

FAST FACTS AND CONCEPTS #294
OPIOID INDUCED CONSTIPATION PART 1: ESTABLISHED MANAGEMENT STRATEGIES

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Background Opioid induced constipation (OIC) affects 45-90% of patients (1, 2) and can cause significant morbidity. It is the most common reason patients avoid and/or discontinue opioids (3, 4) and can often result in an increase in hospital length of stay (5) and overall healthcare costs (6). This *Fast Fact* will describe the physiology of OIC and describe established treatment strategies. *Fast Fact # 295* will discuss newer management strategies.

Physiology OIC is mediated through several different mechanisms including ineffective GI motility, inhibition of mucosal transport of electrolytes and fluids, and interference with the defecation reflex (7). The greatest risk factor for developing OIC is duration of opioid therapy. Route of delivery or increased opioid dosing does not appear to affect the risk of developing OIC (2). While patients usually develop tolerance to most other side effects from opioids, they do not develop tolerance to OIC (1).

Non-pharmacologic Therapies Physical activity, scheduled toileting, fiber, and adequate fluid intake have been traditional non-pharmacologic mainstays for preserving GI regularity in constipation (8). However, there is no specific evidence in favor for any of these interventions to treat OIC and adherence may be challenging for chronically ill patients.

Pharmacologic Therapies In general, patients with regular opioid exposure will require pharmacologic therapy to appropriately manage OIC. Both stimulant and osmotic laxatives have shown to be effective in treating OIC and are considered the cornerstone of treatment. Failure of oral pharmacologic therapy usually requires more invasive rectal based interventions or one of the newer treatment modalities (see *Fast Fact #295*).

- **Stimulant Laxatives:** Senna and bisacodyl are the main stimulant laxatives available in the US and work by increasing enteric muscle contraction and GI motility. The onset of action for oral senna and bisacodyl is around 6-12 hours. Starting dose for senna is two 8.6 mg tabs; bisacodyl is one 10mg tab. However, higher doses are usually needed for OIC. Senna can be safely dosed up to 12 tabs daily and bisacodyl up to 30 mg (9). Both medications are relatively inexpensive. Because stimulant laxatives cause intestinal contractions their use can be limited by abdominal cramps and pain. This can sometimes be avoided by dividing the total dose into smaller more frequent doses (9).
- **Osmotic Laxatives:** These include non-absorbable sugar molecules such as polyethylene glycol (PEG), lactulose, and sorbitol, as well as poorly absorbed salt-based molecules like milk of magnesia and magnesium citrate. Osmotic laxatives have limited intestinal absorption leading to an increase in colonic intraluminal water through oncotic pressure. With increased intraluminal volume and distension, reflex peristalsis subsequently occurs. Additionally, the increase in intraluminal water also leads to softer stool and allows for easier intestinal transit. The starting daily dose for PEG is 17 g, for lactulose is 15 ml, and 30 ml for 70% sorbitol solution. Osmotic laxatives will have a linear effect on bowel function with dose increases; the maximum effective daily dose of PEG is 68 g (10), lactulose is 60 ml, and for sorbitol is 150 ml. The onset of action for osmotic laxatives tends to be variable ranging from 12 to 48 hours, but when used regularly patients will have a more consistent effect. Osmotic laxatives generally do not lead to a loss of fluids or electrolytes as they only bind to orally taken fluid. With this, PEG requires 125 ml of fluid per 17 g dose (11) and similarly ~200 ml is recommended with every 30 ml of lactulose (12). Major side effects from osmotic laxatives include abdominal cramping, pain, and flatulence. Lactulose and sorbitol tend to have more of these side effects than PEG (11). While sorbitol and lactulose have shown similar efficacy, sorbitol tends to be more cost effective (13). Magnesium based compounds (milk of magnesia and magnesium citrate) are also effective, but the magnesium load can be dangerous for patients with renal insufficiency.
- **Rectal Based Laxatives:** Unfortunately, there is a lack of clinical research to support rectal based laxatives, but anecdotally they are often used for refractory constipation. Stimulant suppositories such as bisacodyl and rectal vault lubricants such as glycerin are inexpensive. Their onset is usually within 10-15 minutes and can be dosed daily (9). Warm tap water and milk of molasses enemas (12) can be

dosed more frequently (up to every two hours). They work by causing rectal distension and reflex defecation. Other enema formulations, such as phosphate or saline enemas, should be used with caution in renal insufficiency due to concern for electrolyte shifts.

- **Manual Evacuation:** Digital stimulation and manual disimpaction may be necessary if fecal impaction is suspected. Due to the discomfort associated with manual evacuations, these are often interventions of last resort and may require pre-medication with pain medications and/or anxiolytics.
- **Ineffective Therapies:** Docusate sodium not demonstrated efficacy in randomized controlled studies for OIC compared with placebo (14). Bulk forming laxatives (psyllium or fiber) require at least 1.5 L of water to be effective and can actually lead to worsened constipation with inadequate fluid intake. Consequently, most guidelines do not routinely recommend their use (11,15,16).

Practical Advice A consistent bowel regimen is essential in preventing constipation in patients on chronic opioid therapy. Providers should educate their patients about the signs and symptoms of OIC and seek appropriate consultation in a timely manner. A scheduled stimulant laxative regimen such as Senna 2 tabs twice daily should be prescribed at the onset of regular opioid use regardless of opioid dosing. The goal for the bowel regimen should be an unforced bowel movement at least every other day. If a patient has not had a bowel movement in 48 hours, increasing stimulant laxative dose and/or adding an osmotic laxative is appropriate. Failure of oral laxative therapy usually requires rectal based interventions and/or one of the newer treatment modalities (see *Fast Fact #295*).

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