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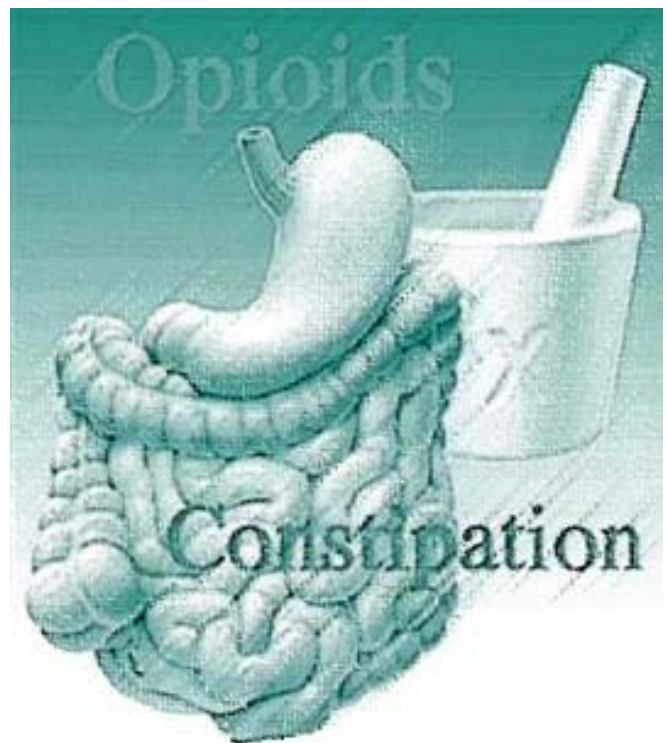# Managing Opioid-Induced Constipation in Ambulatory-Care Patients

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Contents

Introduction

    Constipation is a frequent side effect of opioids since these agents decrease peristaltic activity in the gastrointestinal (GI) tract. Because of the mechanisms involved in opioid-induced constipation, some treatments that may be applicable for common, functional constipation are inappropriate for ambulatory-care patients prescribed opioid analgesics.

    Also in these patients, the distress of constipation may add to the discomfort already present from pain, and they might decrease or discontinue the opioid to avoid constipation. So, motivating such patients to comply with their opioid therapy also requires a special approach for managing constipation.

Constipation as a potential side effect should be considered whenever an opioid medication is prescribed.

Functional Constipation

Constipation is broadly defined as the *passage of hard, dry stools less frequently than the patient's usual bowel-habit pattern* (McMillan 2004). Patients and healthcare providers may differ in their assessments of whether the patient is constipated, and *frequency of bowel movement is not the most critical factor*.

For example, a group of patients who considered themselves constipated and reported that they had 3 or fewer bowel movements per week for at least 6 months kept diaries of bowel activity for the next 4 weeks. Because the diaries showed that more than half actually had an average of 6 bowel movements per week, the investigators did not consider them as constipated. Regardless of their stool frequency, however, the patients reported difficulty in defecation, which suggests that they considered this a more important criterion than frequency (Yuan 2005).

Some patients, especially the elderly, expect to have at least one bowel movement each day; otherwise, they believe they are constipated. Other patients may think that having only 2 to 3 weekly bowel movements is not being constipated. Actual frequency of bowel movements in a population of people who are not seeking medical care is extremely variable, ranging from 3 bowel movements per day to 3 per week (Drossman et al. 1982), further complicating assessment of constipation based on frequency.

One literature review indicated that functional constipation is a common problem, affecting 12% to 19% of the North American population (Higgins and Johanson 2004). Similar rates of functional constipation (15%) were found in a study of 10,000 United States adults aged 18 or older (Stewart et al. 1999).

