

## Opioid-induced Constipation – Mechanisms, Relevance and Management

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### Abstract

Opiates inhibit propulsive gastrointestinal motility and intestinal secretion in both the small and large intestine. The clinical result may be opioid-induced constipation (OIC), presenting with one or more of the following symptoms: sense of abdominal fullness, bloated abdomen, infrequent stools, hard stools, difficult defecation and a sense of incomplete emptying of the bowels. The reported frequency of constipation on opioid treatment covers a wide range – up to two-thirds of patients. This also applies to transdermal systems. Symptom evaluation is mostly sufficient to establish the diagnosis. Only a few trials have been conducted on the use of laxatives in OIC. There are currently three approaches to prevent or treat OIC by co-administering an opiate antagonist. Methylnaltrexone and alvimopan are systemically active antagonists with poor penetration of the brain. A fixed combination of oxycodone with naloxone in a ratio of 2:1 has been shown to counteract constipation in patients without antagonising pain relief. Due to high first-pass elimination in the liver, naloxone only antagonises the opiate locally. A high awareness of OIC is mandatory for optimal pain management by either asking the patient whether he or she needs treatment or by prophylactic co-administration of an opiate antagonist.

### Keywords

Opioids, oxycodone, methylnaltrexone, alvimopan, naloxone, constipation

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After ingested nutrients are emptied from the stomach into the small intestine, they are enzymatically split into their molecular components. This leads to a high osmotic load requiring large amounts of fluid to be secreted, with most of it being reabsorbed after completion of nutrient absorption. Around two litres enter the colon every day, with only 100–200g of it being excreted. Therefore, the colon has to reabsorb 90–95% of the water from its contents.

In addition to water absorption, the colon serves two other functions. The first is allowing the colonic flora to split undigested dietary fibre into short-chain carbonic acids (acetate, propionate, lactate and butyrate). These are partly used as fuel for the colonocytes (and of course for the bacteria), but may also be absorbed and hence contribute to the energy balance of the subject. However, this is of minor importance in a healthy person. The other purpose is retaining faecal material and allowing controlled defecation. From an evolutionary point of view this prevents animals producing a trace of smell, which would allow predators to find their prey more easily. Motility of the small intestine is therefore necessary to mix and propel the digesta, and motility of the colon is required to mix, propel and retain the faeces.

Intrinsic intestinal motility is brought about by a complex system of nerve plexuses within the gut wall. The main trigger of propulsive peristalsis is distension by luminal contents, but it is also modulated

by extrinsic nerves, hormones, drugs and, in the colon, possibly also metabolites from bacterial digestion. The impaired motility in constipation may be due to disordered intrinsic motility (idiopathic constipation with or without slow transit), decreased filling (diet poor in fibre), hormones (e.g. pheochromocytoma) and drugs.<sup>1</sup> The most potent drugs in this respect are opiates. Finally, disordered defecation has to be mentioned.

In this article, the epidemiology of opioid-induced constipation (OIC) and current approaches to its treatment and/or prophylaxis are summarised. This is based on a literature search using the PubMed database in May 2010.

### Opioid-induced Constipation

Opiates slow transit through the gastrointestinal tract via endorphin receptors, inhibiting both propulsive motility and secretion (see *Figure 1*).<sup>2,3</sup> This is again reasonable from an evolutionary point of view, since endorphins are released in stressful situations such as escape and it would be disadvantageous to have a call to stool on such an occasion.

Opioid bowel dysfunction is not confined to the colon but also affects other parts of the gastrointestinal tract, resulting in dry mouth, epigastric fullness, gastro-oesophageal reflux, abdominal cramping and bloating.<sup>4–6</sup> Most forms of constipation are due to colonic dysfunction, but this is probably different in OIC. Inhibition of small

intestinal motility is a prominent feature of opioids (however, this is difficult to study in man and is therefore mostly studied in small rodents).<sup>7</sup> This is probably one of the reasons why laxatives (acting on the colon) do not satisfactorily relieve complaints in all patients. Although constipation usually manifests with a low stool frequency, infrequent bowel movements are not relevant as such. The main complaints of patients with OIC are an unpleasant sense of abdominal fullness with swollen abdomen and hard stools that are difficult to evacuate, often with a sense of incomplete bowel emptying. This may become so severe that patients taper or even discontinue opioid intake: they would rather tolerate their pain than continue to suffer from bowel dysfunction.<sup>4,8</sup>

However, bowel dysfunction in patients on opioid treatment is not caused exclusively by opioid medication alone but comprises several components (see Figure 2). This may partly explain the large spread in its frequency of occurrence (see below).

