer pain	Prolonged-release oxycodone)/naloxone compared with prolonged-release oxycodone/placebo	BFI and laxative use	BFI between groups 11.14 ($P < 0.01$); laxative intake 20% lower in naloxone group	Ahmedzai 2012 [3353]

BFI = Bowel Function Index; OIC = opioid induced constipation; SBM = spontaneous bowel movement (i.e., not induced by additional laxative); SCBM = SBM perceived as complete; TID = three times daily.

Table 3 Controlled trials with naloxegol for OIC

Trial design	Population	Intervention	Efficacy variable	Results	Reference
Phase II, randomized, dose-finding, placebo-controlled parallel group trial Duration: 4 weeks	207 patients with nonmalignant or cancer-related pain with fewer than 3 SBMs per week	Naloxegol (5, 25 or 50 mg) compared with placebo	Median change from baseline in SBMs per week at end of week 1	ΔSBMs 2.9 vs 1.0 ($P = 0.002$) for 25 mg compared with placebo; 3.3 vs 0.5 ($P = 0.0001$) for 50 mg compared with placebo	Webster 2013 [42]
Two identical phase III, randomized, placebo-controlled, double-blind parallel group trials Duration: 12 weeks	652 and 700 outpatients with noncancer pain and fewer than 3 SBMs per week	12.5 or 25 mg of naloxegol compared with placebo	12-week response rate (at least 3 SBMs with an increase of at least 1 SBM for $\geq$9 of the 12 weeks, and $\geq$3 of the final 4 weeks)	44.4% vs 29.4% ($P = 0.001$) and 48.7% vs 28.8% ($P = 0.002$) in both trials (25 mg naloxegol compared with placebo), 12.5 mg significant improvements in study 04	Chey 2014 [43]
Phase III, randomized, controlled parallel group trial Duration: 52 weeks	804 patients with chronic noncancer pain and fewer than 3 SBMs per week	Naloxegol 25 mg/day compared with the current SOC (30–1,000 morphine equivalent)	Long-term safety and tolerability	AEs that occurred more frequently for naloxegol compared with SOC were abdominal pain (17.8% vs 3.3%), diarrhea (12.9% vs 5.9%), nausea (9.4% vs 4.1%), headache (9.0% vs 4.8%), flatulence (6.9% vs 1.1%), and upper abdominal pain (5.1% vs 1.1%)	Webster 2014 [162]

AE = adverse event; SBM = spontaneous bowel movement (i.e., not induced by additional laxative); SOC = standard of care.

Table 4 Controlled trials with methylnaltrexone for OIC

Trial design	Population	Intervention	Efficacy variable	Results	Reference
2-day, placebo-controlled, single-blind crossover trial	12 subjects with fewer than 2 stools per week due to chronic methadone use	Day 1: placebo; day 2: oral methylnaltrexone (0.3, 1.0, and 3.0 mg/kg, respectively)	Laxation response, oro-coecal transit time	All patients treated with methylnaltrexone had a laxation response Oro-coecal transit times shortened by methylnaltrexone ($P < 0.001$)	Yuan 2000 [12]
Phase II, randomized, single-dose, placebo-controlled double-blind trial	154 patients with advanced illness and OIC	Single SC injection of 0.15 mg/kg or 0.3 mg/kg compared with placebo	Bowel movement within 4 hours of treatment	Laxation within 4 hours in 62%, 58%, and 14% for 0.15 mg/kg, 0.30 mg/kg, and placebo, respectively	Slatkin 2009 [25]
Randomised, 2-week, double-blind placebo-controlled trial	133 patients with advanced illness and laxative regimen for more than 3 days before the study and OIC	0.15 mg/kg SC of methylnaltrexone compared with placebo every other day	Time to first SBM following treatment initiation	SBM within 4 hours; median time to bowel movement response was 0.5 hours and 2.0 hours in the methylnaltrexone and placebo groups, respectively ($P = 0.013$); fewer methylnaltrexone than placebo patients reported use of laxatives (5.3% compared with 35.2%)	Chamberlain 2009 [22]
Randomized, 4-week placebo-controlled trial	460 patients with chronic noncancer pain	SC injections of 12 mg methylnaltrexone compared with placebo once daily or once every other day	Percentage of injections leading to an SBM within 4 hours	SBMs within 4 hours in 28.9%, 30.2%, and <9.5% (daily, alternative days, and placebo, respectively) ($P < 0.001$)	Michna 2011 [34]

(continued)

Table 4

Trial design	Population	Intervention	Efficacy variable	Results	Reference
Phase II, randomized, double-blind, parallel-group placebo-controlled trial	33 patients with acute OIC after orthopedic surgical procedure, likely to require opioids for ≥7 days postrandomization	Once-daily 12 mg SC methylnaltrexone compared with placebo for up to 4 or 7 days	Time to laxation and percentage of patients experiencing laxation within 2 and 4 hours of first dose	Laxation within 2 hours: 33.3% vs 0% ($P = 0.021$); 4 hours: 38.9% vs 6.7% ($P = 0.046$); median time to laxation 15.8 vs 50.9 hours ($P = 0.0197$) for methylnaltrexone vs placebo	Anissian 2012 [36]

OIC = opioid-induced constipation; SBM = spontaneous bowel movement (i.e., not induced by additional laxative); SC = subcutaneous.

Table 5 Controlled trials with alvimopan for OIC

Trial design	Population	Intervention	Efficacy variable	Results	Reference
Randomized, placebo-controlled double-blind trial	168 patients with nonmalignant pain (N = 148) or opioid dependence (N = 20)	0.5 and 1.0 mg alvimopan compared with placebo	Percentage of patients with SBMs within 8 hours	54%, 43%, and 29% of patients had an SBM within 8 hours after alvimopan 1 mg, 0.5 mg compared with placebo, respectively ($P < 0.001$)	Paulson 2005 [15]
Phase IIb, randomized, placebo-controlled double-blind trial	522 subjects with noncancer pain and OIC	0.5 mg alvimopan BID, 1.0 mg alvimopan BID, and 1.0 mg alvimopan QID compared with placebo	Change in SBM	ΔSBMs with alvimopan 0.5 mg BID (+1.71 mean SBMs/week), alvimopan 1 mg QID (+1.64), and alvimopan 1 mg BID (+2.52) compared with placebo	Webster 2008 [19]
Phase III, randomized, placebo-controlled double-blind trial	518 patients with noncancer pain	0.5 mg alvimopan QID, alvimopan 0.5 mg BID, or placebo for 12 weeks	Percentage of patients with at least 3 SBMs per week and an average increase in baseline SBM of at least 1 SBM/week	72% vs 48% ($P < 0.001$) (alvimopan BID vs placebo); no significant improvement with alvimopan QID (61% vs 48%)	Jansen 2011 [33]
Randomized, placebo-controlled double-blind trial	485 patients with noncancer pain	0.5 mg alvimopan QID, alvimopan 0.5 mg BID, compared with placebo, for 12 weeks	Percentage of patients achieving at least 3 SBMs per week and percentage of patients achieving at least 1 more SBM per week	Higher proportions of SBM responders in both alvimopan groups compared with placebo, but not statistically significant	Irving 2011 [32]

BID = twice daily; OIC = opioid-induced constipation; QID = four times a day; SBM = spontaneous bowel movement (i.e., not induced by additional laxative).

