Evolving paradigms in the treatment of opioid-induced bowel dysfunction

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***Abstract*:** In recent years prescription of opioids has increased significantly. Although effective in pain management, bothersome gastrointestinal adverse effects are experienced by a substantial proportion of opioid-treated patients. This can lead to difficulties with therapy and subsequently inadequate pain relief. Collectively referred to as opioid-induced bowel dysfunction, these adverse effects are the result of binding of exogenous opioids to opioid receptors in the gastrointestinal tract. This leads to disturbance of three important gastrointestinal functions: motility, coordination of sphincter function and secretion. In the clinic this manifests in a wide range of symptoms such as reflux, bloating, abdominal cramping, hard, dry stools, and incomplete evacuation, although the most known adverse effect is opioid-induced constipation. Traditional treatment with laxatives is often insufficient, but in recent years a number of novel pharmacological approaches have been introduced. In this review the pathophysiology, symptomatology and prevalence of opioid-induced bowel dysfunction is presented along with the benefits and caveats of a suggested consensus definition for opioid-induced constipation. Finally, traditional treatment is appraised and compared with the latest pharmacological developments. In conclusion, opioid antagonists restricted to the periphery show promising results, but use of different definitions and outcome measures complicate comparison. However, an international working group has recently suggested a consensus definition for opioid-induced constipation and relevant outcome measures have also been proposed. If investigators within this field adapt the suggested consensus and include symptoms related to dysfunction of the upper gut, it will ease comparison and be a step forward in future research.

Keywords: antagonists, constipation, dysfunction, gut, opioids

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Introduction

The use of opioids to alleviate severe acute and chronic pain has increased several fold in Europe and the USA in recent years [Casati *et al.* 2012]. Accordingly, opioids are the most commonly prescribed treatment for severe pain and it has been estimated that up to 90% of American patients treated at specialized pain centers receive opioids [Benyamin *et al.* 2008]. Despite the increasing use, the British National Institute for Health and Care Excellence (NICE) notes that pain resulting from advanced disease often remains undertreated, due to fear of addiction and concerns related to adverse effects [NICE, 2012].

The most common adverse effects to opioid treatment include nausea, headache, confusion and gastrointestinal (GI)-related symptoms, the latter collectively referred to as opioid-induced bowel dysfunction (OIBD) [Benyamin *et al.* 2008; De Schepper *et al.* 2004; Pappagallo, 2001]. OIBD occurs when exogenous opioids bind to opioid receptors of the enteric nervous system, and consequently disturb normal GI function [Camilleri, 2011; De Schepper *et al.* 2004; Holzer, 2014; Pappagallo, 2001; Wood and Galligan, 2004]. The adverse effects manifest as gastroesophageal reflux, vomiting, bloating, abdominal pain, anorexia, hard stools, constipation and incomplete evacuation. These symptoms can be severe and it is not uncommon for patients to discontinue treatment as a result, which naturally results in inadequate pain management [Looström *et al.* 2011; Pappagallo, 2001]. Opioid-induced constipation

(OIC) is the most well described GI adverse effect, but in recent years the more universal expression OIBD has gained footing in the scientific community along with the acknowledgement that OIBD is the result of a combination of intricate pathophysiological processes of the entire GI tract of which OIC is an important piece [Pappagallo, 2001].

The typical treatment strategy to alleviate OIBD is based on combinations of pharmacological and nonpharmacological approaches, including laxatives coupled with increased dietary fiber and fluid intake, encouraging exercise, biofeedback, among others [Brock *et al.* 2012; Dorn *et al.* 2014]. However, these strategies do not address the underlying pathophysiological mechanisms, and therefore are likely to fall short of adequate relief [Poulsen *et al.* 2014].

Recently, a number of novel pharmacological approaches have been marketed for both constipation and OIC, such as the chloride channel activator lubiprostone and the selective 5-HT4 hydroxytryptamine receptor 4 (5-HT4) serotonin agonist prucalopride, as well as a number of competitive opioid antagonists that target the underlying pathophysiology through antagonism of the μ-opioid receptors in the gut.

