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**PERIPHERALLY-ACTING OPIOID ANTAGONIST –
OPIOID-INDUCED CONSTIPATION
(IN NON-CANCER PAIN)**

MOVANTIK (naloxegol)

Drug Regimen Review Center

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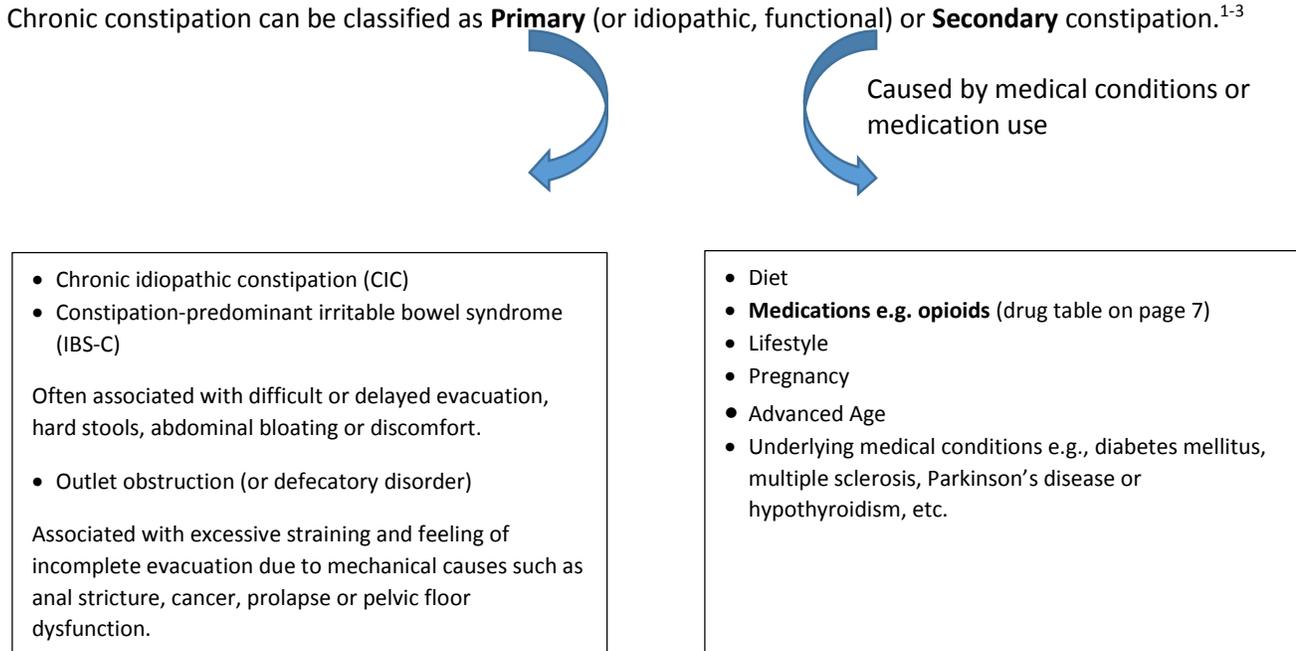
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Introduction

The Peripherally Acting Mu-Opioid Receptor Antagonists For Opioid-Induced Constipation were reviewed by the Utah Medicaid Pharmacy and Therapeutics Committee [56:92 GI Drugs, Miscellaneous: Methylnaltrexone (Relistor®), Naloxegol (Movantik®)] in December 2015. The necessity for clinical criteria was highlighted during the meeting. It was reported and discussed that these agents offer an additional treatment option for patients with opioid-induced constipation i.e. in patients with opioid-induced constipation with an inadequate response to laxatives (i.e. stimulant laxative and osmotic laxative/stool softener), and that these agents reverse the effects of opioids on receptors within the enteric nervous system producing laxation in ~50% of patients in clinical trials. The fact that only ~50% of patients respond well to this therapy may reflect the multi-factorial cause of constipation in many patients with chronic pain.

Chronic constipation can be classified as **Primary** (or idiopathic, functional) or **Secondary** constipation.¹⁻³



Opioid-induced constipation (OIC) is one of the most common side effects of chronic use of opioid analgesics (affects nearly all patients taking opioid treatment) and it will persist unless treated.^{4,5} It is “caused by opioid-mediated reductions in small intestinal and colonic transit, increased fluid absorption, inhibition of gastrointestinal chloride secretion, and stimulation or decreased relaxation of the pyloric and internal anal sphincters.”⁶⁻¹⁰ The exact prevalence of opioid-induced constipation is not known. “In a systematic review of eight studies, opioid-treated patients with noncancer pain reported constipation as the most frequent adverse effect, experienced by 41% compared with 11% of placebo-treated patients.”^{11,12} The consensus article of recommendations of the American Academy of Pain Medicine reports that OIC has been reported in up to 47% of opioid-treated patients.^{6,13} “In palliative care, OIC is suffered by 30-50% of patients.”^{12,14} Others report that prevalence of opioid-induced constipation in non-malignant patients treated with opioids, ranges from 15-81% and increases with duration of use.^{11,15-18} Symptoms are often severe and up to a third of patients stop their opioid in order to have a bowel movement.^{19,20,11,13,16,21-23,66,67} Others have also reported higher prevalence in cancer patients receiving opioids for pain, opioid-induced constipation is estimated to occur in >85% of patients and in those receiving palliative-care it exceeds 94%.^{24,25, 26-33} Opioid-induced constipation is not dose related, occurs both with short and long term use of opioids, but the greatest risk factor is a longer duration of opioid therapy, and patients do not develop tolerance to this constipating effect

(unlike to other effects of opioids).³⁴ Older patients or women may be more prone to OIC.^{6,35} Also, opioid-related adverse effects may be increased in patients with cancer-related pain and renal impairment.³⁶

Lifestyle changes and over-the-counter drugs are first-line treatments for OIC.¹² However, many opioid-treated patients experience refractory constipation and require additional treatment options.¹² Pharmacologic strategies to treat OIC include a bowel regimen with a stool softener and motility agent, prosecretory agents (e.g. lubiprostone), prokinetic agents (e.g. prucalopride), and opioid receptor antagonists.³⁶ Currently available opioid receptor antagonists include naloxegol, methylnaltrexone, alvimopan, and naloxone.³⁷ Naloxegol, methylnaltrexone, and alvimopan are peripherally-acting mu-opioid receptor antagonists (PAMORAs) that selectively target μ -opioid receptors in the gastrointestinal tract³⁸ which causes an increase in intestinal secretion and motility,³⁹ offering the reversal of OIC with limited central nervous system permeability.³⁷ This decreases the likelihood of causing opioid withdrawal or loss of opioid analgesic efficacy. These agents are often used in the treatment of refractory OIC.³⁷ A combination formulation of prolonged release naloxone which has limited systemic absorption and oxycodone is also used for OIC, but this use is only included on Canadian labeling and not on U.S. labeling.³⁸