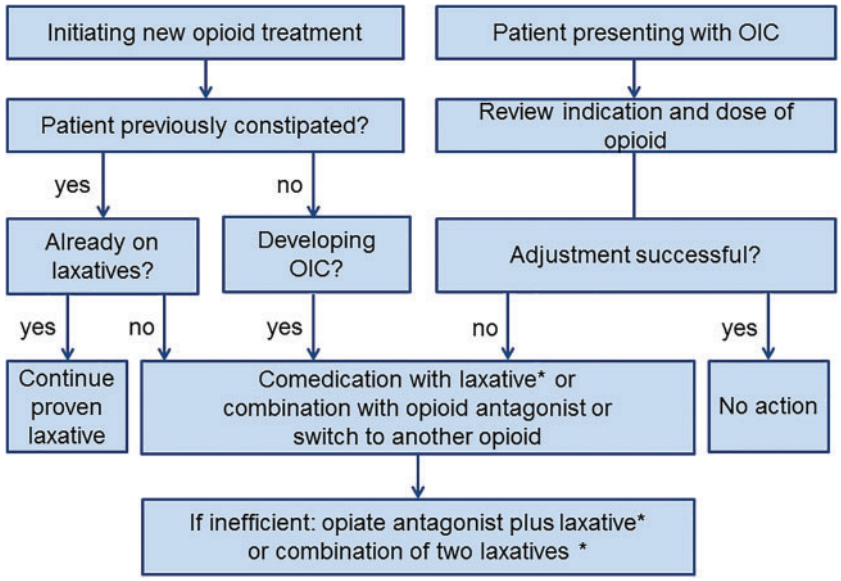

Figure 2 Treatment guidance algorithm for patients initiating opioid treatment and patients presenting with OIC. Patients with previous constipation not responding well to laxatives and given an opioid therapy on top are probably best treated with an agonist-antagonist plus a laxative. *First choice laxatives—bisacodyl, sodium picosulfate, senna, macrogol. OIC = opioid-induced constipation.

pseudo-obstruction or Ogilvie's syndrome occurred in 5.5% of patients in the lactulose group, and in 1.0% of patients in the macrogol group [152]. Lactulose seems similarly effective to treat OIC as senna [144], though numerically inferior to macrogol (Table 1) [143], and it should therefore not be considered first choice.

Gastro-Oesophageal Reflux Symptoms as Part of OIBD Should Be Treated like Primary Reflux Disease

Comment: There are no published therapeutic trials on gastro-esophageal reflux as part of OIBD, but there is no reason to assume that conventional reflux treatment could not ameliorate reflux symptoms in OIBD.

Patients with Nausea Secondary to Opioid Treatment Should Be Offered Dopamine Antagonists

Comment: Published evidence shows no or only minor positive effects of metoclopramide on nausea and vomiting when morphine was given parenterally in acute pain [153,154]. However, when given for chronic pain, positive results on nausea were reported in an uncontrolled study [155]. Data on the neurokinin-1-receptor-antagonist aprepitant are insufficient to recommend its use [156].

Treatment of OIC with New Laxatives (Prucalopride, Lubiprostone) May Be Promising; However, to Date, There Are Insufficient Data to Warrant Such Treatments in OIC Patients

Comment: In recent years, a few new drugs have been proposed for the medical treatment of patients with chronic constipation [157]. Among these, prucalopride (a potent and highly selective agonist of 5-HT_4 serotonin receptors) [158] and lubiprostone (a chloride [Cl^-] channel activator derived from prostaglandin E1) [159] are currently sold in Europe and the United States, respectively. Both these drugs have also been tested in patients complaining of OIC (Table 1). Concerning prucalopride, there is only one published study available showing that both the 2 mg and 4 mg once-daily doses significantly increase spontaneous bowel movements in these patients, but only during the first two weeks of treatment [29]. Concerning lubiprostone, the available data (two published studies [142,145] and four abstracts [38,40,41,44]) seem to suggest that the drug may be useful in the treatment of OIC, even though it is possible that this effect is limited to some subtypes of patients. Compared with placebo, lubiprostone was able to improve symptoms related to OIC [142]. Another

study showed no advantage over the less expensive senna [145].

Peripherally Acting μ-Opioid Receptor Antagonists

Peripherally Acting μ-Opioid Receptor Antagonists Effectively Reduce OIC

Comment: Attempts have been made to develop opioid antagonists that block peripheral opioid receptors and reduce OIC. They do not have access to opioid receptors within the central nervous system and therefore spare central analgesic opioid function. Sixteen RCTs on the following four peripherally acting μ-opioid receptor antagonists (PAMORAs) have been identified: naloxone (either alone or in fixed-ratio combination with oxycodone), methylnaltrexone, naloxegol, and alvimopan. On the whole, they provide evidence for efficacy of PAMORAs for OIC, and partly also for OIBD [160].

In Patients with Chronic Cancer or Noncancer Pain, Prolonged-Release Naloxone/Oxycodone Combination Effectively Reduces OIC While Maintaining Equal Analgesia to Prolonged-Release Oxycodone Alone

Comment: Following oral administration, naloxone has nearly no systemic bioavailability due to extensive first-pass hepatic metabolism [161]. Therefore it acts almost exclusively on opioid receptors in the GI tract and spares central analgesia. Prolonged-release (PR) naloxone/oxycodone combination was tested in four RCTs in 974 patients with chronic pain [18,23,35,160]. Oxycodone dose per 24 hours ranged between 40 mg and 120 mg, and trial duration from four to 12 weeks. Oxycodone/naloxone (2:1 fixed ratio)-treated patients exhibited improved BFI, the primary outcome in all studies, compared with those treated by oxycodone/placebo (mean difference ranged from 11.1 to 17.5 points across studies) (Table 2). No serious adverse events were reported. Notably, one RCT tested the effect of 2 mg or 4 mg of naloxone (not prolonged release) alone, or placebo, in nine patients taking stable doses of opioids who had OIC [13]. Oral naloxone-treated patients had some improvement in bowel frequency, but reversal of analgesia was experienced by three of the nine patients.

Oral Naloxegol Is Effective and Safe in Reducing OIC in Patients with Chronic Pain

Comment: Naloxegol, a PEGylated derivative of naloxone, is taken orally and is not transported across the blood-brain barrier. Results of three trials in more than 1,500 patients show that, at a daily dose of 25 mg, the number of days per week with spontaneous and normal bowel movements increased significantly compared with placebo (Table 3). Pain intensities and opioid requirements did not change, and no withdrawal symptoms or serious cardiovascular events were observed [42,43]. The advantage of the drug is that it can be used orally in the community regardless of the opioid taken by the patient.

Methylnaltrexone Injections Can Effectively Relieve OIC in Patients with Postoperative Cancer and Noncancer Chronic Pain

Comment: Due to its chemical structure, methylnaltrexone does not cross the blood-brain barrier and acts only peripherally. The five identified RCTs in this category (>800 patients) varied considerably in terms of number of randomized patients (22 to 460), treatment duration (single dose to four weeks), diagnosis (cancer pain, chronic noncancer pain, methadone maintenance), and dose (0.15 mg/kg; 0.30 mg/kg or 12 mg administered daily or every other day, intravenously, or by subcutaneous injection) [12,22,25,34,36]. The outcome in most studies was either time to first bowel movement after the injection or, more commonly, the percentage of patients achieving bowel movement within two to four hours of treatment. All studies showed significantly better outcome with methylnaltrexone compared with placebo (Table 4). Secondary outcomes such as decreased laxative use also improved. The treatment was generally well tolerated, although cases of GI perforation in association with methylnaltrexone use have been reported [163]. Recent findings suggest that methylnaltrexone can lead to increased morphine demands for postoperative pain control [164].