> ### Practice Pointers
> ### Managing Opioid-Induced Constipation
>
> ■ Constipation during opioid therapy is common, if not inevitable, and may be different from ordinary functional constipation.
>
> ■ Clinicians should anticipate the constipating side effects of opioid analgesics and discuss them with patients before starting opioid therapy.
>
> ■ Many patients with prior constipation rely on self-management and OTC remedies, and they may not mention these to healthcare providers when starting opioid therapy.
>
> ■ Given the high variability among patients, characterizing a person as constipated based only on the number of bowel movements per day or week is inappropriate.
>
> ■ Prevention is the best approach to managing constipation, and an appropriate regimen should be tailored for each patient's needs when beginning opioid therapy.
>
> ■ Because treating constipation is based mostly on clinical or personal experience, common myths and misconceptions exist among clinicians and patients.
>
> ■ Available evidence does not suggest that opioid-induced constipation can be managed merely by increasing intake of fluids or dietary fiber, unless the patient is dehydrated or consuming a fiber-deficient diet.
>
> ■ In patients with mild constipation and little physical activity, moderate increases in activity level, as tolerated, can be beneficial.
>
> ■ Bulk-forming laxatives are not appropriate in opioid-induced constipation, because peristalsis is inhibited in these patients.
>
> ■ Effective treatment and management of opioid-induced constipation usually requires laxatives; most commonly, a combination stool softener and stimulant.

Opioid-Induced Constipation

Constipation resulting from opioid use is the most common component of a more general condition – opioid-induced bowel dysfunction, OBD (Yuan 2005). Signs and symptoms of OBD shared in common with functional constipation include: dry hard stools, straining during evacuation, incomplete evacuation, bloating, abdominal distension, and retention of contents of

the gut. Unlike functional constipation, OBD also can include cramping, nausea and vomiting, and gastric reflux (Yuan 2005; Talley 2004; Kurz and Sessler 2003; Pappagallo 2001). All of these signs and symptoms result from the actions of opioids on receptors throughout the GI tract (Yuan 2005).

Prevalence

The reported prevalence of opioid-induced constipation varies among studies. Some use different definitions of constipation, and others use self-reporting by patients rather than the investigators' criteria. In one study, 95% of patients interviewed by nurses in a hospital oncology unit reported constipation as the major side effect of their opioid pain-control regimen (Robinson et al. 2000).

Constipation typically afflicts at least 41% of patients receiving long-term potent-opioid therapy.

A meta-analysis reviewed 11 studies including patients with chronic, non-cancer pain in whom the effects of oral therapy with potent opioids such as morphine, methadone, hydromorphone, or fentanyl were compared with those of placebo. Constipation was the most common adverse event, experienced by 41% of the 1025 patients in the study (Kalso et al. 2004).

Regardless of how prevalence is measured, opioid-induced constipation is a major problem. Some clinicians assume it to be virtually universal in patients who are prescribed opioid analgesics (Hanks et al. 2003).

Role of Opioid Receptors

The effects of opioid analgesics are mediated by specific opioid receptors. Three well-defined opioid receptors important in humans are mu (μ), kappa (κ), and delta (δ) (Yuan 2005).

Opioid receptors in the brain modulate pain perception; peripheral receptors affect bowel motility.

Activation of mu receptors by an agonist such as morphine can have any of several effects, depending on receptor location. Mu opioid receptors in the brain modulate pain perception and can depress respiratory function, while those in the GI tract decrease bowel motility (Gutstein and Akil 2001).

Opioid receptor activation within the bowel wall interferes with normal tone and contractility, delaying transit time of the fecal contents. Increased contractions of circular muscles cause non-propulsive kneading and churning, increasing fluid absorption, which dries and hardens the stool. At the same time, longitudinal propulsive peristalsis is decreased, providing additional time for drying of the stool. In addition to these effects, anal sphincter tone is increased, so reflexive relaxation in response to rectal distension is reduced making defecation more difficult (Gutstein and Akil 2001; McMillan 2004; Yuan 2005).

Tolerance commonly develops to opioids during long-term use, requiring increased doses to achieve the same analgesia (Thompson and Ray 2005). Although some tolerance develops to the effects of opioids on gastrointestinal motility, constipation often persists unless remedial measures are taken (Gutstein and Akil 2001).

Differential Opioid Effects

Few published reports compare the constipating effects of the various opioid analgesics or evaluate the opioid-related adverse effects associated with specific routes of administration (Hanks et al. 2003). Some controlled studies have shown less frequent laxative use in patients treated with transdermal fentanyl than in those treated with morphine (Radbruch et al. 2000; Ahmedzai and Brooks 1997; Donner et al. 1996; Payne et al. 1998). This finding could be due to the route of administration, or to the adverse-event profile of each opioid; hence, further evaluation is needed.

