

## FAST FACTS AND CONCEPTS #295 OPIOID INDUCED CONSTIPATION PART II: NEWER THERAPIES

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**Background** *Fast Fact #294* introduces OIC and discusses well-established treatments. This *Fast Fact* discusses emerging management approaches. In general, these agents are used for refractory OIC, which implies persistent and distressing symptoms despite exposure to typically effective doses of stimulant and osmotic laxatives. When exactly to use these emerging therapies remains largely empiric.

**Opioid Antagonists** Since the majority of symptoms associated with OIC are secondary to stimulation of  $\mu$ -opioid receptors in the gut, opioid antagonists offer an attractive pharmacologic rationale for OIC (1).

***Naloxone***: Until recently, naloxone was the only available opioid antagonist for OIC treatment. Typically, patients orally ingest the contents of IV ampules. Naloxone has a high first pass metabolism, so it is possible for patients who take it orally to have peripheral  $\mu$ -opioid receptor antagonism *without* significant impact on central receptors which could lead to opioid withdrawal and loss of analgesia (2). In a small, non-controlled study, 80% of chronic opioid users had bowel evacuation in 1-4 hours after naloxone administration. Unfortunately, over two-thirds reported a 10-15% loss of analgesia and nearly one-third had withdrawal symptoms (3). Therefore, if used, it is recommended to start at a low dose of 0.8 mg twice daily. Effective doses typically need to be at least 10% of equivalent daily morphine dose, so naloxone usually requires slow up-titration with max dosing of 12 mg daily (2).

***Methylnaltrexone bromide***: Methylnaltrexone is a peripherally-acting  $\mu$ -opioid receptor antagonist. It is a methylated form of naltrexone and formulated as a subcutaneous injection. It is less able to cross the blood brain barrier, reducing the risk of altering analgesia or inducing central opioid withdrawal. An industry-funded randomized controlled trial of chronic opioid users showed that weight based methylnaltrexone dosing led to laxation in nearly half of subjects within 4 hours as opposed to 15% of placebo (4). A subsequent meta-analysis of 6 separate trials with methylnaltrexone demonstrated the number needed to treat (NNT) is 3 for OIC patients that have failed to respond to standard laxative therapy (5). Its use is limited by cost which averages \$55 per dose, and it is also contraindicated when bowel obstruction is suspected or for patients with compromised bowel integrity. The most common side effects are nausea, diarrhea, and cramping – which can be severely painful.

***Naloxegol***: Two oral peripheral acting  $\mu$ -opioid receptor antagonists are available in the US: alvimopam, which is only approved for post-operative ileus, and naloxegol (pegylated naloxone), which has recently been approved for OIC in non-cancer patients. Two separate phase-three clinical trials showed an increase from 1 to >3 bowel movements per week in non-cancer patients on chronic opioids with daily dosed naloxegol compared to placebo. There was also a significant improvement in a subset of patients who had failed traditional laxative therapy as well (7). Both 12.5 mg and 25 mg have been studied; the 25 mg dose has a higher success rate but is associated with more abdominal pain, nausea, vomiting and diarrhea (7). Its current price is approximately \$300 for 30 pills.

### Other Agents

***Lubiprostone***: Lubiprostone is a selective chloride channel-2 activator that acts locally on the small intestine to increase fluid secretion and GI motility. It is FDA approved for OIC. Two randomized controlled trials in non-cancer chronic opioid users demonstrated an increase in frequency of spontaneous bowel movements by week 8. Moreover, approximately 40% of subjects had a bowel movement at 24 hours, 60% within 48 hours, and 27% of subjects had > 3 bowel movements per week (8,9). The most studied dose is 24 mcg orally twice per day. Common side effects included nausea, diarrhea and abdominal distension. Curiously, lubiprostone does not appear to be effective for methadone induced constipation (10).

***Linaclotide*** has a different mechanism than lubiprostone, but is also a small intestinal secretagogue. It currently is approved for irritable bowel syndrome. Though there is interest in its efficacy in OIC, it has yet to be specifically studied in this population.

*Prucalopride* is a serotonin receptor type-4 agonist which is available in Canada and parts of Europe and Asia to treat chronic constipation. It is a prokinetic agent which has shown promise for treating OIC in a phase 2 study (5). It is unclear if or when it will be released in the US.

**Practical Advice** Traditional oral and rectal laxatives have been the mainstay of treatment in OIC for many years. However, recent development of novel approaches to treat OIC show promise for the future. Of the pharmacologic interventions described above, methylnaltrexone has been the best studied and shown to be the most efficacious. It is reasonable to give methylnaltrexone after failure of oral laxatives (see *Fast Facts* #294) in OIC, and potentially can be used prior to using more invasive rectal based interventions. With time and more clinical trials, other oral formulations targeting OIC may become more standard of care. Patient and caregiver education about the importance of adherence to recommended therapy and guidance about signs and symptoms of OIC is essential to ensure effective treatment.

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