Alvimopan Is Approved in the United States for Use in Hospitalized Patients for Preventing or Decreasing the Course of Postoperative Ileus After Bowel Resection; Long-Term Safety Studies Indicated that It May Possibly Increase the Risk of Cardiovascular Events; There Is Some Evidence that Alvimopan Reduces OIC in Subjects with Chronic Opioid Intake

The selective peripheral action of alvimopan is related to its large molecular size and zwitter-ionic form. Four RCTs studied alvimopan in OIC in more than 1,500 patients for preventing or decreasing the course of postoperative ileus after bowel resection (Table 5). Two of them showed a significant improvement in the number of patients demonstrating bowel movements, the number of bowel movements, and/or reduced duration of time to first bowel movement [15,19]. However, the primary end point of three spontaneous bowel movements per week in two other studies was not [32], or was only partly, met [33]. Notably, opioid-naïve patients with “acute OIC” need much higher doses of alvimopan (12 mg) to reduce the length of postoperative ileus after bowel surgery than patients with chronic opioid treatment (1–2 mg) [165].

Three other PAMORAs are being developed for OIC [47,166]: bevenopran (Cubist Pharmaceuticals), TD-1211 (Theravance, South San Francisco, CA, USA), and naldemedine (S-297995, Shionogi, Osaka, Japan). An oral form of methylnaltrexone is also under development for treating OIC in patients on opioid therapy for chronic noncancer pain. Clinical RCT data are not available.

Both Laxatives and Opioid Antagonists for OIC Have Benefits on QoL

Comment: In the trials evaluating a fixed combination of prolonged-release oxycodone/naloxone, bowel function and QoL were investigated using the BFI and other tools. In the three phase III trials, performed with the majority of patients with moderate-to-severe nonmalignant pain, significant improvements in constipation were observed in patients taking PR oxycodone/naloxone compared with those taking PR oxycodone. The improvement in constipation was generally seen within one week of treatment and lasted the duration of the trials [18,23]. In an assessment of PR oxycodone/naloxone, using the QoL tool SF-36, significant improvements were observed in the subscales of social functioning, vitality, and general health at week 12 of treatment [167].

A large noninterventional study of clinical practice observed improvements in QoL for PR oxycodone/naloxone-treated patients. Patients with severe chronic pain of various etiologies treated with PR oxycodone/naloxone demonstrated significant reductions in constipation in both opioid-naïve and opioid-tolerant patients [168]. The Short-Form Brief Pain Inventory demonstrated an improvement of 43% (in 2023 patients) after four weeks of treatment [168].

In an RCT, both senna and lubiprostone improved QoL and constipation-related symptoms in OIC in postoperative orthopedic patients treated with opioids, with no significant between-group differences [158].

Noncancer patients taking prucalopride reported a greater improvement in their constipation severity and the efficacy of treatment than patients taking placebo, as measured by the patient-reported PAC-SYM and PAC-QoL questionnaires (patient assessment of constipation symptoms and patient assessment of constipation symptoms and quality of life, respectively) [140]. However, the effect was only significant during the first two weeks of treatment.

Patients with OIC treated with 25 mg naloxegol once daily, a peripherally acting μ-opioid receptor antagonist, reported improved median total patient-reported scores on the PAC-QoL questionnaire compared with patients taking placebo. During the double-blind treatment period, the 25 mg naloxegol group reported a statistically significant improvement in SF-36 scale scores for mental health, social functioning, physical functioning, and vitality compared with patients receiving placebo. There was no significant difference between placebo and the 5 mg and 50 mg naloxegol dose groups [42].

Summary and Conclusions

OIBD is an increasing problem due to the wider use of opioids, including the treatment of nonmalignant pain. Current knowledge is certainly insufficient regarding many aspects of OIC, and more so of OIBD as reflected by our votes regarding the level of evidence (*Appendix*). Though this holds particularly true for the management of the opioid side effects on the upper GI tract, recommendations can be derived from what we know at present (Figure 2). As only about half of the patients taking opioid experience OIC, a general comedication with a laxative or an opiate antagonist would be an overtreatment. Rather, awareness of the problem is mandatory for the treating physician. In addition, prophylaxis could be adjusted to the perceived risks of OiC in a particular patient; for example, it could be prescribed to those who have had constipation as a problem before starting opioids. However, this issue deserves further study in the future.

The conventional laxatives, bisacodyl, sodium picosulfate, macrogol, and senna, seem to be the first choice to treat OIC. The new laxatives, linaclotide, lubiprostone, and prucalopride, may also be effective in selected patients but do not seem to be superior to PAMORAs based on the presently available indirect comparisons. PAMORAs clearly have a proven effect on OIC. Whether PAMORAs have advantages over laxatives through the addressing of OIBD, and not only OIC, needs to be shown in randomized double-blind comparative trials.

Acknowledgments

Editorial assistance was provided by Ogilvy Clinical Sciences, London.

References

1 Katz N. The impact of pain management on quality of life. J Pain Symptom Manage 2002;24:S38–47.

2 Trescot AM, Glaser SE, Hansen H, et al. Effectiveness of opioids in the treatment of chronic non-cancer pain. Pain Physician 2008;11:S181–200.

3 Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med 2015;372:241–8.

4 Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. Am J Surg 2001; 182:S11–8.

5 McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: A systematic review. J Pain 2003;4:231–56.

6 Klepstad P, Borchgrevink PC, Kaasa S. Effects on cancer patients' health-related quality of life after the start of morphine therapy. J Pain Symptom Manage 2000;20:19–26.

7 Camilleri M. Opioid-induced constipation: Challenges and therapeutic opportunities. Am J Gastroenterol 2011;106:835–42.

8 Rachinger-Adam B, Conzen P, Azad SC. Pharmacology of peripheral opioid receptors. Curr Opin Anaesthesiol 2011;24:408–13.

9 Keefer L, Drossman DA, Guthrie E, et al. Centrally mediated disorders of gastrointestinal pain. Gastroenterology 2016;150:1408–19.

10 Panchal SJ, Müller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: Prevalence, pathophysiology and burden. Int J Clin Pract 2007; 61:1181–7.

11 Coluzzi F, Pappagallo M. Opioid therapy for chronic noncancer pain: Practice guidelines for initiation and maintenance of therapy. Minerva Anestesiol 2005; 71:425–33.

12 Yuan CS, Foss JF, O'Connor M, et al. Methylnaltrexone for reversal of constipation due to chronic methadone use: A randomized controlled trial. JAMA 2000;283:367–72.

13 Liu M, Wittbrodt E. Low-dose oral naloxone reverses opioid-induced constipation and analgesia. J Pain Symptom Manage 2002;23:48–53.

14 Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med 2003;4:340–51.

15 Paulson DM, Kennedy DT, Donovick RA, et al. Alvimopan: An oral, peripherally acting, mu-opioid receptor antagonist for the treatment of opioid-induced bowel dysfunction—a 21-day treatment-randomized clinical trial. J Pain 2005;6:184–92.

16 Gray D, Spence D. The prevalence of constipation in patients receiving methadone maintenance treatment for opioid dependency. J Sub Use 2005; 10:397–401.

17 Cook SF, Lanza L, Zhou X, et al. Gastrointestinal side effects in chronic opioid users: Results from a population-based survey. Aliment Pharmacol Ther 2008;27:1224–32.