Stool impaction of the rectum deserves to be specifically mentioned. Retained stools may form massive, firm lumps that are impossible to defecate. The rectoanal inhibitory reflex is elicited and leads to sphincter relaxation with soiling. Impaction may even lead to bowel obstruction and urinary retention. Opiate treatment is a major culprit of this embarrassing condition. The classic treatment is manual disimpaction. Macrogol has been shown to circumvent this most unpleasant procedure.<sup>9</sup>

## Epidemiology

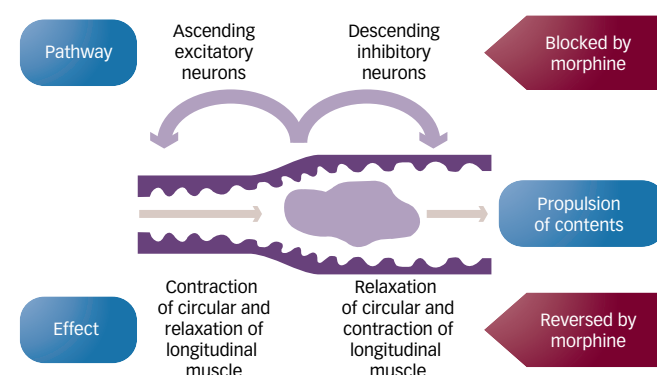
The reported frequency of constipation in patients on opioid treatment is quite variable (see Figure 3). Potential reasons for this variability include the type of opiate, dose–response effects, form of application (oral or transdermal), different or imprecise definitions and methodology of assessment of constipation. However, when looking at the respective publications it was not possible to find a reassuring explanation.

Transdermal application of opioids could be expected not to cause OIC since the intestines are not directly exposed. Despite this, transdermal fentanyl and buprenorphine do become systemically available and reach the intestines via the bloodstream. Although the transdermal route seems to be accompanied with slightly less constipation than other opiates, the problem of OIC is far from being solved (see Figure 3). Some authors consider the occurrence of OIC to be so frequent and bothersome that they recommend simultaneous prescription of a laxative alongside the opiate.<sup>28</sup> Some guidelines on the topic,<sup>29,30</sup> although not all,<sup>31</sup> are also in favour of prophylactic laxative treatment.

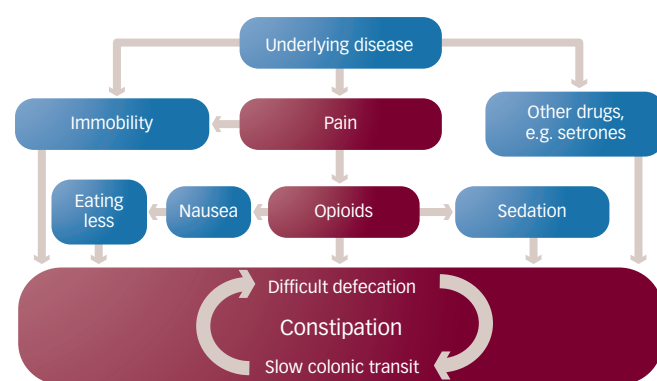
## Diagnosis

In general, no technical diagnostic procedures are required to diagnose OIC. Active symptom evaluation by asking the patient about OIC symptoms is the mainstay of diagnosis. It should be emphasised that stool frequency alone is an insufficient criterion for the presence of OIC, as discussed above. If the timely relation between the start of opioid treatment and the onset of symptoms is obvious, there is no need to evaluate a differential diagnosis. In other cases, colonoscopy has to be considered. A digital rectal examination is advisable to exclude stool impaction of the rectum. Validated instruments, such as the Bowel Function Index (BFI) and the Patient Assessment on Constipation Symptoms (PAC-SYM) questionnaire, are helpful to