Patient Assessment & Treatment

Before starting opioid therapy, patients should be asked if they currently are constipated and if it is a problem for them (Talley 2004). Although patients' perceptions of constipation are highly subjective, this discussion can help clinicians develop a treatment plan for preventing or managing this expected side effect of opioids.

Patient-provided information may also reveal conditions that could contribute to constipation (Yuan 2005; Talley 2004; McMillan 2004; Fine and Portnoy 2004). Delayed, infrequent, or uncomfortable bowel movements could be a side effect of the pain itself. Some patients with mild, long-standing constipation take over-the-counter (OTC) bulk laxatives and may not think to mention this to a healthcare provider. If these patients develop opioid-induced constipation, the result can be painful, colicky symptoms (Yuan 2005). The **Table** (adapted from McMillan 2004) lists some additional topics and potentially contributing factors to cover during evaluation of the patient with preexisting constipation.

Ask patients if they are constipated prior to starting opioid therapy.

> ### Components of Patient Assessment
>
> - Daily activity level & adequate dietary habits – food, fiber, fluid intake.
> - Ability to chew and swallow (patient may opt for soft foods, usually low in fiber content).
> - Ability to use toilet facilities; adequate privacy.
> - Current drug therapy – other medications, including OTC drugs, can cause constipation (eg, anti-hypertensives, anticholinergics, antidepressants, iron/calcium supplements).
> - Underlying medical problems or conditions (eg, neurologic disorders; metabolic and endocrine disorders, such as diabetes; intestinal obstruction; dehydration).
> - Duration of constipation and related symptoms (eg, straining, incomplete bowel emptying, flatulence, hemorrhoids).
> - Diarrhea or leakage of stools – severe constipation can result in fecal impaction, which interferes with bowel control; liquid stool may trickle around the impaction and leak out.
> - Abdominal and anorectal examinations to rule out obstruction, fissures, hemorrhoids, etc.

Prevention

A goal in patients taking opioids is to achieve a complete bowel movement at least every 2 to 3 days without difficulty (no hard stools, no straining). However, as noted above, frequency of defecation is less important than comfortable evacuation (Yuan 2005).

To help prevent opioid-induced constipation, and potential noncompliance with treatment, patients prescribed long-term opioid medications should be considered for a scheduled regimen of laxatives (Hanks et al. 2003), especially if constipation is a preexisting problem. Using lower doses of opioids will not prevent constipation because the dose that produces constipation is approximately 4-fold *less* than the analgesic dose (Yuan 2005; Yuan and Foss 2000).

Non-Pharmacologic Tx: Myths & Facts

Reminding patients of some commonsense toileting principles may help moderate opioid-induced constipation. For example, patients should be encouraged not to suppress the urge to defecate, and they should use public bathrooms instead of waiting until they get home. Some patients may benefit from training their bowels by sitting on the toilet at about the same time every day. Having adequate privacy may be important for some patients.

Certain popular beliefs about constipation are held by patients and healthcare professionals. Investigations of the scientific literature, however, have produced little or no evidence to support those beliefs, so some may be more myth than fact, such as the following:

Dietary Fiber – One common myth is that a low-fiber diet may cause consti-
pation, but comparisons of patients with constipation and those without
have shown no differences in fiber intake (Müller-Lissner et al. 2005). Pa-
tients with opioid-induced constipation would not benefit from additional
dietary fiber unless their current intake is deficient. If fiber is excessively
increased it might put these patients at risk for bowel obstruction due to the
decreased peristalsis, delayed gastric emptying, and prolonged intestinal transit time that
occur in opioid-induced constipation (Yuan 2005).

Dietary fiber should not be increased in patients with opioid-induced constipation, because of possible obstruction.

Hydration – There is no evidence that constipation can be successfully treated merely by
increasing fluid intake, unless there is evidence of dehydration. In that case, constipation
might be ameliorated to some extent by added fluids (Müller-Lissner et al. 2005, Yuan
2005).

Physical activity – Whether increased physical activity reduces opioid-in-
duced constipation has not been specifically investigated. And, although
modest physical activity may help some patients with mild constipation,
there is no evidence that more severe and chronic constipation is benefit-
ted by exercise alone (Bingham and Cummings 1989). In one study of
functional constipation in nursing home residents, it was found that in-
creased physical activity, as part of an *overall* program that included dietary manage-
ment and laxative use, resulted in an improvement in constipation symptoms (Karam and
Nies 1994).