“Until recently, PAMORAs were restricted to subcutaneous route (SubQ) or to narrow patient populations.”⁴⁰ Alvimopan (Entereg) SubQ currently has a narrow indication for post-operative ileus⁴¹ and is not available on an outpatient basis,³⁷ which limits its overall potential utilization. Methylnaltrexone was the first opioid receptor antagonist approved specifically for OIC, and was shown in a systematic review to be effective in inducing laxation in patients with OIC and where conventional laxatives have failed.⁴² Methylnaltrexone (Relistor) SubQ is indicated for opioid-induced constipation with chronic non-cancer pain, and opioid-induced constipation in patients with advanced illness receiving palliative care after failing laxative therapy.⁴³ Patients using methylnaltrexone experienced more flatulence and dizziness, and no evidence of opioid withdrawal was noted. A serious adverse event occurred where a patient receiving methylnaltrexone experienced severe diarrhea resulting in dehydration and cardiovascular collapse.⁴² Naloxegol (Movantik) is the first orally dosed PAMORA indicated for the treatment of OIC in noncancer patients.^{34,40,44} Naloxegol is composed of naloxone conjugated with a polyethylene glycol (PEG) polymer, which limits its ability to cross the blood-brain barrier.⁴⁵ “When administered at the recommended dose, naloxegol functions peripherally in tissues such as the GI tract, thereby decreasing the constipation associated with opioids.”^{45,46}

Opioid-induced constipation impairs effectiveness of pain management (e.g. non-compliance), causes poor quality of life (QoL; eg. worries and concerns, physical discomfort, psychosocial discomfort), reduces work productivity, and can lead to potentially severe consequences including fecal impaction, bowel obstruction, and bowel perforation.^{6,15,27,34,47,48} According to a recent review (Webster 2015), “close to one-half of patients on long-term opioids experience OIC and, of those, fewer than half get adequate relief from conventional treatment with laxatives.”^{11,12,14,27,49} It is important to manage opioid-induced constipation effectively to reduce office visits, specialty referrals, hospital admissions, and surgical procedures.⁵⁰ This would ultimately lead to a reduction of costs and improved patient quality of life. Webster reported that the economic burden of OIC in higher total healthcare costs is significant compared with non-opioid-treated patients.¹²

In December 2015, the Utah Medicaid P&T committee passed a motion that the agents in this class indicated for opioid-induced constipation (methylnaltrexone and naloxegol) appear to be equally safe and effective, and to include these agents on the PDL as non-preferred until clinical criteria are in place. Utah Medicaid has a prior authorization in place for Relistor (methylnaltrexone) which require that the patient must be receiving opioids as part of a palliative care regimen for advanced illness and documented trial and failure of conventional laxative therapy (also, minimum age requirement 18 years old, diagnosis of opioid induced constipation, rule out mechanical GI obstruction; authorization 4 months).⁵¹ The aim of this review is to ensure appropriate use of naloxegol (Movantik).

Methodology

The Agency for Healthcare Research and Quality (AHRQ; www.guideline.gov), Cochrane Library, the FDA website (including product labeling information), PubMed, UpToDate, Micromedex, Lexicomp, the Institute for Clinical and Economic Review (ICER) website, and the National Institute for Health and Clinical Excellence (NICE) website, were searched for systematic reviews, clinical trials, guidelines, other reports, reviews, efficacy and safety information. As per the hierarchy of evidence, high quality systematic reviews and evidence based guidelines were searched for first, followed by phase 3 randomized controlled trials.

Treatment options

Appendix 1 contains summary tables containing information on the peripheral acting Mu-opioid antagonists (including naloxegol), pure opioid antagonists, prokinetic agents, and common OTC products for the treatment of constipation. The opioid receptor antagonists and prokinetic agents are used for the treatment of refractory OIC.³⁷

Existing treatment standards / First-line agents (well-tolerated and readily available)⁵²

For most people the first critical step in the management of constipation is lifestyle and dietary modification. It is important to conduct a thorough history and physical examination to determine the etiology of constipation so that patients can be treated appropriately. Opioid-induced constipation is typically treated with stimulant laxatives and stool softeners. The recently published consensus article (November 2015) on recommendations of the American Academy of Pain Medicine reports that “existing treatment standards for OIC suggest that opioid rotation, increased fluid and fiber intake, exercise, and over-the-counter (OTC) stool softeners, natural dietary supplements, and laxatives should be considered before evaluating a patient’s need for prescription medications.”^{6,53-56} However, <50% of patients experiencing OIC may achieve their desired treatment outcomes with these first-line treatment options.^{12,49}

Prescription treatments

Peripherally acting mu opioid receptor antagonists may be a treatment option for some patients. Opioid receptor antagonists block the opioid analgesic action on peripheral opioid receptors which causes an increase in intestinal secretion and motility.³⁹ These agents specifically target the opioid receptor-mediated mechanism of OIC (unlike the existing treatment standards mentioned above).

Additionally, the prokinetic agents, lubiprostone and linaclotide, are used in the pharmacological management of OIC.³⁷

The safety and effectiveness of naloxegol, and its potential place in therapy with regards to the other agents in this class, the traditional laxatives (e.g. senna), and miscellaneous laxatives or secretagogues (linaclotide and lubiprostone) is discussed in this report.

Medications specifically FDA-approved for the treatment of opioid-induced constipation in adult patients with chronic noncancer pain include naloxegol (Movantik; oral tablet), methylnaltrexone (Relistor; SubQ), and lubiprostone (Amitiza; oral capsule).

There are additional PAMORAs in **clinical development**¹²:

- Phase 3: Oral (once-daily) Axelopran (TD-1211)⁵⁷
- Phase 3: Oral (once-daily) Naldemedine^{4,58}
- Phase 2: Oral Dolcanatide (SP-333)⁵⁹

Bevenopran phase 3 trials were terminated in 2014.⁶⁰

Off-label use

Currently, use of medications other than naloxegol (Movantik; oral tablet), methylnaltrexone (Relistor; SubQ), and lubiprostone (Amitiza; oral capsule) for the treatment of opioid-induced constipation in adult patients with chronic noncancer pain, would constitute off-label use.

No off-label uses are documented in Micromedex for naloxegol (Movantik) or methylnaltrexone.⁶¹ Micromedex lists opioid-induced bowel dysfunction and postoperative ileus following hysterectomy as non-FDA-approved uses of alvimopan.⁶²

Rodriguez (2014) reviewed the off-label uses of alvimopan (FDA-approved for postoperative ileus after surgeries that include partial bowel resection with primary anastomosis) and methylnaltrexone (at the time of the review FDA-approved for opioid-induced constipation (OIC) in patients with advanced illness who are receiving palliative care and are not responsive to laxative therapy).⁶³

“Literature describing the off-label use of alvimopan in the treatment of OIC and of methylnaltrexone in postoperative ileus was reviewed and included retrospective studies and prospective Phase II-IV trials. Randomized controlled trials did not demonstrate consistent benefit of alvimopan in OIC nor of methylnaltrexone in postoperative ileus. A greater proportion of patients receiving alvimopan for OIC experienced severe adverse cardiovascular events, leading to a risk evaluation and mitigation strategy and discontinuation of its study in this condition. Data are limited and unreplicated for the off-label use of alvimopan for postoperative ileus in patients undergoing abdominal hysterectomy. Individual studies suggest benefit with methylnaltrexone for OIC in unlabeled populations, including patients with non-cancer-related pain, opioid dependence, opioid sedation, and opioid use after orthopedic surgery; however, confirmatory evaluations have not been performed.”⁶³

Note:

In 2014, the FDA approved the additional indication for methylnaltrexone (Relistor) for the treatment of opioid-induced constipation (OIC) in patients taking opioids for noncancer pain (previously, in 2012, the FDA declined the application and requested more data to support the application).⁶⁴

Hospitalizations

Patients often only seek medical treatment when they are experiencing pain which could be prevented if patients receive preventive treatment for constipation when taking opioids. “In the United States alone, treatment for constipation accounts for more than 2.5 million doctor visits annually.”⁶⁵ “In 2010-11 there were 57,506 hospital admissions due to constipation in England, and in 2011, there were 57 deaths registered in England and Wales due to constipation.”⁴ Abramowitz et al. reported on the prevalence and impact of constipation and bowel dysfunction induced by strong opioids; a cross-sectional survey of 520 patients with cancer pain enrolled at 77 centres in France.²⁷ The authors found that “OIC and opioid-induced bowel dysfunction (OIBD) led to hospitalization (16% of patients), pain (75% of patients), and frequent changes in opioid and laxative treatment.”²⁷ This study was conducted in a selected population of cancer patients and there is a need for further studies in larger populations including non-cancer pain patients.²⁷

Saurabh Sethi, MD, and his group at Harvard have pulled data on all subjects from an 8 million hospital-stay database in which constipation (ICD-9 codes 564.0 to 564.09) was the principal diagnosis (not a comorbidity

of another serious condition), from 1997 to 2010 (the National Inpatient Sample (NIS) Database).⁶⁶ “In 1997, there were 21,190 admissions with a principal diagnosis of constipation; by 2010 this had risen to 48,450 (P < .05). Mean length of stay was statistically unchanged (4.0 days in 2010 vs 3.8 days in 1997; P > .05). However, hospital charges increased 287% (\$7406 in 1997 to \$21,273 in 2010; P < .01).”⁶⁶ The increase in the elderly population does not account for the increase and until further studies are conducted, one can only speculate as to what is causing patients to be admitted more often for constipation.⁶⁶

Jeffrey Hertzberg, MD, MS reported that “patients presenting with severe and painful constipation can resemble those with complete bowel obstruction or even acute abdomen. In the emergency department, staff may feel that the only way to rule out a severe abdominal process is to admit, treat constipation from below, and observe for return of normal bowel function. This is expensive and wasteful—and in the era of hospital-acquired infections, it’s a dangerous modality for treating a simple condition.”⁶⁶

Clinical Guidelines and related evidence

Please refer to appendix 3 for additional information from the guidelines.

In the treatment of constipation, international guidelines (World Gastroenterology Organization, Italian Association of Hospital Gastroenterologists, and Italian Society of Colo-Rectal Surgery) and the American Society of Colon and Rectal Surgeons recommend that non-pharmacologic measures, including increased fluid intake, fiber intake, and physical activity, are tried first to promote defecation, followed by pharmacologic measures.⁶⁷⁻⁶⁹

If non-pharmacologic measures do not promote a normal bowel movement pattern (≥ 3 spontaneous bowel movements per week⁷⁰), then the American Society of Interventional Pain Physicians recommends that OIC be treated with bowel regimens, or laxatives, to promote defecation.⁷¹ According to the VA/DoD clinical practice guideline for management of opioid therapy for chronic pain (2010)³⁵, routinely initiate a stimulant-based bowel regimen (“generally consist of a bowel stimulant and a stool softener as well as general measures, such as increased fluid intake, increased dietary fiber, and adequate exercise”) at commencement of chronic OT, and if possible, reduce or discontinue other drugs that may cause or contribute to constipation. The guidance also states that if the initial regimen is inadequate, mild hyperosmotic, saline, and emollient laxatives may be added, and that bulk-producing laxatives, such as psyllium and polycarbophil, are not recommended and are relatively contraindicated as they may exacerbate constipation and lead to intestinal obstruction in patients with poor fluid intake.³⁵

Constipating Drugs^{1,72}

Adapted from Treatment Options for Constipation (Geriatric Lexi-Drugs)⁷² and Diagnostic Approach to Chronic Constipation in Adults¹

Antacids, especially with calcium*	Guanfacine
Anticholinergics	Iron
Anticonvulsants	Irritant laxatives
Antihistamines	Levodopa
Calcium	Monoamine Oxidase Inhibitors (MAOIs)
Calcium Channel Blockers (CCB’s)	Opioids
Clonidine, Guanabenz	Tricyclic Antidepressants
Diuretics	Vinca alkaloids
Disopyramide	5-HT3 antagonists

*Bold text is common vs less common in other medications

The National Institute for Health and Care Excellence (NICE) Appraisal Committee was informed by clinical experts that people with OIC would use a stimulant laxative and an osmotic laxative before moving on to other treatments such as methylnaltrexone.⁷³ “The clinical experts stated that the decision to move on to

other treatments will depend on the severity of constipation symptoms and the person's own quality of life after using laxatives. The Committee understood that there is no formal treatment pathway for people with OIC. It noted that there was currently limited evidence on which to base any clinical guidelines for OIC, and that what guidance exists is based on clinical consensus rather than study evidence.”⁷³

According to NICE guidance, “Naloxegol is recommended, within its marketing authorisation, as an option for treating opioid induced constipation in adults whose constipation has not adequately responded to laxatives.

- An inadequate response is defined as opioid-induced constipation symptoms of at least moderate severity in at least 1 of the 4 stool symptom domains (that is, incomplete bowel movement, hard stools, straining or false alarms) while taking at least 1 laxative class for at least 4 days during the prior 2 weeks.”⁷³

In palliative care, the NICE guideline⁷⁴ does not currently recommend specific drugs for treatment of constipation. Laxative treatment (to be taken regularly at an effective dose) for all patients initiating strong opioids is recommended. According to their updated evidence (May 2014): “Evidence suggests that mu-opioid receptor antagonists appear to be safe and effective treatments for opioid-induced constipation. However, evidence of the efficacy of these drugs in a palliative care setting, particularly when compared with optimised laxative therapy, is limited.”⁷⁴

“The Canadian Society of Palliative Care Physicians recommends against using stool softeners alone to prevent opioid induced constipation. Stool softeners and motility agents are essential to prevent constipation, for example, Colace 100-300 mg/day + Senokot 2-6 tablets twice daily.”³⁶

The British Columbia Medical Services Commission guidance on Palliative care for the patient with incurable cancer or advanced disease. Part 2: pain and symptom management (2011 Sep 30)⁷⁵ include constipation management strategies. For patients with opioid-induced constipation, oral stimulant and osmotic laxatives are recommended first, and methylnaltrexone can be considered for refractory cases.⁷⁵ “Cancer, GI malignancy, GI ulcer, Ogilvie's syndrome and concomitant use of certain medications (e.g., NSAIDs, steroids and bevacizumab) may increase the risk of GI perforation in patients receiving methylnaltrexone. (Health Canada MedEffect Notice)”⁷⁵

Most recent consensus recommendations

Argoff CE, et al. Consensus Recommendations of the American Academy of Pain Medicine on Initiating Prescription Therapies for Opioid-Induced Constipation (Nov 2015)⁶ Endorsed by the American Gastroenterological Association.⁶

The authors of this recently published Consensus Article state that it highlights the need to consider selected factors before evaluating whether treatment with OIC prescription medication is warranted (not intended to provide specific treatment recommendations).⁶ The article present the views and recommendations of a multidisciplinary consensus panel.