**Figure 1: Neuromuscular Basis of the Peristaltic Reflex and Its Inhibition by Opioids**

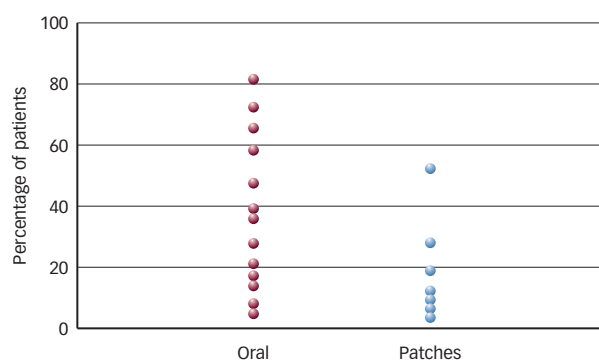


**Figure 2: Pathogenesis of Constipation in Chronic Pain Patients**



Although very important, opiate use is only one factor in the pathogenesis of constipation. Immobility and sedation impair defecation. Slow transit leads to smaller, harder stools that are difficult to evacuate. Obstruction of the rectum with stools in turn slows transit.

**Figure 3: Reported Frequencies of Opioid-induced Constipation**



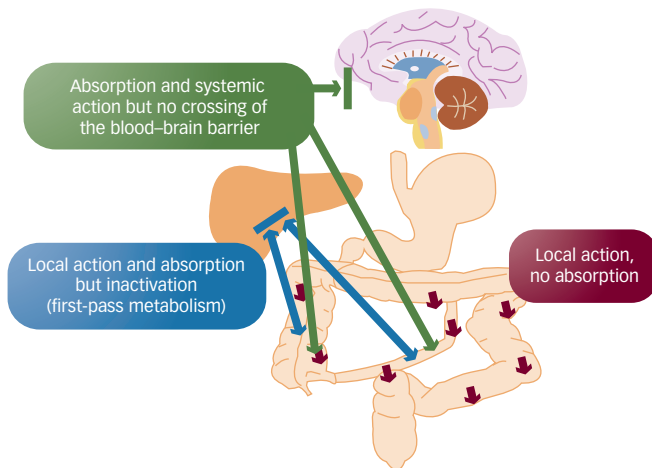
Respective studies were identified by a systematic literature search. For the sake of clarity, only papers published since 2005 are shown in the figure, since older studies have been reviewed previously, giving a mean prevalence between 15 and 41%.<sup>5,6,10</sup> Reported data are displayed separately for the oral<sup>11–23</sup> and transdermal route using patches.<sup>11,16,20,24–27</sup>

assess the impairment in quality of life caused by OIC and may help to establish the indication for its treatment.

## Treatment

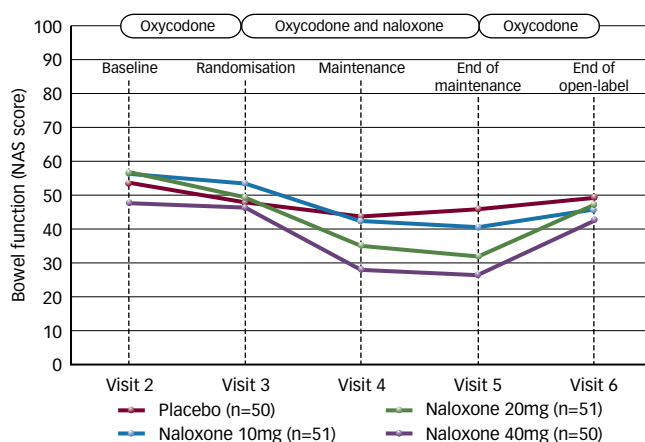
The lifestyle measures frequently recommended for idiopathic constipation, such as regular toilet visits, physical activity and a fibre-rich diet, have not been formally evaluated in OIC, but they are unlikely to be successful.

**Figure 4: Potential Ways to Antagonise Opiate Effects on Intestinal Receptors without Interfering with the Central Nervous Analgesic Action**



The possibility of a locally acting opiate antagonist not being absorbed (red) has not been exploited. Local action but inactivation in the liver (blue) has been achieved with the fixed oxycodone–naloxone combination (Targin®). Systemic antagonistic action without penetrating the brain (green) involves methylnaltrexone and alvimopan.

**Figure 5: Bowel Function Index in Patients Treated with the Fixed Oxycodone–Naloxone Combination (Targin®)**



Oxycodone was given during the entire study period while naloxone was added from visit 3 to visit 5 only. NAS = numerical analogue scale.

Adapted from Meissner et al., 2009,<sup>39</sup> with permission from Elsevier.