In this review the pathophysiology, symptomatology and prevalence of OIBD are presented as background information. Recent approaches towards the development of a consensus definition for OIC suggested by an international multidisciplinary working group is reviewed [Camilleri *et al.* 2014]. Finally, traditional recommended treatment strategies are appraised and compared with the latest pharmacological developments.

Pathophysiology: opioid receptors and the gut

A detailed description of the underlying pathophysiology of OIBD is beyond the scope of this review (for a comprehensive review, the reader is referred to Kurz and Sessler) [Kurz and Sessler, 2003]. However, in order to understand the diverse clinical presentations of OIBD, an overview of pathophysiology is presented below and illustrated in Figure 1.

Three types of opioid receptors are involved in controlling normal GI function: μ-, δ- and κ-receptors [Galligan and Akbarali, 2014; Holzer, 2014]. In animal studies δ- and κ-subtype receptors are expressed primarily in the stomach and proximal colon [Camilleri, 2011; Holzer, 2004; Sternini *et al.* 2004]. μ-receptors are the most widely expressed throughout the GI tract and predominantly localized on myenteric and submucosal neurons and on immune cells in the lamina propria [Galligan and Akbarali, 2014; Kurz and Sessler, 2003; Sternini *et al.* 2004].

Endogenous ligands and most exogenous opioids activate μ-receptors [Greenwood-Van Meerveld *et al.* 2004]. This triggers a comprehensive intracellular signaling pathway, which ultimately results in inhibition of the enzymatic conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) through adenylate cyclase. Consequently, opioids decrease the formation of cAMP, which otherwise would have activated several target molecules to regulate cellular functions [Galligan and Akbarali, 2014; Sharma *et al.* 1975]. This is likely the main effect, but opioids are also involved in direct activation of K^+-channels (membrane hyperpolarization) and inhibition of Ca^{++}-channels (decreased neurotransmitter release) [Sharma *et al.* 1975]. Overall the result is reduced release of neurotransmitters and decreased neuronal activity.

Activation of μ-receptors in the GI tract by exogenous opioid results in disturbance of three essential GI functions: motility, coordination of sphincter function and secretion. In the esophagus, opioids induce nonpropulsive peristaltic contractions [Kraichely *et al.* 2010]. In the small and large intestine the contractile tone in the circular muscle layer is increased and in parallel there is a decreased tonic inhibition of the muscle tone [Frantzides *et al.* 1992; Sarna and Otterson, 1990; Telford *et al.* 1989]. This is accompanied by enhanced rhythmic contractions and occurrence of high-amplitude nonpropulsive phasic contractions. The net result is increased segmental spastic tone and less propulsive peristalsis [De Schepper *et al.* 2004; Kraichely *et al.* 2010; Sarna and Otterson, 1990; Telford *et al.* 1989; Thomas, 2008].

In terms of sphincter function, opioid-induced sphincter of Oddi dysfunction with biliary-like type of pain attacks is a well known side effect [Helm *et al.* 1988; Sharma, 2002; Torres *et al.* n.d.]. Similar results have been found for the lower esophageal sphincter where opioid treatment mainly induced inhibition of sphincter relaxation