18 Simpson K, Leyendecker P, Hopp M, et al. Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate-to-severe noncancer pain. Curr Med Res Opin 2008;24:3503–12.

19 Webster L, Jansen JP, Peppin J, et al. Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist for the treatment of opioid-induced bowel dysfunction: Results from a randomized, double-blind, placebo-controlled, dose-finding study in subjects taking opioids for chronic non-cancer pain. Pain 2008;137:428–40.

20 Bell TJ, Panchal SJ, Miaskowski C, et al. The prevalence, severity, and impact of opioid-induced bowel dysfunction: Results of a US and European Patient Survey (PROBE 1). Pain Med 2009;10:35–42.

21 Candrilli SD, Davis KL, Iyer S. Impact of constipation on opioid use patterns, health care resource utilization, and costs in cancer patients on opioid therapy. J Pain Palliat Care Pharmacother 2009;23:231–41.

22 Chamberlain BH, Cross K, Winston JL, et al. Methylnaltrexone treatment of opioid-induced constipation in patients with advanced illness. J Pain Symptom Manage 2009;38:683–90.

23 Lowenstein O, Leyendecker P, Hopp M, et al. Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: A randomised controlled trial. Exp Opin Pharmacother 2009;10:531–43.

24 Meissner W, Dohrn B, Reinhart K. Enteral naloxone reduces gastric tube reflux and frequency of pneumonia in critical care patients during opioid analgesia. Crit Care Med 2003;31:776–80.

25 Slatkin N, Thomas J, Lipman AG, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. J Support Oncol 2009;7:39–46.

26 Hjalte F, Berggen AC, Bergendahl H, Hjortsberg C. The direct and indirect costs of opioid-induced constipation. J Pain Symptom Manage 2010;40:696–703.

27 Penning-van Beest FJ, van der Haak P, Klok RM, et al. Quality of life in relation to constipation among opioid users. J Med Econ 2010;13:129–35.

28 Rosti G, Gatti A, Costantini A, Sabato AF, Zucco F. Opioid-related bowel dysfunction: Prevalence and

identification of predictive factors in a large sample of Italian patients on chronic treatment. Eur Rev Med Pharmacol Sci 2010;14:1045–50.

29 Sloots CE, Poen AC, Kerstens R, et al. Effects of prucalopride on colonic transit, anorectal function and bowel habits in patients with chronic constipation. Aliment Pharmacol Ther 2002;16:759–67.

30 Tuteja AK, Biskupiak J, Stoddard GJ, Lipman AG. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. Neurogastroenterol Motil 2010;22:424–30.

31 Wee B, Adams A, Thompson K, et al. How much does it cost a specialist palliative care unit to manage constipation in patients receiving opioid therapy. J Pain Symptom Manage 2010;39:644–54.

32 Irving G, Penzes J, Ramjattan B, et al. A randomized, placebo-controlled phase 3 trial (study SB-767905/013) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. J Pain 2011;12:175–84.

33 Jansen JP, Lorch D, Langan J, et al. A randomized, placebo-controlled phase 3 trial (Study SB-767905/012) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. J Pain 2011;12:185–93.

34 Michna E, Blonsky ER, Schulman S, et al. Subcutaneous methylnaltrexone for treatment of opioid-induced constipation in patients with chronic, nonmalignant pain: A randomized controlled study. J Pain 2011;12:554–62.

35 Ahmedzai SH, Nauck F, Bar-Sela G, et al. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. Palliat Med 2012;26:50–60.

36 Anissian L, Schwartz HW, Vincent K, et al. Subcutaneous methylnaltrexone for treatment of acute opioid-induced constipation: Phase 2 study in rehabilitation after orthopedic surgery. J Hosp Med 2012;7:67–72.

37 Abramowitz L, Béziaud N, Labreze L, et al. Prevalence and impact of constipation and bowel dysfunction induced by strong opioids: A cross-sectional survey of 520 patients with cancer pain: DYONISOS study. J Med Econ 2013;16:1423–33.

38 Cryer B, Mareya S, Joswick T, et al. Spontaneous bowel movement frequency is improved over 12 weeks of lubiprostone therapy in opioid-induced constipation patients regardless of gender, age, or race: Pooled analysis of three well-controlled studies. Am J Gastroenterol 2013;108:S567.

39 Ivanova JI, Birnbaum HG, Yushkina Y, et al. The prevalence and economic impact of prescription opioid-related side effects among patients with chronic noncancer pain. J Opioid Manage 2013; 9:239–54.

40 Joswick T, Mareya SM, Lichtlen P, Woldegeorgis F, Ueno R. Time to onset of lubiprostone treatment effect in chronic non-cancer pain patients with opioid-induced constipation: Data from two phase 3, randomized, double-blind, placebo-controlled trials. Gastroenterology 2013;144:S540.

41 Mareya S, Drossman D, Joswick T, et al. Lubiprostone effectively relieves opioid-induced constipation in patients using on-diphenylheptane opioids for non-cancer pain: Pooled analysis of three randomized controlled trials. Gastroenterology 2013; 144:S539–40.

42 Webster L, Dhar S, Eldon M, et al. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. Pain 2013;154:1542–50.

43 Chey WD, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with non-cancer pain. N Engl J Med 2014;370:2387–96.

44 Spierings EL, Drossman DA, Cryer BL, Losch-Beridon T, Ueno R. A pooled analysis of response to lubiprostone in patients with opioid induced constipation receiving non-methadone opioids versus methadone. Gastroenterology 2014;146:S360.

45 Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): A patient-centered approach to grading evidence in the medical literature. Am Fam Physician 2004;69:548–56.

46 Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401–6.

47 Camilleri M, Drossman DA, Becker G, et al. Emerging treatments in neurogastroenterology: A multidisciplinary working group consensus statement on opioid-induced constipation. Neurogastroenterol Motil 2014;26:1386–95.

48 Gaertner J, Siemens W, Camilleri M, et al. Definitions and outcome measures of clinical trials regarding opioid-induced constipation: A systematic review. J Clin Gastroenterol 2015;49:9–16.

49 Brock C, Olesen SS, Olesen AE, et al. Opioid-induced bowel dysfunction: Pathophysiology and management. Drugs 2012;72:1847–65.

50 Zhong F, Christianson JA, Davis BM, Bielefeldt K. Dichotomizing axons in spinal and vagal afferents of the mouse stomach. Dig Dis Sci 2008; 53:194–203.

51 Knowles CH, Aziz Q. Basic and clinical aspects of gastrointestinal pain. Pain 2009;141:191–209.

52 Lottrup C, Olesen SS, Drewes AM. The pain system in oesophageal disorders: Mechanisms, clinical characteristics and treatment. Gastroenterol Res Pract 2011;2011:910420.

53 Arendt-Nielsen L, Laursen RJ, Drewes AM. Referred pain as an indicator for neural plasticity. Prog Brain Res 2000;129:346–56.

54 Drewes AM, Arendt-Nielsen L, Jensen JH, et al. Experimental pain in the stomach: A model based on electrical stimulation guided by gastroscopy. Gut 1997;41:753–7.

55 Brinkert W, Dimcevski G, Arendt-Nielsen L, Drewes AM, Wilder-Smith OHG. Dysmenorrhoea is associated with hypersensitivity in the sigmoid colon and rectum. Pain 2007;132:S46–51.

56 Frøkjær JB, Andersen SD, Gale J, et al. An experimental study of viscero-visceral hyperalgesia using an ultra-sound-based multimodal sensory testing approach. Pain 2005;119:191–200.