The authors report that no guidelines published to date have provided a specific threshold for initiating pharmacologic prescription therapy.

- 1) **Most effective method for assessing OIC:** The Panel recommends the **Bowel Function Index (BFI)** for assessing OIC.⁶
“The BFI is a simple, clinically responsive, and validated tool with a clear published threshold for constipation.”⁶ The panel states “the BFI may be supplemented with additional outcome measures as necessary on the basis of clinical judgment and individual patient needs.”⁶ It is a 3-item questionnaire

with a 7-day recall-period that is administered by study personnel or clinician to measure constipation from the patient's perspective.⁶

- 2) **The threshold in OIC symptom severity at which to consider initiation of OIC-targeted prescription medications in clinical practice:** The Panel recommends a score of ≥ 30 points on the BFI for consideration of prescription medications in patients with previous or current use of first-line interventions.

Clinical Efficacy

Systematic Reviews & Meta-analyses

The Cochrane Library, Pubmed, and Embase were searched for relevant systematic reviews regarding the use of naloxegol for the treatment of OIC. One Cochrane review (McNicol et al. 2008⁷⁶) and one other review (Ford et al. 2013⁷⁷) were identified in the Cochrane library. One additional systematic review was identified in Pubmed (Siemens, et al. 2015⁷⁸). Reviews before 2008 were not included because more recent systematic reviews had been performed and the included newer agents for OIC. A systematic review (other review in Cochrane Library) evaluating the efficacy and side-effect profiles of lactulose, docusate sodium, and sennosides compared to PEG in opioid -induced constipation was also identified (Ruston et al. 2013⁷⁹). Copies of abstracts have been included in appendix 2.

The systematic review and meta-analysis by McNicol et al. (2008) investigated alvimopan (nine studies), methylnaltrexone (six studies), naloxone (seven studies), and nalbuphine (one study) in the treatment of opioid-induced bowel dysfunction (OBD), which includes constipation, incomplete evacuation, increased acid reflux, and bloating.⁷⁶ They found insufficient evidence for the safety or efficacy of naloxone or nalbuphine. Alvimopan and methylnaltrexone were found to have adverse events similar to placebo and to be better than placebo in treating constipation. Alvimopan seemed to be safe and efficacious in treating postoperative ileus. However, they did not find enough compelling evidence to make firm conclusions regarding opioid antagonists in the treatment of OBD.⁷⁶

A more recent systematic review by Ford et al. (2013) examined the efficacy of opioid receptor antagonists (methylnaltrexone, naloxone, and alvimopan) and prokinetic agents (prucalopride, lubiprostone, and linaclotide).⁷⁷ They identified acceptable studies for methylnaltrexone (six studies), naloxone (four studies), alvimopan (four studies), and prucalopride (one study). Two studies were identified for lubiprostone but were not included in the analyses because of issues with the reporting of the data. No studies of linaclotide in OIC were identified. They concluded that opioid receptor antagonists are safe and effective in the treatment of OIC, and that more data are needed to assess the safety and efficacy of prucalopride and lubiprostone in OIC.⁷⁷

A 2015 systematic review by Siemens et al. (2015) examined methylnaltrexone (seven studies), alvimopan (three studies), naloxegol (three studies), prucalopride (one study), and lubiprostone (two studies).⁷⁸ They found that methylnaltrexone and naloxegol were effective for all objective outcome measures, including increasing bowel movement (BM) frequency, BM within 4 h, and time to first BM. Lubiprostone was effective for all objective outcome measures, but the effect sizes were small to moderate. Naloxone and alvimopan were effective only for the BM frequency measures. Prucalopride was effective for the BM frequency measures. Nausea, diarrhea, and abdominal pain were the most frequent adverse events, except for alvimopan (cardiac events) and prucalopride (severe abdominal pain, headache).⁷⁸

Both stimulant and non-stimulant laxatives are effective compared to placebo, but there is not enough comparative effectiveness evidence to support the use of a particular agent over another.⁸⁰ A review by Mounsey et al. (2015) recommends that the first pharmacological step in the treatment of OIC be the use of OTC products beginning with an osmotic laxative, followed by stool softener plus stimulant laxative if an osmotic laxative is ineffective. They further recommend the use of opioid receptor antagonists if the patient has been unsuccessful with lifestyle modifications and OTC self-care for constipation and they are taking opioids.⁸¹

NICE states that there is insufficient evidence to differentiate the efficacy of naloxegol from methylnaltrexone and naloxone-oxycodone.⁷³

Randomized Controlled Trials (RCTs)

As reported and discussed in the P&T report and meeting in December 2015, pivotal randomized, double-blind, placebo-controlled efficacy trials for naloxegol (KODIAK-04/-05 enrolling a total of 1352 patients)⁸²⁻⁸⁴ document its ability to reverse opioid-induced constipation. A copy of the abstract (Chey WD, et al. 2014⁸⁴) has been included in appendix 2. The primary endpoint was ≥ 3 spontaneous bowel movements per week, efficacy in 9 of 12 weeks (an increase from baseline of ≥ 1 spontaneous bowel movement per week in nine or more of the 12 weeks of study), and efficacy in 3 of the final 4 weeks of the study period. Naloxegol demonstrated statistical superiority compared to patients treated with placebo, and the improvement was similar in patients who reported failure with laxatives in the past and regardless of daily opioid dose.⁸³ The most consistent efficacy of naloxegol was seen with the 25 mg dose once daily.⁸⁵ In the pivotal phase III trials, “response rates were significantly higher with 25 mg of naloxegol than with placebo (intention-to-treat population: study 04, 44.4% vs. 29.4%, $P=0.001$; study 05, 39.7% vs. 29.3%, $P=0.02$; patients with an inadequate response to laxatives: study 04, 48.7% vs. 28.8%, $P=0.002$; study 05, 46.8% vs. 31.4%, $P=0.01$); in study 04, response rates were also higher in the group treated with 12.5 mg of naloxegol (intention-to-treat population, 40.8% vs. 29.4%, $P=0.02$; patients with an inadequate response to laxatives, 42.6% vs. 28.8%, $P=0.03$).”⁸⁴ “A shorter time to the first postdose spontaneous bowel movement and a higher mean number of days per week with one or more spontaneous bowel movements were observed with 25 mg of naloxegol versus placebo in both studies ($P<0.001$) and with 12.5 mg of naloxegol in study 04 ($P<0.001$). Pain scores and daily opioid dose were similar among the three groups.”⁸⁴

Safety

“The most common adverse reactions in clinical trials ($\geq 3\%$) are: abdominal pain, diarrhea, nausea, flatulence, vomiting, and headache.”⁴⁴ “The majority of gastrointestinal adverse reactions are graded as mild to moderate, occur early in treatment and resolve with continued treatment.”⁷³ In the phase III pivotal trials adverse events (primarily gastrointestinal) occurred most frequently in the groups treated with 25 mg of naloxegol.⁸⁴

Based on current evidence, naloxegol and other PAMORAs act peripherally without affecting the central nervous system. However, it is recommended that use be avoided in patients with conditions that compromise the blood brain barrier until safety can be demonstrated due to potential for serious withdrawal and reversal of analgesia.¹²