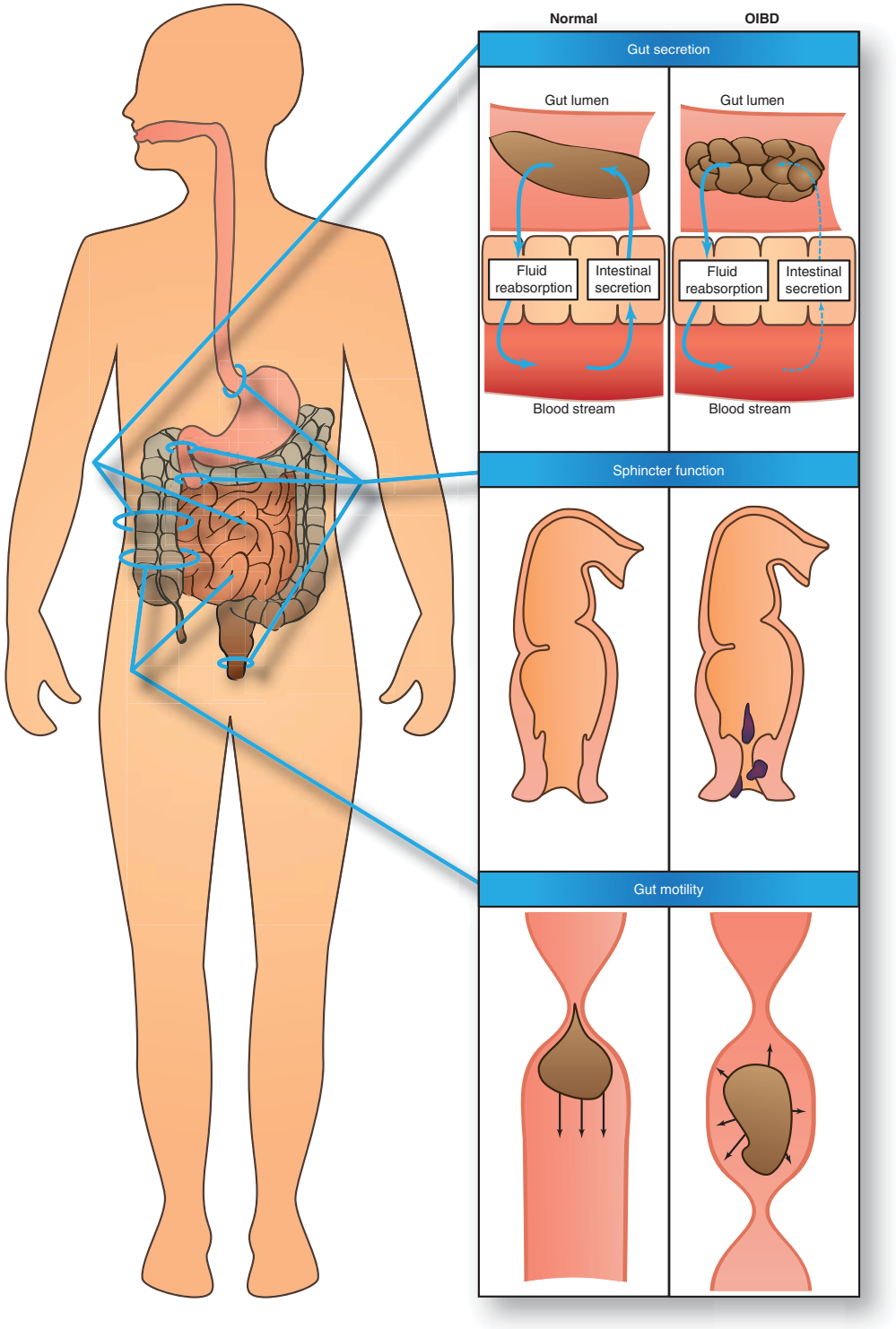

Figure 1. Pathophysiology of opioid-induced bowel dysfunction. First row: decreased gut secretion of electrolytes and water to the intestinal lumen results in a dryer, harder stool. Second row: increased sphincter resting tone and decreased rectal sensitivity results in straining, which can result in hemorrhoids as illustrated, and the sensation of incomplete evacuation. Third row: increased contractile tone in the circular muscle layer and decreased tonic inhibition of the muscle tone along with occurrence of high-amplitude nonpropulsive phasic contractions in the small and large intestine results in stasis and reduced propulsive peristalsis.

[Dowlatshahi *et al.* 1985]. In the anal canal, the tone of the internal sphincter has been shown to be increased and there is an accompanying decreased rectal sensitivity, which has been associated with straining and the sensation of incomplete evacuation [Göke *et al.* 1992; Musial *et al.* 1992]. Gut secretion is reduced as a direct result of inhibited cAMP and vasoactive intestinal peptide production [Furness and Costa, 1987; Huizinga and Lammers, 2009]. Moreover, stool water content is indirectly affected due to stasis and increased passive absorption of water. In concert, this results in dryer and harder stools [Thomas, 2008].