57 Brock C, Andresen T, Frøkjær JB, et al. Central pain mechanisms following combined acid and capsaicin perfusion of the human oesophagus. Eur J Pain 2009;14:273–81.

58 Sami SA, Rössel P, Dimcevski G, et al. Cortical changes to experimental sensitization of the human esophagus. Neuroscience 2006;140:269–79.

59 Holzer P, Ahmedzai SH, Niederle N, et al. Opioid-induced bowel dysfunction in cancer-related pain: Causes, consequences, and a novel approach for its management. J Opioid Manag 2009;5:145–51.

60 Olesen AE, Drewes AM. Validated tools for evaluating opioid-induced bowel dysfunction. Adv Ther 2011;28:279–94.

61 Rentz AM, Yu R, Müller-Lissner S, Leyendecker P. Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-induced constipation. J Med Econ 2009;12:371–83.

62 Kulich KR, Madisch A, Pacini F, et al. Reliability and validity of the Gastrointestinal Symptom Rating Scale (GSRS) and Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire in dyspepsia: A six-country study. Health Qual Life Outcomes 2008; 6:12.

63 Scott SM. Manometric techniques for the evaluation of colonic motor activity: Current status. Neurogastroenterol Motil 2003;15:483–513.

64 Smith K, Hopp M, Mundin G, et al. Naloxone as part of a prolonged release oxycodone/naloxone combination reduces oxycodone-induced slowing of gastrointestinal transit in healthy volunteers. Expert Opin Investig Drugs 2011;20:427–39.

65 Wallon C, Braaf Y, Wolving M, Olaison G, Söderholm JD. Endoscopic biopsies in Ussing chambers evaluated for studies of macromolecular permeability in the human colon. Scand J Gastroenterol 2005;40:586–95.

66 Marciani L, Garsed KC, Hoad CL, et al. Stimulation of colonic motility by oral PEG electrolyte bowel preparation assessed by MRI: Comparison of split vs single dose. Neurogastroenterol Motil 2014; 26:1426–36.

67 Sandberg TH, Nilsson M, Poulsen JL, et al. A novel semi-automatic segmentation method for volumetric assessment of the colon based on magnetic resonance imaging. Abdom Imaging 2015;40:2232–41.

68 Sharma SS. Sphincter of Oddi dysfunction in patients addicted to opium: An unrecognized entity. Gastrointest Endosc 2002;55:427–30.

69 Sun WM, Read NW, Verlinden M. Effects of loperamide oxide on gastrointestinal transit time and anorectal function in patients with chronic diarrhoea and faecal incontinence. Scand J Gastroenterol 1997; 32:34–8.

70 Alqudah M, Gregersen H, Drewes AM, McMahon BP. Identification of component muscle function in the ano-rectal region of healthy controls using EndoFLIP distension. Neurogastroenterol Motil 2012;24:e591–9.

71 Carrington EV, Brokjaer A, Craven H, et al. Traditional measures of normal anal sphincter function using high-resolution anorectal manometry (HRAM) in 115 healthy volunteers. Neurogastroenterol Motil 2014;26:625–35.

72 Matsumoto AK, Babul N, Ahdieh H. Oxymorphone extended-release tablets relieve moderate to severe

pain and improve physical function in osteoarthritis: Results of a randomized, double-blind, placebo- and active-controlled phase III trial. Pain Med 2005; 6:357–66.

73 Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. Pain 2004;112:372–80.

74 Afilalo M, Morlion B. Efficacy of tapentadol ER for managing moderate to severe chronic pain. Pain Physician 2013;16:27–40.

75 Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: Results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. Expert Opin Pharmacother 2010;11:1787–804.

76 Steigerwald I, Schenk M, Lahne U, et al. Effectiveness and tolerability of tapentadol prolonged release compared with prior opioid therapy for the management of severe, chronic osteoarthritis pain. Clin Drug Investig 2013;33:607–19.

77 Wild JE, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. Pain Pract 2010;10:416–27.

78 Staats PS, Markowitz J, Schein J. Incidence of constipation associated with long-acting opioid therapy: A comparative study. South Med J 2004; 97:129–34.

79 Kress HG, Von der Laage D, Hoerauf KH, et al. A randomized, open, parallel group, multicenter trial to investigate analgesic efficacy and safety of a new transdermal fentanyl patch compared to standard opioid treatment in cancer pain. J Pain Symptom Manage 2008;36:268–79.

80 Wolff RF, Aune D, Truyers C, et al. Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain. Curr Med Res Opin 2012; 28:833–45.

81 Breivik H, Ljosaa TM, Stengaard-Pedersen K, et al. A 6-month, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patients naïve to potent opioids. Scand J Pain 2010;1:122–41.

82 Devulder J, Richarz U, Nataraja SH. Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain. Curr Med Res Opin 2005;21:1555–68.

83 Bell T, Annunziata K, Leslie JB. Opioid-induced constipation negatively impacts pain management, productivity, and health- related quality of life: Findings from the National Health and Wellness Survey. J Opioid Manag 2009;5:137–44.

84 Holzer P. Pharmacology of opioids and their effects on gastrointestinal function. Am J Gastroenterol Suppl 2014;2:9–16.

85 Kurz A, Sessler DI. Opioid-induced bowel dysfunction: Pathophysiology and potential new therapies. Drugs 2003;63:649–71.

86 Sternini C, Patierno S, Selmer IS, Kirchgessner A. The opioid system in the gastrointestinal tract. Neurogastroenterol Motil 2004;16:3–16.

87 McKay JS, Linaker BD, Turnberg LA. Influence of opiates on ion transport across rabbit ileal mucosa. Gastroenterology 1981;80:279–84.

88 Bagnol D, Mansour A, Akil H, Watson SJ. Cellular localization and distribution of the cloned mu and kappa opioid receptors in rat gastrointestinal tract. Neuroscience 1997;81:579–91.

89 Holzer P. Treatment of opioid-induced gut dysfunction. Expert Opin Investig Drugs 2007;16:181–94.

90 Camilleri M, Malagelada JR, Stangilellini V, et al. Dose-related effects of synthetic human and naloxone on fed gastrointestinal motility. Am J Physiol 1986;251:147–54.

91 Galligan JJ, Akbarali HI. Molecular physiology of enteric opioid receptors. Am J Gastroenterol Suppl 2014;2:17–21.

92 Sharma SK, Nirenberg M, Klee WA. Morphine receptors as regulators of adenylate cyclase activity. Proc Natl Acad Sci U S A 1975;72:590.

93 Wood JD, Galligan JJ. Function of opioids in the enteric nervous system. Neurogastroenterol Motil 2004;16:17–28.

94 Roy S, Liu HC, Loh HH. mu-Opioid receptor-knockout mice: The role of mu-opioid receptor in gastrointestinal transit. Brain Res Mol Brain Res 1998;56:281–3.

95 Manara L, Bianchi G, Ferretti P, Tavani A. Inhibition of gastrointestinal transit by morphine in rats results primarily from direct drug action on gut opioid sites. J Pharmacol Exp Ther 1986;237:945–9.

96 Bauer AJ, Sarr MC, Szurszewski JH. Opioids inhibit neuromuscular transmission in circular muscle of human and baboon jejunum. Gastroenterol 1991; 101:970–6.

97 Gonenne J, Camilleri M, Ferber I, et al. Effect of alvimopan and codeine on gastrointestinal transit: A randomized controlled study. Clin Gastroenterol Hepatol 2005;3:784–91.