Naloxegol and methylnaltrexone are contraindicated in patients with impaired structural integrity of the GI tract based on methylnaltrexone data. In reviewing post-marketing, Adverse Event Reporting System (AERS) data, reflecting approximately one year of usage (4/08 to 10/09), Mackey identified 7 cases of

gastrointestinal perforation in patients receiving methylnaltrexone. Each patient had a pathological or anatomic abnormality in the upper or lower GI tract, including; metastatic colon cancer with previous hemicolectomy, peptic ulcer, bevacizumab use, volvulus, ALS, peptic ulcer and bowel obstruction. Abdominal pain preceded perforation in four of patients and occurred following the first dose in four patients.⁸⁶

Naloxegol is metabolized through the CYP 3A4 and is contraindicated in combination with strong CYP3A4 inhibitors due to the potential for increased exposure to naloxegol and the risk of opioid withdrawal reactions. It is recommended to avoid concomitant use of naloxegol with moderate CYP3A4 inhibitors, grapefruit products, or CYP3A4 inducers.⁴⁴

Long-term safety over 52 weeks has been reported (KODIAK-08 Randomized, open-label, multicenter, safety and tolerability extension trial).^{83,87} Gottfridsson C, et al. (2013) reported on the evaluation of the effect of naloxegol on cardiac repolarization. A randomized, placebo- and positive-controlled crossover QT/QTc study was conducted (52 healthy men were enrolled; mean age 28 years), according to International Conference on Harmonisation E14 guidelines, to characterize the effect of naloxegol on cardiac repolarization.⁸⁸ The authors concluded that “naloxegol at 25 and 150 mg was not associated with QT/QTc interval prolongation in these healthy men, and at the proposed therapeutic dose of 25 mg/d, naloxegol is not expected to have a clinically relevant effect on cardiac repolarization in patients with OIC.”⁸⁸ A copy of abstracts have been included in appendix 2.

Naloxegol's place in therapy and potential criteria to be reviewed

Factors and limitations to consider:

- **Diagnosis (OIC):** In March 2015, a multidisciplinary consensus panel organized through the American Academy of Pain Medicine Foundation (AAPMF) endorsed the OIC definition of another multidisciplinary consensus group: “a change from baseline bowel habits upon initiation of opioids that is characterized by any of the following symptoms:
 - Reduced bowel movement frequency
 - Development or worsening of straining to pass stool
 - A sense of incomplete rectal evacuation
 - Harder stool consistency”^{12,39}OIC may develop soon after opioid treatment initiation so this definition without a timeframe is useful.¹² It also allows subjective reporting.¹² The AAPMF endorsed the Bowel Function Index (BFI) as the best method suited for assessing OIC in most clinical settings.^{12,89} The BFI is a patient-reported outcome tool concerning ease of defecation, incomplete evacuation, and patients’ judgment of constipation.¹²
- **Differential diagnosis:** A consultation with a gastroenterologist may be useful. Comorbid or underlying conditions should be excluded e.g. obstructing colon cancer, dyssynergic defecation, large rectocele, Parkinson’s disease, or diabetes.
- **Other drugs could have an additive constipating effect** including anticholinergics, drugs with anticholinergic activity e.g. tricyclic antidepressants, iron supplements and others (see table on page 7) - Consider alternatives where possible or reducing doses of other constipating drugs (if appropriate).
- **Switching of opioid?** There is some evidence and reports available that some opioids (e.g. transdermal opioids⁹⁰) cause less OIC than others possibly due to unique properties of the drugs or no contact with GI mucosa. Less OIC was reported with transdermal opioids in a systematic review (Tassinari et al.) of transdermal opioids compared to long-acting morphine.^{12,91} However, the Centre for Reviews and Dissemination (CRD) states that “Due to limitations including questionable trial quality, low sample numbers, and inconsistency in some analyses, these conclusions require cautious interpretation.”⁹² Cook et al. (population-based survey) reported that prevalence of constipation was relatively low for tramadol

(17%) and for propoxyphene (21%).⁹³ In contrast, Cook et al. report the prevalence of constipation for other opioids that are more commonly associated with OIC (with morphine as the most commonly associated with OIC): 67% of patients receiving morphine, 38% of patients receiving oxycodone, 34% of patients receiving codeine, and 32% of patients receiving hydrocodone had OIC.^{12,48,93} However, several factors could affect results of OIC prevalence reports including opioid dosage, variable methodologies, and constipation therapy (type and amount).¹²

- **Adjusting dose(s) of OTC laxatives:** It is reported that many patients will improve after adjusting doses of OTC laxatives. Also, it is important to ensure a trial of 2 or more laxative agents including a stimulant laxative, such as senna or bisacodyl. Coyne et al. for example evaluated opioid-induced constipation in patients with chronic noncancer pain in the USA, Canada, Germany, and the UK (descriptive analysis of baseline patient-reported outcomes and retrospective chart review) and found that “prevalence of inadequate response to one laxative agent was 94%; inadequate response to two or more agents from at least two different laxative classes was 27%.”⁵⁵
- **Refractory OIC:** The mechanism of OIC is different from idiopathic or functional constipation. Laxatives do not counter the pharmacologic mechanism of opioid-induced constipation so are often ineffective and patients may need alternative treatment options. The peripherally acting mu-opioid receptor antagonists (PAMORAs) displace opioids from the receptors in the GI tract.
- **Indication & effectiveness of naloxegol:** “Naloxegol is an opioid antagonist indicated for the treatment of opioid-induced constipation in adults with chronic noncancer pain. Significantly more patients responded to naloxegol therapy (40% to 44%) compared with placebo (29%) for the treatment of opioid-induced constipation in 2 large randomized 12-week trials.”⁶¹
- **Opioid receptor antagonists as a class:** Currently available opioid receptor antagonists include naloxegol, methylnaltrexone, alvimopan, and naloxone.³⁷ Of the available opioid receptor antagonists, naloxegol, methylnaltrexone, and alvimopan are the only ones with limited central nervous system permeability,³⁷ which decreases the likelihood of causing opioid withdrawal or loss of opioid analgesic efficacy. Alvimopan currently has a narrow indication for post-operative ileus⁴¹ and is not available on an outpatient basis,³⁷ which limits its overall potential utilization.
- **Place in therapy:** Naloxegol is not an appropriate initial therapy option. The Movantik (naloxegol) FDA product label does not include failure on a laxative, but its UK marketing authorisation is for treating opioid-induced constipation (OIC) in adults whose constipation has had an inadequate response to laxative(s).^{44,73} “The UK summary of product characteristics defines an inadequate response to laxatives as concurrent symptoms of OIC of at least moderate severity while taking at least 1 laxative class for a minimum of 4 days during the last 2 weeks.”⁷³ “The European public assessment report for naloxegol provides further clarification regarding the definition of an inadequate response to laxatives. It states that a person must have been taking 1 laxative class for a minimum of 4 days out of the 14 days prior to the screening visit and report moderate, severe, or very severe symptoms in at least 1 of the 4 stool symptom domains.”⁷³ Bruner et al. report that studies have suggested the efficacy of naloxegol “in patients failing traditional constipation treatments; however, insufficient evidence exists to establish its role in primary prevention of OIC at this time.”⁴⁰ “No evidence exists to recommend one laxative over another.”^{12,39} Fiber/bulking agents are not recommended^{12,94} or should be used with caution in OIC as they can cause fecal impaction and intestinal obstruction with inadequate fluid intake^{95,96} Naloxegol’s oral route of administration, flexibility of use and safety makes it a useful treatment option. Data comparing naloxegol’s efficacy to other agents in attenuating OIC is lacking (no comparative trials and individual drug studies have different methodologies i.e. clinical endpoints and analyses).⁹⁷
- **Adherence:** Insufficient relief of OIC may cause patients to reduce or stop their opioid therapy to relieve their constipation which results in undertreated pain (trying to balance their pain control with their constipation).^{40,48}
- **How is it different from naloxone?** Naloxegol consists of a PEG molecule attached to naloxone which prevents it from crossing the blood-brain barrier.⁷³