Prevalence of opioid-induced bowel dysfunction

Symptoms in patients treated with opioids have been examined in numerous studies, although different definitions have been used. A prospective survey of incidence, prevalence and severity of adverse effects during repeated individualized dosing of morphine for chronic cancer pain found that 95% of all patients reported dry mouth and 88% reported sedation and constipation [Glare *et al.* 2006]. GI symptoms were reported in an observational study in patients taking opioids for chronic noncancer-related pain and it was found that 47% experienced constipation. In the same study gastroesophageal reflux related symptoms were reported by 33% of all patients, nausea by 27% and vomiting by 9%. Furthermore, chronic abdominal pain was reported by 58% [Tuteja *et al.* 2010]. Similar results have been found in a population-based survey along with increased frequency of constipation-related symptoms (including straining, hard stools, bloating and infrequent bowel movements) [Choung *et al.* 2009].

OIC is probably the most well characterized adverse effect in opioid-treated patients. Nonetheless, the prevalence varies substantially between different studies ranging from 15% to 81% in patients without cancer [Allan *et al.* 2001; Bell *et al.* 2009; Cook *et al.* 2008; Kalso *et al.* 2004; Moore and McQuay, 2005]. One of the highest prevalence rates reported derives from a multinational, internet-based survey of 322 chronic opioid users: 81% reported constipation, despite concomitant use of laxatives! [Bell *et al.* 2009]. A larger population-based survey of 2055 patients treated with opioids and laxatives for chronic noncancer pain also found a high prevalence of constipation as 57% reported this [Cook *et al.* 2008]. In comparison, the prevalence of chronic constipation in the general population has been estimated to affect between 2% and 27% of the adult population with an average around 15%, depending on definition used [Higgins and Johanson, 2004; Sanchez and Bercik, 2011; Wirz *et al.* 2012]. Constipation can result in overflow diarrhea where liquid stool passes around the obstruction. Thus, diarrhea-related symptoms (including urgency, loose bowel movements and frequent bowel movements) have also frequently been reported in opioid-treated patients [Bril *et al.* 2011; Wojciech, 2012].

Despite the elaborate focus on OIC, which is often (too) simply defined as a reduction in the number of spontaneous bowel movements (SBMs), infrequent bowel movement ranks only number 5 in self-assessed constipation symptoms, whereas symptoms such as gas, straining and abdominal discomfort are far more prevalent [Johanson and Kralstein, 2007]. This strongly accentuates the limitations of such studies which potentially overlook symptoms regarded more bothersome for the patient.

Narcotic bowel syndrome (NBS) is another subset of OIBD characterized by chronic or frequently recurring abdominal pain that worsens during escalating doses of opioids [Choung *et al.* 2009; Drossman and Szigethy, 2014; Grunkemeier *et al.* 2007]. The paradoxical development of increased pain despite continued or escalating doses of opioids can result in an unfortunate downward spiral with serious consequences for the patient [Grunkemeier *et al.* 2007].

Other risk factors such as high age, low-fiber diet, sex, reduced mobility and different drugs may also contribute to the development of constipation or other GI symptoms in patients with pain [Wirz *et al.* 2012].

Collectively, these findings emphasize the multiplicity of GI-related adverse effects associated with chronic (often defined as $>$ 90 days) and short-term opioid use. While constipation may be the dominant symptom in many cases, it is important to keep in mind the multifaceted presentation of OIBD, as illustrated in Figure 2.

Towards a consensus definition for opioid-induced constipation?

Numerous subjective criteria and objective outcome measures for assessing OIBD and OIC exist

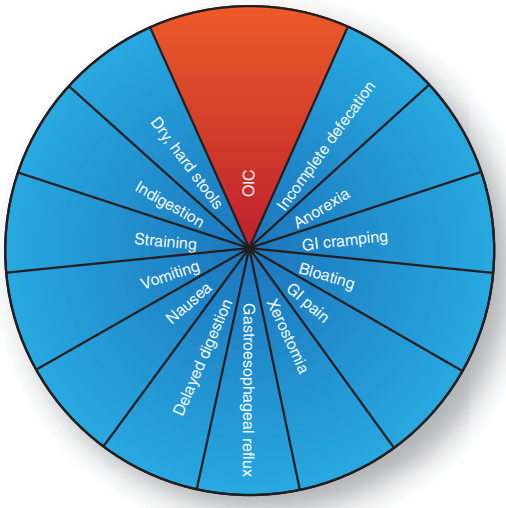

Figure 2. Schematic representation of the relation between opioid-induced constipation (OIC) and opioid-induced bowel dysfunction (OIBD). OIC is the most well known gastrointestinal (GI) adverse effect to opioid treatment, but only a part of the multiplicity of GI-related adverse effects associated with opioid treatment known as OIBD.