## Laxatives

Clinical experience shows that the usual laxatives, alone or in combination, are only partly effective in relieving OIC. This is corroborated by the sparse data available regarding macrogol,<sup>32</sup> bisacodyl,<sup>33</sup> sennosides<sup>34</sup> and, interestingly, by the new 5-HT<sub>4</sub> agonist prucalopride.<sup>35</sup> Treatment success is therefore far from being perfect for all patients and new approaches in the medical management of OIC are desirable.

## Opioid Antagonists

At first glance it looks odd to address the opiate effect with an antagonist because the analgesic action could be offset at the same time as the opioid effects on the intestines. However, the inhibitory action of opioids on gastrointestinal function is mediated by their local rather than their central action. Hence, if it were possible to bring the antagonist to the peripheral  $\mu$ -opioid receptor without allowing it to cross the blood–brain barrier, this could solve the problem of OIC.

There are several approaches to attaining this goal (see Figure 4). The antagonistic effect on the intestines could be brought about locally (from the lumen) or systemically (via the circulation). Regarding the first possibility, an unabsorbable antagonist could be a solution, but this is based on data that have not yet been exploited. A second approach is to give an antagonist orally, which although being absorbed does not produce relevant systemic concentrations. This is in fact feasible since the bioavailability of naloxone is below 3% due to a high first-pass metabolism in the liver, at least within certain dose limits.<sup>36,37</sup> This requires a slow-release formulation in order to expose the entire intestine to naloxone, which is available as a tablet containing oxycodone plus naloxone. Finally, one may administer an antagonist with a low ability to cross the blood–brain barrier, as in the case of methylnaltrexone and alvimopan.

When developing the oxycodone–naloxone combination, it first had to be shown that the analgesic effect was not impaired. Second, the optimal ratio between oxycodone and naloxone had to be found. This was accomplished in a four-arm trial involving 202 patients with chronic pain. In each arm, oxycodone was dosed between 40 and 80mg/day and naloxone was added at a dose of 10, 20 or 40mg. Patients in the fourth arm were given placebo.<sup>39</sup>

Pain intensity as well as bowel function was assessed by numerical analogue scales. The BFI was used to assess bowel function; this index comprises the items ‘ease of defecation’, ‘feeling of incomplete bowel emptying’ and ‘personal judgement of constipation’. The BFI has been validated.<sup>38</sup> While there were no differences between the treatment groups regarding analgesia, an optimal result in terms of avoiding both constipation and diarrhoea was seen when oxycodone and naloxone were given in a 2:1 ratio (see Figure 5).<sup>39</sup> These findings were corroborated in two studies including 322 and 265 patients with non-malignant pain treated with 20–50mg and 60–80mg of oxycodone daily, respectively, and randomised to naloxone at half the dose of oxycodone or placebo.<sup>40,41</sup> The fixed combination has therefore been marketed under the name Targin® in the 2:1 dose ratio.

Methylnaltrexone was shown to improve OIC in three trials of moderate size in patients with advanced, mostly malignant, disease (n=133–154 patients).<sup>42–44</sup> It is approved for this patient group when palliative care is required. The drug is given via subcutaneous injection.

Alvimopan was given to patients scheduled for bowel resection or hysterectomy two hours prior to the procedure until discharge or day seven. The drug shortened the time to reach the primary efficacy end-point (i.e. the composite of time to recovery of upper and lower gastrointestinal function) by about half a day and time to discharge from hospital by about one day.<sup>45–48</sup> Alvimopan is approved for the prevention of post-operative ileus in major abdominal surgery in the US, but not in the EU and not for OIC.

## Conclusions

It is obvious that OIC is a frequent adverse event, occurring in up to two-thirds of patients treated with potent opioids. However, not all patients are affected by OIC, with some patients even reporting diarrhoea.<sup>11</sup> From the data discussed above (as well as from personal experience in clinical practice), prophylactic laxative prescription for all patients, as recommended by some

authors and even guidelines,<sup>28–30</sup> seems to be overtreatment. Such a regimen would almost certainly subject many patients to embarrassing diarrhoea. Hence, the respective recommendations in guidelines should be challenged. Two other approaches seem much better suited: either one should specifically ask whether patients are experiencing the symptoms of OIC as soon as opioid treatment has been started, or one can *a priori* 'neutralise' the constipating effect of the opiate by prescribing the oxycodone–naloxone combination. ■



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