- **Comparator(s):**
 - a) Methylnaltrexone is in the same class (Peripheral Acting Mu-opioid Antagonists) and it has the same indication so it is a relevant comparator, but it is administered subcutaneously. The NICE Appraisal Committee was informed that “naloxegol would be an alternative to methylnaltrexone and would be similarly positioned in the treatment pathway after treatment with a stimulant and osmotic laxative has failed.”⁷³ The NICE technology appraisal [TA277] of methylnaltrexone for treating opioid-induced bowel dysfunction in people with advanced illness receiving palliative care was terminated and it is stated that NICE is unable to recommend the use in the NHS of methylnaltrexone for treating opioid-induced bowel dysfunction in people with advanced illness receiving palliative care because no evidence submission was received from the manufacturer of the technology.⁹⁸
 - b) Oxycodone-naloxone combination is not approved in the US, and the NICE Appraisal Committee was informed that it is not used frequently in the UK because of the fixed-ratio combination making it impossible to titrate oxycodone without titrating naloxone.⁷³
 - c) Alvimopan oral tablets is in the same class (Peripheral Acting Mu-opioid Antagonists), but cannot be considered a relevant comparator because it has a different indication (Post-operative ileus) and it has a black box warning that it is for short term hospital use only, because an increased incidence of myocardial infarction was reported in a long term clinical trial.
- **Other treatments with different mechanisms indicated in the treatment of OIC:**
 - Lubiprostone (Amitiza; oral capsule) is a “bicyclic fatty acid that acts locally at the apical portion of the intestine as a chloride channel activator, specifically ClC-2, thereby increasing intestinal fluid secretion and intestinal motility. When used for opioid induced constipation, activation of apical ClC-2 channels bypasses the antisecretory action of opiates resulting from suppression of secretomotor neuron excitability. ClC-2 activation does not alter serum sodium or potassium concentrations.”⁹⁹ It is indicated in the treatment of chronic idiopathic constipation; treatment of opioid-induced constipation with chronic non-cancer pain; and treatment of irritable bowel syndrome with constipation in adult women.⁹⁹ Lubiprostone is not recommended in patients treated with diphenylheptane opioids such as methadone or propoxyphene because the effects of lubiprostone are reduced in a dose-dependent manner by these opioids.^{12,100}
 - Currently, apart from naloxegol, methylnaltrexone and lubiprostone, use of any other medications for the treatment of opioid-induced constipation in adult patients with chronic noncancer pain, would constitute off-label use.
 - Linaclotide is currently approved in the United States for the treatment of adults with IBS-C or CIC, and not for the treatment of OIC. However, its effectiveness in the treatment of OIC is currently being evaluated in phase II trial(s). It has been reported that Ironwood and Allergan will make a decision regarding advancement of the OIC program following a review of results from the linaclotide colonic release Phase IIb trial in adults with IBS-C and continued analysis of the full commercial opportunity (data from the linaclotide colonic release Phase IIb trial is expected in the second half of 2016).¹⁰¹ “Linaclotide and its active metabolite bind and agonize guanylate cyclase-C on the luminal surface of intestinal epithelium. Intracellular and extracellular cyclic guanosine monophosphate (cGMP) concentrations are subsequently increased resulting in chloride and bicarbonate secretion into the intestinal lumen. Intestinal fluid increases and GI transit time is decreased. Increased extracellular cGMP may decrease visceral pain by reducing pain-sensing nerve activity.”¹⁰²
 - Prucalopride (a new, selective 5-HT₄) agonist and enterokinetic) is approved in other countries for chronic constipation (in adults in whom laxatives fail to provide adequate relief), but not in the US.^{6,103} It has been evaluated in patients with noncancer pain and OIC and the authors concluded that in this population with OIC, prucalopride improved bowel function and was safe and well tolerated (phase II double-blind, placebo-controlled study of 196 patients; 4 weeks).^{6,104}

- **Special Populations:**
 - **Pediatrics:** Safety and effectiveness of Movantik in this population has not been established.
 - **Geriatrics:** “Gerontological guidelines recommend the use of opioids after acetaminophen for pain management in elderly patients owing to the risks associated with traditional nonsteroidal anti-inflammatory drugs (eg, gastrointestinal toxicity, exacerbation of renal failure, cardiovascular effects).”^{48,105,106} In this population it is important to consider that constipation could also be related to or OIC worsened by other medications (also age-related physiologic changes that affect drug distribution and elimination and decreased hepatic and renal function that affect drug metabolism and excretion), comorbidities, immobility, or lack of adequate hydration (which is very often an issue with elderly patients).⁴⁸ Stimulant laxatives may not be appropriate in some elderly patients due to an increased risk for hypokalemia.^{48,107}
 - **Comorbidities:** Patients with certain medical conditions (eg, Parkinson disease, supranuclear palsy) may be at increased risk for aspiration of polyethylene glycol-balanced electrolyte solution (osmotic laxative).^{48,107}
 - **Pregnancy:** Movantik - Category C (should only be used if the potential benefit justifies the potential risk). There are no adequate or well-controlled studies in pregnant women.⁴⁴
 - **Breastfeeding:** Discontinue Movantik or discontinue breastfeeding (unknown whether present in human milk, but present in rat milk and is absorbed in rat pups; potential for opioid withdrawal in infant and other serious adverse effects).⁴⁴
- **Adverse effects/Safety:** Refer to safety section and appendix 1. “Adverse events were mainly gastrointestinal in origin and usually transient and mild. There were no signs of opioid withdrawal in the studies. Safety and tolerability were also shown in a long-term safety study.”⁸⁵ It is also important to consider that complications and adverse effects can occur with OIC e.g. “dyspepsia, reflux, bloating, spasm, cramping, fecal impaction, urinary obstruction or infection, pain, hospitalizations, lessened quality of life, and interference with the pain treatment regimen.”¹² Currently, there is no evidence supporting use of naloxegol beyond 12 months or validating superiority over other pharmacologic therapies.
- **Dependence:** No risk of abuse. It is a peripherally acting opioid antagonist that does not cross the blood brain barrier and therefore does not cause CNS effects and is not addictive. The DEA therefore reclassified it from its original Schedule II drug classification to prescription drug.
- **Duplication of therapy/Concomitant use:**
 - Potential for additive effects with other opioid antagonists