[Gaertner *et al.* 2015; Olesen and Drewes, 2011]. The Patient Assessment of Constipation Symptoms questionnaire is one of the most widely used subjective instruments and has proven reliable in the assessment of treatment for OIC [Frank *et al.* 1999; Slappendel *et al.* 2006]. Other mentionable questionnaires are the Bowel Function Index specifically designed for OIC [Rentz *et al.* 2009] and the Bristol Stool Chart (BSC), which registers stool frequency and consistency on a seven-point scale [Lewis and Heaton, 1997]. Although these tools are valuable both clinically and in research, the lack of a consensus definition for OIC hampers comparison between OIC trials. A recent systematic review of 47 clinical trials evaluating OIC found that a clear definition for OIC was only provided in one-third (34%) of the trials [Gaertner *et al.* 2015]. Among the publications that provided a definition for OIC, it most frequently relied on history of present or recent opioid therapy; defecation frequency (most often, fewer than three SBMs per week); and at least two of the following symptoms at least 25% of the time: straining, hard or lumpy stool, incomplete evacuation and infrequent stools [Camilleri *et al.* 2014; Gaertner *et al.* 2015].

Consequently, due to the multifaceted presentation of OIBD and OIC, where a reduction in number of SBMs is not necessarily the most bothersome symptom for the patient, these definitions do not necessarily identify all patients who suffer from GI adverse effects following opioid administration [Clark and Currow, 2013]. Hence, OIBD and OIC is more likely underdiagnosed than overdiagnosed, supported by the fact that many opioid-treated patients report normal stool frequency, but still experience symptoms of OIBD [Bell *et al.* 2009].

This clearly demonstrates the need for a consensus definition in order to better encompass the clinical presentation of OIBD and OIC, but also in order to adequately compare studies evaluating efficacy of different treatments strategies. However, only recently a consensus definition for OIC has been suggested by an international multidisciplinary working group [Camilleri *et al.* 2014]. The authors suggest the following definition for OIC: 'A change when initiating opioid therapy from baseline bowel habits 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'.

The essential improvement in this definition is the deviation from a specific number of bowel movements per week, often being a mandatory criterion, to a definition that encompasses individual changes in bowel habits. Furthermore, this definition considers not only the normal 'baseline' bowel habits of each individual patient and the fact that patients may have pre-existing constipation, but also the fact that patients' response to opioid treatment is known to vary immensely, based on for example, genetic factors [Lötsch *et al.* 2004; Stamer *et al.* 2005].

However, a substantial drawback with the focus on change in bowel habits is that many patients have been treated with opioids for years and do not recall their 'normal' bowel habits, that is, before opioid therapy. Even though psychometric validation is warranted, this improvement of the definition is an important step towards a more covering definition, especially in patients who report 'normal' stool frequency, but still experience other symptoms of OIC. Nonetheless, as stated above, OIC is only a part of the OIBD complex (Figure 2). Thus, a definition that covers the whole spectrum of symptoms would be more suitable in clinical studies, as it reflects the clinical presentation even better. Such a definition will be

more complex as many adverse effects should be included. However, as many symptoms will be new for the patient (in contrast to constipation which is very prevalent in the typical older patient) the sensitivity and validity may be better.

Existing and emerging paradigms

Satisfactory management of OIBD remains a challenge [Bell *et al.* 2009; Dorn *et al.* 2014]. The current recommendation of combining laxatives with dietary changes and lifestyle changes is often insufficient as it does not target the underlying problem and because the majority of patients receiving chronic pain treatment suffer from comorbidities resulting in, for example, less mobility [Diego *et al.* 2011; Dorn *et al.* 2014].