98 Kraichely RE, Arora AS, Murray JA. Opiate-induced oesophageal dysmotility. Aliment Pharmacol Ther 2010;31:601–6.

99 Penagini R, Allocca M, Cantù P, et al. Relationship between motor function of the proximal stomach and transient lower oesophageal sphincter relaxation after morphine. Gut 2004;53:1227–31.

100 Hawkes ND, Rhodes J, Evans BK, et al. Naloxone treatment for irritable bowel syndrome - a randomized controlled trial with an oral formulation. Aliment Pharmacol Ther 2002;16:1649–54.

101 Mori T, Shibasaki Y, Matsumoto K, et al. Mechanisms that underlie μ-opioid receptor agonist-induced constipation: Differential involvement of μ-opioid receptor sites and responsible regions. J Pharmacol Experiment Ther 2013; 347:91–9.

102 Xu S, Etropolski M, Upmalis D, et al. Pharmacokinetic and pharmacodynamic modeling of opioid-induced gastrointestinal side effects in patients receiving tapentadol IR and oxycodone IR. Pharm Res 2012;29:2555–64.

103 Thomas J. Opioid-induced bowel dysfunction. J Pain Symptom Manage 2008;35:103–13.

104 Barrett KE, Keely SJ. Chloride secretion by the intestinal epithelium: Molecular basis and regulatory aspects. Annu Rev Physiol 2000;62:535–72.

105 Kromer W. Endogenous and exogenous opioids in the control of gastrointestinal motility and secretion. Pharmacol Rev 1988;40:121–62.

106 Glad H, Ainsworth MA, Svendsen P, Fahrenkrug J, Schaffalitzky de Muckadell OB. Effect of vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide on pancreatic, hepatic and duodenal mucosal bicarbonate secretion in the pig. Digestion 2003;67:56–66.

107 Dowlatshahi K, Evander A, Walther B, Skinner DB. Influence of morphine on the distal oesophagus and the lower oesophageal sphincter—A manometric study. Gut 1985;26:802–6.

108 Drewes AM, Krarup AL, Olesen AE, et al. Pharmacology of the esophagus. Ann N Y Acad Sci 2014;1325:57–68.

109 Penagini R, Bartesaghi B, Zannini P, Negri G, Bianchi PA. Lower oesophageal sphincter hypersensitivity to opioid receptor stimulation in patients with idiopathic achalasia. Gut 1993;34:16–20.

110 Penagini R, Bianchi PA. Effect of morphine on gastroesophageal reflux and transient lower esophageal sphincter relaxation. Gastroenterol 1997;113:409–14.

111 McMahon BP, Frøkjær JB, Kunwald P, et al. The Functional Lumen Imaging Probe (FLIP) for evaluation of the esophagogastric junction. Am J Physiol Gastrointest Liver Physiol 2007; 292:G377–84.

112 Stacher G, Steinringer H, Schneider C, et al. Effects of the prodrug loperamide oxide, loperamide, and placebo on jejunal motor activity. Dig Dis Sci 1992;37:198–204.

113 Green BT, Calvin A, O'Grady SM, Brown DR. Kinin-induced anion-dependent secretion in porcine ileum: Characterization and involvement of opioid- and cannabinoid-sensitive enteric neural circuits. J Pharmacol Exp Ther 2003;305:733–9.

114 Coelho JCU, Runkel N, Herfarth C, Senninger N. Effect of analgesic drugs on the electromyographic activity of the gastrointestinal tract and sphincter of Oddi and on biliary pressure. Ann Surg 1986; 204:53–8.

115 Wu S-D, Zhang Z-H, Jin J-Z, et al. Effects of narcotic analgesic drugs on human Oddi's sphincter motility. World J Gastroenterol 2004;10:2901–4.

116 Brown NJ, Rumsey RDE, Bogentoft C, Read NW. The effect of an opiate receptor antagonist on the ileal brake mechanism in the rat. Pharmacol 1993; 47:230–6.

117 Burleigh DE, D'Mello A. Neural and pharmacologic factors affecting motility of the internal anal sphincter. Gastroenterol 1983;84:409–17.

118 Bouvier M, Kirschner G, Gonella J. Actions of morphine and enkephalins on the internal anal sphincter of the cat: Relevance for the physiological role of opiates. J Auton Nerv Syst 1986;16:219–32.

119 Moss J, Rosow CE. Development of peripheral opioid antagonists: New insights into opioid effects. Mayo Clin Proc 2008;83:1116–30.

120 Holzer P. Non-analgesic effects of opioids: Management of opioid-induced constipation by peripheral opioid receptor antagonists: prevention or withdrawal? Curr Pharm Des 2012;18:6010–20.

121 Yuan CS, Foss J, O'Connor M, Roizen M, Moss J. Effects of low-dose morphine on gastric emptying in healthy volunteers. J Clin Pharmacol 1998; 38:1017–20.

122 Yuan CS, Foss JF, O'Connor M, et al. Effects of intravenous methylnaltrexone on opioid-induced gut motility and transit time changes in subjects receiving chronic methadone therapy: A pilot study. Pain 1999;83:631–5.

123 Hawkes ND, Richardson C, Evans BK, et al. Effect of an enteric-release formulation of naloxone on intestinal transit in volunteers taking codeine. Aliment Pharmacol Ther 2001;15:625–30.

124 Yuan CS, Doshan H, Charney MR, et al. Tolerability, gut effects, and pharmacokinetics of methylnaltrexone following repeated intravenous administration in humans. J Clin Pharmacol 2005; 45:538–46.

125 Netzer P, Sendensky A, Wissmeyer MP, et al. The effect of naloxone-3-glucuronide on colonic transit time in healthy men after acute morphine administration: A placebo-controlled double-blinded crossover preclinical volunteer study. Aliment Pharmacol Ther 2008;28:1334–41.

126 Kreek MJ, Schaefer RA, Hahn EF, Fishman J. Naloxone, a specific opioid antagonist, reverses chronic idiopathic constipation. Lancet 1983; 1:261–2.

127 Schang JC, Devroede G. Beneficial effects of naloxone in a patient with intestinal pseudoobstruction. Am J Gastroenterol 1985;80:407–11.

128 Narducci F, Bassotti G, Granata MT, et al. Functional dyspepsia and chronic idiopathic gastric stasis. Role of endogenous opiates. Arch Intern Med 1986;146:716–20.

129 McMillan SC. Assessing and managing opiate-induced constipation in adults with cancer. Cancer Control 2004;11:1–9.

130 Thune A, Baker RA, Saccone GTP, Owen H, Toouli J. Differing effects of pethidine and morphine on human sphincter of Oddi motility. Br J Surg 1990;77:992–5.

131 Mehendale SR, Yuan CS. Opioid-induced gastrointestinal dysfunction. Dig Dis 2006;24:105–12.

132 Morlion B, Clemens KE, Dunlop W. Quality of life and healthcare resource in patients receiving opioids for chronic pain: A review of the place of oxycodone/naloxone. Clin Drug Investig 2015;35:1–11.

133 Guest JF, Clegg JP, Helter MT. Cost-effectiveness of macrogol 4000 compared to lactulose in the treatment of chronic functional constipation in the UK. Curr Med Res Opin 2008;24:1841–52.

134 Bharucha AE, Pemberton JH, Locke GR III. American Gastroenterological Association technical review on constipation. Gastroenterology 2013; 144:218–38.