It is not known whether increased activity significantly benefits patients with opioid-induced constipation.

It can reasonably be assumed that, as a matter of general health, people need to ingest a
certain amount of fiber and fluids daily and to maintain a sensible level of physical activity.
Many people in today's society probably are deficient in these areas, and it should be a goal in
overall health maintenance to achieve recommended levels. But whether deficiencies in fiber and fluid intake and physical activity cause or contribute to constipation is questionable. Even more doubtful is whether correcting those deficiencies alone can successfully treat constipation (Müller-Lissner et al. 2005).

Pharmacologic Tx: Laxatives

Effective management of opioid-induced constipation involves using stool softening and/or bowel stimulating laxative agents. Those typically used in treating opioid-induced constipation are summarized in the *Table* (products are available OTC, except those marked Rx).

Laxatives for Opioid-Induced Constipation (Yuan 2005)

Type	Examples	Mechanism of Action	Comments
Stool Softeners Surfactant	Docusate	Softens stool by facilitating admixture of fat and water.	Use in combination with stimulant laxative.
Osmotic	Lactulose *(Rx only)* Magnesium hydroxide Magnesium sulfate Polyethylene glycol *(Rx only)* Sodium phosphate	Draw water into the lumen of the colon, thus hydrating the stool.	Different agents have different degrees of effect; some may cause electrolyte imbalance.
Lubricant	Mineral oil	Lubricates intestine, delays absorption of fecal water in the colon, and softens the stool.	Use in combination with other laxatives, when stool is hard and dry.
Stimulants	Bisacodyl Cascara sagrada Senna	Irritate sensory nerve endings, increasing muscle contractions; reduce water absorption.	Counteracts lack of propulsive activity induced by opioids; use in combination with stool softener.
Combination	Docusate/senna	See above.	See above.
Bulk Producers	Methylcellulose Psyllium Malt soup extract Calcium polycarbophil	Stimulate water absorption.	***Do Not Use.***

Stool softeners – exert their effects by retaining water in the stool so that bowel evacuation is easier for patients who have hard, dry stools. Surfactant agents like docusate facilitate the admixture of fat and water in the feces. Osmotic laxatives include lactulose, magnesium hydroxide and sulfate (which are stimulating as well), and polyethylene glycol (PEG). These laxatives cause water to be held within the stool, preventing drying and hardening. Mineral oil is used as a lubricant, and also helps retain water in the stool (Yuan 2005); however, mineral oil sometimes results in incontinence of liquid stool, staining undergarments.

Stimulant laxatives – strengthen intestinal muscle contractions, overcoming the decreased peristalsis resulting from the opioid, and may be required on a daily basis. Stimulant laxatives (aloe, cascara, senna compounds, cas-anthranol, bisacodyl, castor oil, sodium picosulfate) are usually recommended for short-term use but can be combined with stool softeners for longer-term management of opioid-induced constipation (Yuan 2005).

Used appropriately and at recommended doses, stimulant laxatives are not habit-forming, do not induce tolerance, and are not harmful to the colon (Müller-Lissner et al. 2005). In patients failing to respond adequately to stool softeners, stimulant laxatives may be used chronically (Yuan 2005).

Used appropriately at recommended doses, stimulant laxatives are not habit-forming, do not induce tolerance, and are not harmful to the colon.

Combination laxatives – provide optimal effectiveness while minimizing adverse effects and simplifying the bowel regimen. However, ready-made combinations of stool softening and stimulant laxatives tend to be more expensive, so cost and individual patient acceptability might influence prescribing choice (Yuan 2005).

Combination laxation has been colloquially but memorably described by one clinician as a "Mush-Push" strategy (Howard A. Heit, MD, in Leavitt 2004). The two components might include a stool softener such as docusate and a mild bowel stimulant such as a senna-containing product.

Bulk-forming laxatives – include indigestible hydrophilic colloids, such as methylcellulose and psyllium, which absorb water, producing bulk that distends the colon and stimulates peristalsis. *Bulk-forming laxatives are not appropriate in opioid-induced constipation*; as the colon stretches to accommodate the bulk, it does not respond respectively with propulsive action due to opioid effects. Failure to move the bulk along can cause painful, colicky symptoms and may result in obstruction (Yuan 2005).