As the main focus often has been to increase the number of SBMs, other OIBD symptoms may persist. In the following an overview of the current treatment possibilities and pharmacological approaches is presented, and a comparison of the drug class with most alternatives, opioid antagonists, is summarized in Table 1.

Laxatives

Laxatives can be divided into different subgroups, including osmotic agents (magnesium, lactulose, polyethylene glycol), stimulants (bisacodyl, senna), bulking agents (methylcellulose, psyllium) and stool softeners (anionic surfactants). Studies comparing different laxative regimens in patients with OIC are very limited. Although traditional laxatives have proven useful in inducing bowel movements, there is no convincing evidence to suggest which, if any, laxative is optimal for OIC [Ahmedzai and Boland, 2010; Camilleri *et al.* 2014; Candy *et al.* 2011]. The few clinical trials comparing laxatives conclude that commonly used agents have comparable, suboptimal efficacy for OIC [Agra *et al.* 1998; Freedman *et al.* 1997; Ramesh *et al.* 1998; Ruston *et al.* 2013]. This consideration is also supported by a study in patients with chronic pain who reported their bowel habits before and after initiating treatment with oral opioids. All had laxatives prescribed together with opioids, and almost half were using two or more different types. Prior to opioid treatment, 70% reported at least three SBMs per week. After initiating oral opioid therapy, 55% reported having at least three bowel movements per week, but 81% still reported constipation as an opioid-induced adverse effect [Bell *et al.* 2009]. For further details about mechanisms and recommendations for laxatives, see studies by Lembo and Camilleri, and Rao [Lembo and Camilleri, 2003; Rao, 2007].

However, as stated earlier, the pronounced focus on bowel movements as outcome measure in older studies evaluating the effect of laxatives on OIC makes it difficult to assess their effect on other presentations of OIBD.

Chloride channel activator

Lubiprostone is derived from prostaglandin E1 and acts by specifically activating the CIC-2 chloride channels on the apical side of GI epithelial cells. It induces chloride secretion and thereby softens stool consistency [Lacy and Chey, 2009; Owen, 2008]. It was originally indicated for chronic constipation and irritable bowel syndrome with constipation, where effect of treatment was demonstrated by an increase in SBM frequency, but more importantly, stool consistency improved, and straining, bloating and severity of constipation decreased [Owen, 2008; Wong and Camilleri, 2011].

In 2013, lubiprostone was also approved in the USA for treatment of OIC in adult patients with noncancer pain [Camilleri *et al.* 2014]. Significant effect was demonstrated on the primary combined efficacy endpoint in a randomized, placebo-controlled phase III trial with an approximate number needed to treat of six. Furthermore, straining, stool consistency and constipation severity were also significantly improved in the lubiprostone group [Mazen Jamal *et al.* 2012]. One drawback is that methadone inhibits lubiprostone-induced chloride secretion in *in vitro* enterocytes, and although speculative it may have little or no effect in methadone-treated patients [Cuppoletti *et al.* 2013].

Selective 5-HT4 agonist

Prucalopride is a selective 5-HT4 agonist that alters colonic motility *via* serotonin 5-HT4 receptors in the gut. Primarily indicated and approved in many countries for chronic idiopathic constipation in women, but has demonstrated efficacy in patients with OIC in one randomized controlled trial from 2010 [Sloots *et al.* 2010]. However, the effect was only significant at 2 weeks of treatment but not after 4 weeks and the drug is not approved for OIC. However,

Table 1. Current pharmaceutical approaches for opioid-induced bowel dysfunction targeted at the peripheral opioid receptors.