Utah Medicaid Utilization Data

OIC AGENTS - FFS Patients*

Generic	Brand	1/1/2012 - 12/31/2012		1/1/2013 - 12/31/2013		1/1/2014 - 12/31/2014		1/1/2015 - 12/31/2015	
		RX	PT	RX	PT	RX	PT	RX	PT
Methylnaltrexone Bromide	Relistor Subcutaneous Injection 08MG/0.4ML	0	0	0	0	0	0	0	0
Methylnaltrexone Bromide	Relistor Subcutaneous Injection 12MG/0.6ML	2	1	2	2	0	0	0	0
Methylnaltrexone Bromide	Relistor Subcutaneous Injection Kit 12MG/0.6ML	0	0	2	1	0	0	0	0
Naloxegol Oxalate	Movantik Tablet 12.5MG	0	0	0	0	0	0	0	0
Naloxegol Oxalate	Movantik Tablet 25.0MG	0	0	0	0	0	0	7	6

* PRESCRIPTION CLAIMS FOR UTAH MEDICAID PATIENTS IN ALL COUNTIES, WITH NO HISTORY OF ACO ENROLLMENT

OIC AGENTS - All Patients

Generic	Brand	1/1/2012 - 12/31/2012		1/1/2013 - 12/31/2013		1/1/2014 - 12/31/2014		1/1/2015 - 12/31/2015	
		RX	PT	RX	PT	RX	PT	RX	PT
Methylnaltrexone Bromide	Relistor Subcutaneous Injection 08MG/0.4ML	0	0	1	1	0	0	0	0
Methylnaltrexone Bromide	Relistor Subcutaneous Injection 12MG/0.6ML	4	3	2	2	0	0	6	2
Methylnaltrexone Bromide	Relistor Subcutaneous Injection Kit 12MG/0.6ML	0	0	2	1	0	0	0	0
Naloxegol Oxalate	Movantik Tablet 12.5MG	0	0	0	0	0	0	4	3
Naloxegol Oxalate	Movantik Tablet 25.0MG	0	0	0	0	0	0	51	24

A. Concurrent opioid use

OPIOIDS			2012		2013		2014		2015
Patients who filled a prescription for an opioid, defined as AHFS class code 28080800, within 30 days of filling a prescription for Naloxegol.		0	0%	0	0%	0	0%	22	81%
TOTAL PATIENTS USING NALOXEGOL		0		0		0		27	

5 Patients (1 FFS patient) filled prescriptions for naloxegol and not for an opioid (through Medicaid claims) within 30 days of filling a prescription for naloxegol.

B. Was a stimulant laxative filled prior to naloxegol?

STIMULANT LAXATIVES			2012		2013		2014		2015
Patients taking both Naloxegol and an opioid, who also filled a prescription for Bisacodyl or Senna within 60 days prior to filling a prescription for Naloxegol.		0	0%	0	0%	0	0%	0	0%
TOTAL PATIENTS USING NALOXEGOL WITH OPIOID		0		0		0		22	

Only includes patients where a medical claim was made for a laxative.

C. Did patients receiving naloxegol have any of the following constipation diagnosis codes submitted whilst filling naloxegol (within 30 days of naloxegol fill)?

ICD-9 BASED DIAGNOSIS*	ICD	2012		2013		2014		2015	
Constipation	5640	0	0%	0	0%	0	0%	0	0%
Unspecified Constipation	56400	0	0%	0	0%	0	0%	3	11%
Slow Transit Constipation	56401	0	0%	0	0%	0	0%	0	0%
Other Dysfunction Constipation	56402	0	0%	0	0%	0	0%	0	0%
Other Constipation	56409	0	0%	0	0%	0	0%	1	4%
Impaction of Intestine	5603	0	0%	0	0%	0	0%	0	0%
Fecal Impaction	56032	0	0%	0	0%	0	0%	0	0%
Other Impaction	56039	0	0%	0	0%	0	0%	0	0%
TOTAL PATIENTS USING NALOXEGOL		0		0		0		27	

* Diagnosis date within 30 days of a Naloxegol prescription fill.

ICD-10 BASED DIAGNOSIS*	ICD	2012		2013		2014		2015	
Other Functional Intestinal Disorders	K59							0	0%
Constipation	K590							0	0%
Unspecified Constipation	K5900							0	0%
Slow Transit Constipation	K5901							0	0%
Outlet Dysfunction Constipation	K5902							0	0%
Other Constipation	K5909							0	0%
TOTAL PATIENTS USING NALOXEGOL								27	

* Diagnosis date within 30 days of a Naloxegol prescription fill.

The ICD-9 diagnosis code¹⁰⁸ **564.09 Other constipation** (Short description: Constipation NEC) converts directly to: 2015/16 ICD-10-CM K59.09 Other constipation.

“Disease Synonyms: Atonic constipation; Chronic constipation; Chronic constipation with overflow; Chronic constipation without overflow; Constipation due to atony of colon (disorder); Constipation due to neurogenic bowel; Constipation due to spasm of colon; Constipation, atonic; Constipation, neurogenic; Constipation, spastic; Drug-induced constipation; Neurogenic constipation; On examination - defecation reflex abnormal – constipated; **Opioid induced constipation in therapeutic use; Opioid induced constipation, therapeutic use;** Spastic constipation”¹⁰⁸

D. Patients that filled prescriptions for naloxegol with constipation diagnosis codes (at any point during the four-year study period)

Patient	Date	Diagnosis	Medication
#1	12/06/12	CONSTIPATION, UNSPECIFIED	
	01/02/13	CONSTIPATION, UNSPECIFIED	
	10/21/13	CONSTIPATION, UNSPECIFIED	
	02/04/14	CONSTIPATION, UNSPECIFIED	
	04/15/14	CONSTIPATION, UNSPECIFIED	
	05/30/14	CONSTIPATION, UNSPECIFIED	
	10/10/15		Movantik Tablet 12.5MG
	11/25/15		Movantik Tablet 12.5MG
#2	08/22/14	CONSTIPATION, UNSPECIFIED	
	10/21/15		Movantik Tablet 25.0MG
	11/20/15		Movantik Tablet 25.0MG
#3	02/24/12	CONSTIPATION, UNSPECIFIED	
	06/09/15		Movantik Tablet 25.0MG
	07/06/15		Movantik Tablet 25.0MG
	07/06/15	CONSTIPATION, UNSPECIFIED	
	07/31/15		Movantik Tablet 25.0MG
	08/03/15	CONSTIPATION, UNSPECIFIED	
	09/03/15		Movantik Tablet 25.0MG
#4	10/24/12	CONSTIPATION, UNSPECIFIED	
	11/07/14	CONSTIPATION, UNSPECIFIED	
	02/17/15	CONSTIPATION, UNSPECIFIED	
	10/08/15		Movantik Tablet 25.0MG
	11/09/15		Movantik Tablet 25.0MG
	12/07/15		Movantik Tablet 25.0MG
#5	07/29/13	CONSTIPATION, UNSPECIFIED	
	10/01/14	CONSTIPATION, UNSPECIFIED	
	10/01/15		Movantik Tablet 25.0MG
	10/25/15		Movantik Tablet 25.0MG
	12/01/15		Movantik Tablet 25.0MG
#6	07/15/14	CONSTIPATION, UNSPECIFIED	
	06/04/15		Movantik Tablet 25.0MG
	08/18/15		Movantik Tablet 25.0MG
#7	08/15/14	CONSTIPATION, UNSPECIFIED	
	09/23/14	CONSTIPATION, UNSPECIFIED	
	11/04/14	CONSTIPATION, UNSPECIFIED	
	02/25/15	CONSTIPATION, UNSPECIFIED	
	10/23/15		Movantik Tablet 25.0MG