Authors' Commentary:

Clinical views differ concerning the management of potential opioid-induced constipation from "wait and see" to starting with a full bowel regimen immediately. Some patients may need a comprehensive laxative regimen from the beginning if they seem to be overly concerned about not having a bowel movement every day.

For less anxious patients, it could be sufficient to point out that constipation is a common occurrence with opioid therapy, and that some dietary and life-style changes could be helpful as a beginning, followed by laxatives if necessary. The patient might first be advised: (A) if deficiency exists, increase the intake of fluids, fruit, fruit juices, and vegetables, (B) increase activity as appropriate, and (C) practice good toileting habits.

Those simple measures may not be sufficient to prevent constipation, and laxatives will be needed. These could be chosen from one of the osmotic laxatives (magnesium hydroxide, magnesium citrate, or sodium phosphate), or a stool softener (sodium docusate); most of these will require daily administration. It may be necessary to later add a stimulant laxative (senna or bisacodyl) every 2 to 3 days, increasing to daily if needed. Lactulose and polyethylene glycol are still more aggressive approaches. As a suitable regimen is found for each patient, the dosage and schedule should be adjusted to optimize the response.

Because constipation is such a common side effect, many clinicians advise a daily stool softener for each patient at the very start of opioid therapy, with senna taken every two to three days if needed, instead of the stepwise increase.

Alternative Pharmacotherapies

Opioid-Receptor Antagonists

Many patients remain constipated despite lifestyle changes and the aggressive use of laxatives. Oral opioid-receptor antagonists, including naloxone, naltrexone, and nalmefene have been suggested as being potentially helpful in ameliorating opioid effects in the GI tract. However, these agents may be of limited use because they also cross the blood-brain barrier and can reverse analgesic effects of opioids, or induce uncomfortable opioid withdrawal symptoms (Friedman and Dello Buono 2001; Gutstein and Akil 2001).

Selective Antagonists

Methylnaltrexone and alvimopan are newer agents that block peripheral opioid receptors in the gut. Unlike the opioid antagonists naloxone and naltrexone, these antagonists do not cross the blood-brain barrier. As a result, they antagonize only the peripherally located opioid receptors in the GI tract, so their action reverses opioid-induced constipation without precipitating withdrawal symptoms or affecting or reversing the analgesic effects of opioids (Ho et al. 2003; Kurz and Sessler 2003; Schmidt 2001; Foss 2001).

New opioid antagonists block GI effects but not the analgesic effects of opioids.

Although these 2 drugs have similar actions in selectively antagonizing opioid receptors in the GI tract, they differ in their molecular structure (Yuan 2005). Because they are still in clinical trials, as of summer 2006, it is too early to know whether they also differ in effectiveness or side effects.

Prokinetic agents

The prokinetic agents metoclopramide and misoprostol enhance the propulsion of intestinal contents. These drugs have been used on a limited basis to treat slow-transit constipation, but only when conventional treatments have been unsuccessful (Longo and Vernava 1993). Tegaserod is a newer agent, which improves constipation in irritable bowel syndrome, but it is doubtful that it would be effective alone for opioid-induced constipation (Yuan 2005). Prokinetic agents have adverse effects, and the U.S. Food and Drug Administration has not approved them for use in chronic constipation.

Prokinetic agents have not been approved for use in opioid-induced constipation.

Summary

Constipation is an expected side effect of opioid analgesics and should be discussed with patients before opioid therapy begins. Because opioid-induced constipation can be severe and adversely impact a patient's quality of life and compliance with therapy, prevention is the best approach. This entails recommending certain lifestyle or dietary adjustments and/or initiating a scheduled regimen of laxatives when the opioid is prescribed. Laxative therapy may be needed throughout opioid therapy and beyond.

For patients who are already taking opioid analgesics and develop constipation, effective management entails a composite of clinical strategies, including behavioral and lifestyle changes (diet, activity, and fluid intake, as appropriate). Most importantly, aggressive therapy with laxatives should be directed toward the patient's underlying symptoms and pathophysiologic changes.

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