Drug	Pharmacological mechanism	Efficacy	Disadvantages
Combined prolonged release naloxone and oxycodone	Nonselective, competitive opioid receptor antagonist [Meissner *et al.* 2000]	Significant improvement in bowel function compared to oxycodone as assessed by BFI, number of complete SBMs, and PAC-SYM score. Laxative use reduced [Burness and Keating, 2014; Löwenstein *et al.* 2009; Simpson *et al.* 2008]	Only marketed in oral formulation in combination with oxycodone Does not allow for opioid rotation or as add on to existing therapy
Methylnaltrexone	Peripherally acting, competitive μ-opioid receptor antagonist [Herndon *et al.* 2002]	Effective in inducing laxation in opioid treated patients within four hours of administration compared to placebo [Thomas *et al.* 2008]	Only available in subcutaneous formulation and only approved in palliative care in patients with advanced illness
Alvimopan	Peripherally acting, competitive μ-opioid receptor antagonist [Camilleri, 2005; Schmidt, 2001]	Significant increase in weekly SBMs compared to placebo. Improvement in a number of OIBD-related symptoms [Webster *et al.* 2008]	Cardiovascular safety concerns Only approved in the USA following partial small or large bowel resection with primary anastomosis in hospitalized patients
Naloxegol	Peripherally acting, competitive μ-opioid receptor antagonist [Corsetti and Tack, 2015; Eldon *et al.* 2007]	Significantly higher response rates for a composite primary endpoint compared with placebo. Shorter time to first postdose SBM, and higher number of days per week with one or more SBMs [Chey *et al.* 2014]	Interaction with CYP3A4 inducers or inhibitors can affect plasma concentration

BFI, Bowel Function Index; CYP3A4, cytochrome P450 3A4; OIBD, opioid-induced bowel dysfunction; PAC-SYM, Patient Assessment of Constipation Symptoms; SBM, spontaneous bowel movement.

it cannot be excluded to be effective in some patients when prescribed off label.

Tapentadol

Another approach to minimize the GI adverse effects of opioid treatment is to use opioids with additional effects, such as tapentadol. Besides μ-opioid receptor agonism, it has a noradrenergic reuptake inhibitory action that results in an additional analgesic effect [Tzschentke *et al.* 2009; Wade and Spruill, 2009]. Consequently for an equianalgesic dose, fewer opioid receptors (including those in the gut) are blocked, thereby improving the adverse effect profile [Afilalo and Morlion, 2013]. In an animal model it was demonstrated that nausea and vomiting were markedly reduced after tapentadol administration compared with equianalgesic doses of morphine [Tzschentke *et al.* 2009]. These results have been confirmed in a number of clinical studies in which tapentadol has demonstrated a superior GI tolerability profile and fewer treatment discontinuations compared with oxycodon [Buynak *et al.* 2010; Steigerwald *et al.* 2013; Wade and Spruill, 2009; Wild *et al.* 2010]. However, it is a relatively new drug for which more clinical experience is needed, and comparison to other opioids and the new peripheral-acting opioid antagonists is still lacking.

Opioid antagonists

In contrast to other treatment strategies for OIBD, competitive opioid antagonists target the underlying pathophysiology: blockage of the μ-opioid receptors in the gut. This drug class possesses the majority of alternatives, mainly separated by their pharmacokinetic properties.

Naloxone is a pure competitive antagonist. As a potent antidote, it is often administered intravenously or as an intramuscular injection to treat opioid overdose. Hereby, naloxone antagonizes both the centrally and peripherally mediated effects of opioids. However, when given orally a substantial amount of the drug reaches the

systemic circulation, and has the capacity to cross the blood–brain barrier and cause reversal of the centrally mediated analgesia and opioid withdrawal symptoms. This is the main reason why orally formulated naloxone is not marketed as a standalone product to treat OIBD, despite improvement of GI symptoms [Meissner *et al.* 2000; Vondrackova *et al.* 2008].

Consequently, peripheral restriction is a crucial property for an opioid antagonist to be a successful candidate in the treatment of OIBD. One approach has been a combined oral *prolonged release* formulation of oxycodone and *prolonged release* naloxone in a 2:1 ratio. The aim of this formulation has been to counteract OIBD through the local antagonistic effect of naloxone in the gut, while maintaining peripheral and central analgesia due to the low bioavailability (<2%) of oral, prolonged release, low-dose naloxone [Smith *et al.* 2012]. Studies have shown promising analgesic efficacy as well as improvement in OIBD-related symptoms [Burness and Keating, 2014; Leppert, 2013a; Sykes, 1996]. However, as naloxone is primarily metabolized in the liver, there is a risk of increased bioavailability in patients with severe hepatic impairment [Kraft, 2008; Leppert, 2013b]. Furthermore, the maximum recommended daily dose may not be sufficient to relieve the pain. Additionally, the fixed combination to oxycodone necessitates opioid rotation in patients who are treated with other opioids, and although recommendations exist this may be difficult outside specialist centers [Drewes *et al.* 2013].