135 Eswaran S, Muir J, Chey WD. Fiber and functional gastrointestinal disorders. Am J Gastroenterol 2013;108:718–27.

136 Drossman DA, Morris CB, Edwards H, et al. Diagnosis, characterization, and 3-month outcome after detoxification of 39 patients with narcotic bowel syndrome. Am J Gastroenterol 2012; 107:1426–40.

137 Hardcastle JD, Wilkins JL. The action of sennosides and related compounds on human colon and rectum. Gut 1970;11:1038–42.

138 Bassotti G, Chiarioni G, Germani U, et al. Endoluminal instillation of bisacodyl in patients with severe (slow transit type) constipation is useful to test residual colonic propulsive activity. Digestion 1999;60:69–73.

139 Hervé S, Savoye G, Behbahani A, et al. Results of 24-h manometric recording of colonic motor activity with endoluminal instillation of bisacodyl in patients with severe chronic slow transit constipation. Neurogastroenterol Motil 2004;6:397–402.

140 Sloots C, Rykx A, Cools M, Kerstens R, De Pauw M. Efficacy and safety of prucalopride in patients with chronic noncancer pain suffering from opioid-induced constipation. Dig Dis Sci 2010;55:2912–21.

141 Lowenstein O, Leyendecker P, Lux EA, et al. Efficacy and safety of combined prolonged- release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: Results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. BMC Clin Pharmacol 2010;10:12.

142 Cryer B, Katz S, Vallejo R, Popescu A, Ueno R. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Med 2014;15:1825–34.

143 Freedman MD, Schwartz HJ, Roby R, Fleisher S. Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate induced constipation: A double-blinded placebo-controlled trial. J Clin Pharmacol 1997; 37:904–7.

144 Agra Y, Sacristán A, González M, et al. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. J Pain Symptom Manage 1998;15:1–7.

145 Marciniak CM, Toledo S, Lee J, et al. Lubiprostone vs Senna in postoperative orthopedic surgery patients with opioid-induced constipation: A double-blind, active-comparator trial. World J Gastroenterol 2014;20:16323–33.

146 Jamal MM, Adams AB, Jansen JP, Webster LR. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. Am J Gastroenterol 2015;110:725–32.

147 Wirz S, Nadstawek J, Elsen C, Junker U, Wartenberg HC. Laxative management in ambulatory cancer patients on opioid therapy: A prospective, open-label investigation of polyethylene glycol, sodium picosulphate and lactulose. Eur J Cancer Care 2012;21:131–40.

148 Ishihara M, Ikesue H, Matsunaga H. A multi-institutional study analyzing effect of prophylactic medication for prevention of opioid-induced gastrointestinal dysfunction. Clin J Pain 2012;28:373–81.

149 Pottegård A, Knudsen TB, van Heesch K, et al. Information on risk of constipation for Danish users of opioids, and their laxative use. Int J Clin Pharm 2014;36:291–4.

150 Attar A, Lémann M, Ferguson A, et al. Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. Gut 1999;44:226–30.

151 Basilisco G, Marino B, Passerini L, Ogliari C. Abdominal distension after colonic lactulose fermentation recorded by a new extensometer. Neurogastroenterol Motil 2003;15:427–33.

152 van der Spoel JI, Oudemans-van Straaten HM, Kuiper MA, et al. Laxation of critically ill patients with lactulose or polyethylene glycol: A two-center randomized, double-blind, placebo-controlled trial. Crit Care Med 2007;35:2726–31.

153 Bradshaw M, Sen A. Use of a prophylactic antiemetic with morphine in acute pain: Randomised controlled trial. Emerg Med J 2006;23:210–3.

154 Simpson PM, Bendall JC, Middleton PM. Review article: Prophylactic metoclopramide for patients receiving intravenous morphine in the emergency setting: A systematic review and meta-analysis of randomized controlled trials. Emerg Med Australas 2011;23:452–7.

155 Mordarski S. Pain management in the elderly: Transdermal fentanyl for the treatment of pain caused by osteoarthritis of the knee and hip. Biomed Res Int 2014;2014:262961.

156 Hartrick CT, Tang YS, Hunstad D, et al. Aprepitant vs multimodal prophylaxis in the prevention of nausea and vomiting following extended-release epidural morphine. Pain Pract 2010;10:245–8.

157 Bassotti G, Blandizzi C. Understanding and treating refractory constipation. World J Gastrointest Pharmacol Ther 2014;5:77–85.

158 Keating GM. Prucalopride: A review of its use in the management of chronic constipation. Drugs 2013;73:1935–50.

159 Chamberlain SM, Rao SS. Safety evaluation of lubiprostone in the treatment of constipation and irritable bowel syndrome. Expert Opin Drug Saf 2012;11:841–50.

160 Meissner W, Leyendecker P, Mueller-Lissner S, et al. A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. Eur J Pain 2009;13:56–64.

161 De Schepper HU, Cremonini F, Park MI, Camilleri M. Opioids and the gut: Pharmacology and current clinical experience. Neurogastroenterol Motil 2004; 16:383–94.

162 Webster L, Chey WD, Tack J, et al. Randomised clinical trial: The long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. Aliment Pharmacol Ther 2014;40:771–9.

163 Mackey AC, Green L, Greene P, Avigan M. Methylnaltrexone and gastrointestinal perforation. J Pain Symptom Manage 2010;40:e1–3.

164 Jagla C, Martus P, Stein C. Peripheral opioid receptor blockade increases postoperative morphine demands–a randomized, double-blind, placebo-controlled trial. Pain 2014;155:2056–62.

165 Vaughan-Shaw PG, Fecher IC, Harris S, Knight JS. A meta-analysis of the effectiveness of the opioid receptor antagonist alvimopan in reducing hospital length of stay and time to GI recovery in patients

enrolled in a standardized accelerated recovery program after abdominal surgery. Dis Colon Rectum 2012;55:611–20.

166 Kraft MD. Emerging pharmacologic options for treating postoperative ileus. Am J Health Syst Pharm 2007;64:S13–20.

167 Dunlop W, Uhl R, Khan I, Taylor A, Barton G. Quality of life benefits and cost impact of prolonged release oxycodone/naloxone versus prolonged release oxycodone in patients with moderate-to-severe non-malignant pain and opioid-induced constipation: A UK cost-utility analysis. J Med Econ 2012;15:564–75.

168 Schutter U, Schutter U, Grunert S, et al. Innovative pain therapy with a fixed combination of prolonged-release oxycodone/naloxone: A large observational study under conditions of daily practice. Curr Med Res Opin 2010; 26:1377–87.

APPENDIX

Studies on OIBD were identified with the terms: *Nausea* or *heartburn* or *regurgitation* or *fullness* or *dyspepsia* or *vomiting* or *appetite* or *distension* or *bloating* or *abdominal pain* or *abdominal discomfort* or *constipation* or *gastrointestinal transit* or *slow transit* or *delayed transit* or *colon transit* or *defecation* or *abnormal defecation* or *difficult defecation* or *dysmotility* or *hypomotility* or *motility disorder* or *motility dysfunction* or *straining* or *stool* or *stool evacuation* or *incomplete evacuation* or *hard stools* or *infrequent stools* or *toilet* or *bowel function* or *bowel movement.*

These were combined using the set operator AND with studies identified with the terms: *Opiate alkaloids* or *opiate analgesics* or *opiate* or *opioid* or *narcotics* or *morphine* or *oxycodone* or *fentanyl* or *tramadol* or *codeine* or *hydromorphone* or *buprenorphine* or *methadone* or *hydrocodone* or *tapentadol* or *levorphanol* or *propoxyphene* or *tilidine.*

Studies were further categorized as relating to prevalence, mechanism of OIBD, non-pharmacologic treatment, pharmacologic treatment and opiate antagonists by combining the results above and five further sets of search terms.

To identify studies relating to prevalence, the initial results were combined, using the set operator AND, with the terms: *Epidemiology* or *prevalence* or *frequency* or *occurrence* or *population* or *cost* or *burden* or *economic*.

To identify studies relating to mechanisms of OIBD, the initial results were combined, using the set operator AND, with the terms: *Motility* or *reflux* or *esophageal motility* or *gastric emptying* or *colon motility* or *intestinal motility* or *small intestinal motility* or *secretion* or *salivary secretion* or *intestinal secretion* or *inhibition* or *sphincter.*

To identify studies relating to non-pharmacologic treatments, the initial results were combined, using the set operator AND, with the terms: *Dietary fiber* or *ispaghula* or *plantago* or *linseed* or *flaxseed* or *flax seed* or *wholegrain* or *dietary fiber* or *bulking agents* or *physical activity* or *physiotherapy* or *exercise* or *sport* or *drink* or *fluid intake* or *acupuncture* or *massage* or *osteopathy.*

To identify studies relating to pharmacologic treatments, the initial results were combined, using the set operator AND, with the terms: *Laxative* or *macrogol* or *polyethyleneglycol* or *PEG* or *lactulose* or *sobitol* or *bisacodyl* or *picosulfate* or *senna* or *sennoside* or *danthron* or *serotonin receptor agonist* or *5-HT 4 receptors agonist* or *guanylate cyclase* or *chloride channel* or *prucalopride* or *lubiprostone* or *linaclotide* or *erythromycin* or *neostigmine.*

In total, the search yielded 10,832 unique citations. For inclusion, all studies were required to be performed in an adult population who were receiving opioid or opiate drugs and who had a confirmed diagnosis of OIBD based on clinical symptoms, physician's opinion, or specific diagnostic criteria specified by study investigators. Citations identified within the treatment categories were also required to be randomized controlled trials, comparing pharmacologic or non-pharmacologic therapies with a control measure. There was no minimum duration of therapy, but quantitative assessment of response to therapy was required. Where trials deemed it necessary, results should be supplemented by negative investigations. Only publications published in the English language were included in the analysis.

Using the above inclusion and exclusion criteria, the identified citations were screened independently by two investigators for relevance; by title and then abstract to reduce the citation list to 124 and then 52 citations, respectively. Full publications of the 52 citations were assessed and following discussion to resolve any disagreement, a final list of 33 citations was generated [12–44].

Voting results table: Votes for each statement with an accompanying level of agreement, the strength of the evidence and the strength of the recommendation (when applicable).

Statement	Level of agreement Agree/neutral/ disagree	Level of evidence Strong/ moderate/ weak	Strength of recommendation Strong/ weak
1.1 The definition of OIC/OIBD is based on a clinical evaluation relating to a change in bowel habits during opioid therapy	10/0/0	0/6/4	
1.2 The symptoms of OIC are related to the colon, whereas OIBD manifests with symptoms throughout the GI tract	10/0/0	0/0/10	
1.3 Subjective reports of OIC are based on validated questionnaires, whereas there is no consensus about assessment of OIBD	10/0/0	9/1/0	
1.4 Objective assessment of OIBD has focused on motility, but there are only a few human studies on opioid effects on secretion and sphincter function	10/0/0	4/6/0	
2.1 Data on prevalence of OIC differs widely based on the definitions used and origin of the studies, but not on gender	10/0/0	4/6/0	
2.2 The type of pure opioid drugs does not influence the prevalence of OIC symptoms	10/0/0	0/10/0	
2.3 Dose and frequency of opioids influences likelihood of OIC symptoms	10/0/0	0/7/3	
2.4 Transdermal preparations of fentanyl is associated with lower incidence of OIC than oral opioids	6/1/3	1/3/6	
2.5 Duration of opioid therapy influences the impact of OIC symptoms	10/0/0	0/10/0	
3.1 Opioid receptors are spread throughout the GI tract from the mid-oesophagus to rectum and are involved in a variety of cellular functions	10/0/0	10/0/0	
3.2 Opioid agonists administration results in slowing of normal GI motility, segmentation, increased tone and uncoordinated motility reflected in e.g., increased transit times agreement	10/0/0	4/6/0	
3.3 Opioids result in increased absorption and decreased secretion of fluids in the gut, leading to dry feces and less propulsive motility	10/0/0	0/5/5	
3.4 Opioids increase sphincter tone, which may cause symptoms such as sphincter of Oddi spasms and difficult defecation	10/0/0	0/10/0	
3.5 Opioid antagonists counteract the effects of opioids in the human gut on motility, fluid transport, and sphincter function	10/0/0	0/10/0	
4.1 QoL can be worse due to side effects of opioids	10/0/0	2/8/0	
4.2 Assessment of QoL in patients with OIC/OIBD can assist therapeutic choices	10/0/0	0/10/0	
5.1 Non-pharmacological treatments of OIC include dietary recommendations and life-style modifications	10/0/0	0/0/10	0/10
6.1 The choice of a laxative to treat OIC/OIBD depends on the perceived efficacy and the preference of the patient. Indirect evidence favours bisacodyl, sodium picosulfate, macrogol, and sennosides as first choice	10/0/0	0/4/6	5/5
6.2 Sugars and sugar alcohols such as lactulose, lactose, and sorbitol should not be used to prevent or treat OIC	10/0/0	0/9/1	3/7
6.3 Gastro-esophageal reflux symptoms as part of OIBD should be treated like primary reflux disease	10/0/0	0/0/10	0/10
6.4 Patients with nausea secondary to opioid treatment should be offered dopamine antagonists	9/1/0	0/0/10	0/10
	10/0/0	0/10/0	1/9

(continued)

Statement	Level of agreement Agree/neutral/ disagree	Level of evidence Strong/ moderate/ weak	Strength of recommendation Strong/ weak
6.5 Treatment of OIC with new laxatives (prucalopride, lubiprostone) may be promising; however, to date, there are insufficient data to warrant such treatments in OIC patients			
7.1 Peripherally acting ?-opioid receptor antagonists (PAMORAs) effectively reduce OIC	10/0/0	10/0/0	10/0
7.2 In patients with chronic cancer or non-cancer pain, prolonged release naloxone/oxycodone combination effectively reduces OIC while maintaining equal analgesia to prolonged release oxycodone alone	10/0/0	10/0/0	10/0
7.3 Naloxegol is effective and safe in reducing OIC in patients with chronic pain	10/0/0	10/0/0	3/6
7.4 Methylnaltrexone injections can effectively relieve OIC in patients with post-operative, cancer and non-cancer chronic pain. However, concerns regarding reversal of analgesia and intestinal perforation in relation to its post-operative use have been raised	10/0/0	10/0/0	10/0
7.5 Alvimopan is approved for in-hospital use in the USA for preventing or shortening the course of postoperative ileus after bowel resection. Long-term safety studies indicated that it may possibly increase the risk for cardiovascular events. There is some evidence that alvimopan reduces OIC in subjects with chronic opioid intake	10/0/0	10/0/0	
7.6 Both laxatives and opioid antagonists for OIC have benefits on QoL	10/0/0	3/7/0	10/0