Methylnaltrexone bromide, a drug originally designed to shorten the length of postoperative ileus, is another approach [Portenoy *et al.* 2008]. It is a peripherally acting μ-opioid receptor antagonist and a derivative of the opioid antagonist naltrexone with an ammonium group that restricts it to the periphery [Herndon *et al.* 2002]. Methylnaltrexone bromide has been shown to relieve OIC and induce laxation [Schmidt, 2001; Thomas *et al.* 2008], and was the first peripherally acting μ-opioid receptor antagonist to be approved for the treatment of OIBD. However, it is only available in a subcutaneous formulation and only approved in palliative care in patients with advanced illness, and therefore it is of limited benefit for the general population with OIBD.

Alvimopan is another oral peripherally acting μ-opioid receptor antagonist that has been shown to increase the number of SBMs in opioid-treated patients [Camilleri, 2005; Paulson *et al.* 2005; Roberts *et al.* 2002]. However, cardiovascular safety concerns (increased risk of myocardial infarction) halted further development. Yet, the US Food and Drug Administration approved alvimopan for postoperative ileus following partial small or large bowel resection with primary anastomosis in hospitalized patients. It is only registered in the USA and hence it is of little benefit to the general OIBD population.

Naloxegol is a pegylated naloxone molecule. Pegylation is a process where a polyethylene glycol (PEG) moiety is attached to a therapeutically useful molecule in order to alter functionality and structural properties [Roberts *et al.* 2002]. Due to the pegylation the molecule is too large to pass the blood–brain barrier and is peripherally restricted [Webster *et al.* 2013]. It is administered orally once a day, but the key advantage is that it can be added to existing opioid therapy and thereby also allows for opioid rotation. It has proven efficacious compared with placebo on a number of different outcome measures [Chey *et al.* 2014] and has an acceptable safety profile [Bui *et al.* 2014a, 2014b; Webster *et al.* 2014, n.d.].

Other peripherally acting μ-opioid receptor antagonists in earlier stages of development are ADL-5945 and ADL-7445 (Cubist, Lexington, Massachusetts, USA) and TD-1211 (Theravance Biopharma Inc., San Francisco, California, USA). ADL-5945 and ADL-7445 have proven tolerable and effective in producing SBMs in phase I trials, but to the authors' knowledge no phase II data have been published, even though a phase II study was announced in 2010 [Herndon *et al.* 2002]. The TD-1211 has been shown to be well tolerated and has a linear pharmacokinetic profile, but is still being evaluated in phase II trials [Belsey *et al.* 2010; Herndon *et al.* 2002].

Conclusion

Opioid consumption is increasing. Despite this, pain resulting from advanced disease remains undertreated due to fear of addiction and concerns related to adverse effects. OIC is the most well recognized GI adverse effect to opioid treatment, but other potentially more bothersome GI symptoms, collectively referred to as OIBD, are just as common and frequently overlooked by clinicians.

Traditional treatment, combining laxatives with dietary and lifestyle changes, is often insufficient as it does not target the underlying problem. However, new approaches, such as prucalopride and lubiprostone, opioids with effects on the monaminergic systems and drugs targeting the underlying pathophysiology with peripheral restricted opioid antagonists are emerging. That said, a substantial limitation of prior studies is the considerable diversity of definitions and outcome measures used, making it difficult to compare studies evaluating different treatments. However, an international multidisciplinary working group has recently suggested a consensus definition for OIC and in case similar definitions can be made for OIBD, it would be an important step forward not only making it easier to compare traditional treatments with the new developments, but also to simplify clinical practice.

Author contributions

All authors contributed equally to this review.

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