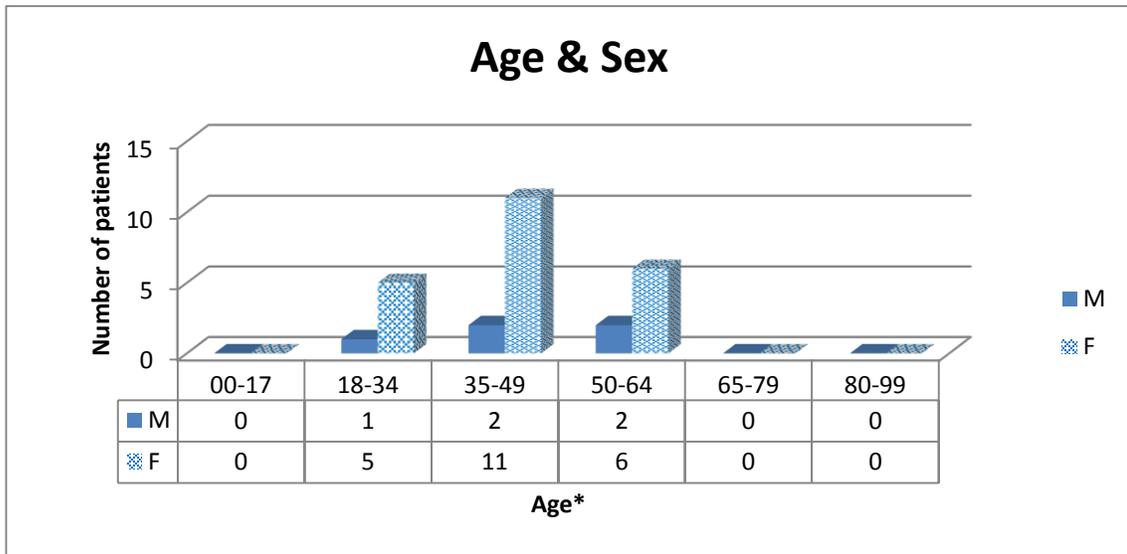
	11/30/15		Movantik Tablet 25.0MG
#8	10/13/12	CONSTIPATION, UNSPECIFIED	
	10/21/15		Movantik Tablet 25.0MG
#9 *	05/15/15	CONSTIPATION, UNSPECIFIED	
	05/19/15		Movantik Tablet 25.0MG
	06/14/15	CONSTIPATION, UNSPECIFIED	
	06/14/15	OTHER CONSTIPATION	
	10/14/15	CONSTIPATION, UNSPECIFIED	
#10	03/02/15	CONSTIPATION	
	04/23/15	CONSTIPATION, UNSPECIFIED	
	07/21/15		Movantik Tablet 25.0MG
	08/20/15		Movantik Tablet 25.0MG
	09/15/15		Movantik Tablet 25.0MG
	10/12/15		Movantik Tablet 25.0MG
	11/09/15		Movantik Tablet 25.0MG
	12/07/15		Movantik Tablet 25.0MG
#11*	08/12/15	CONSTIPATION, UNSPECIFIED	
	08/17/15		Movantik Tablet 25.0MG
#12	07/16/13	CONSTIPATION, UNSPECIFIED	
	11/08/14	CONSTIPATION, UNSPECIFIED	
	12/09/14	CONSTIPATION, UNSPECIFIED	
	02/03/15	CONSTIPATION, UNSPECIFIED	
	07/22/15		Movantik Tablet 25.0MG
#13	09/04/12	CONSTIPATION, UNSPECIFIED	
	02/05/15	CONSTIPATION, UNSPECIFIED	
	11/16/15		Movantik Tablet 12.5MG
#14*	06/26/13	CONSTIPATION, UNSPECIFIED	
	12/16/15		Movantik Tablet 25.0MG
#15	03/09/15	CONSTIPATION, UNSPECIFIED	
	06/04/15		Movantik Tablet 25.0MG
	07/25/15		Movantik Tablet 25.0MG
	10/16/15		Movantik Tablet 25.0MG

*** FFS Patient**

- 3 of the 27 patients (total patients that received naloxegol) had a constipation diagnosis code submitted within 30 days of a naloxegol fill. One patient had 2 different constipation diagnosis codes submitted in the 30-day window.
- 12 of the 27 patients had a constipation diagnosis code submitted at some point during the four-year study period, just not within the 30-day window.
- 12 patients had no record of a constipation diagnosis at any time during the four-year study period.

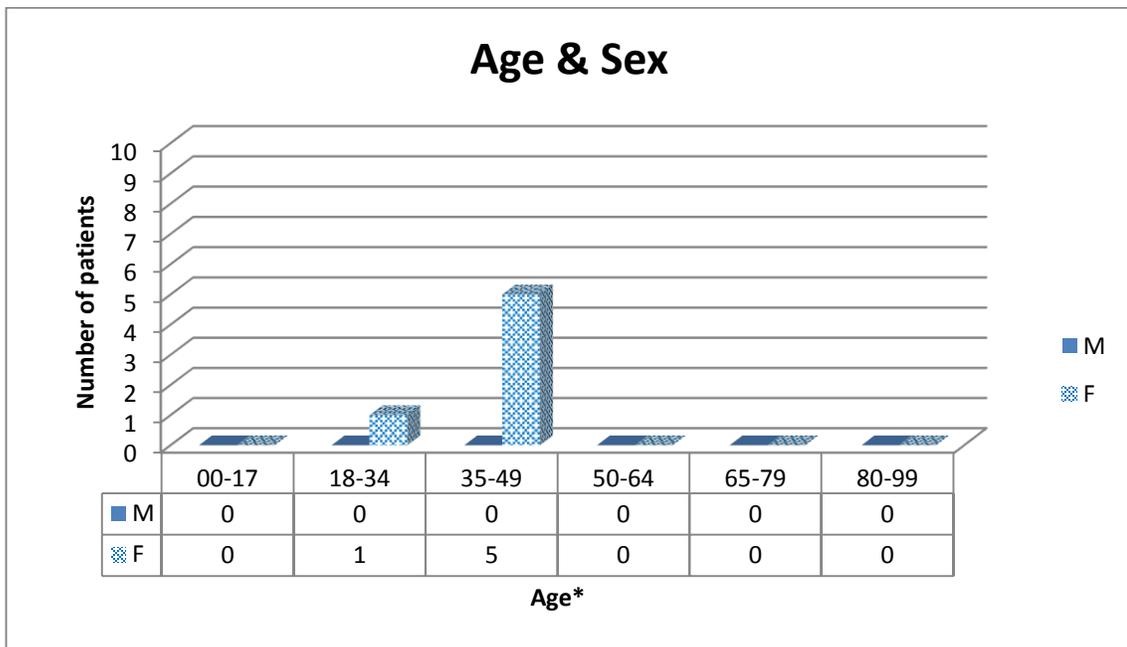
E. Age and Sex of patients that filled prescriptions for naloxegol in the Utah Medicaid population (2012-2015).

a. All patients (27 total; 5 male and 22 female)



* Age at first fill.

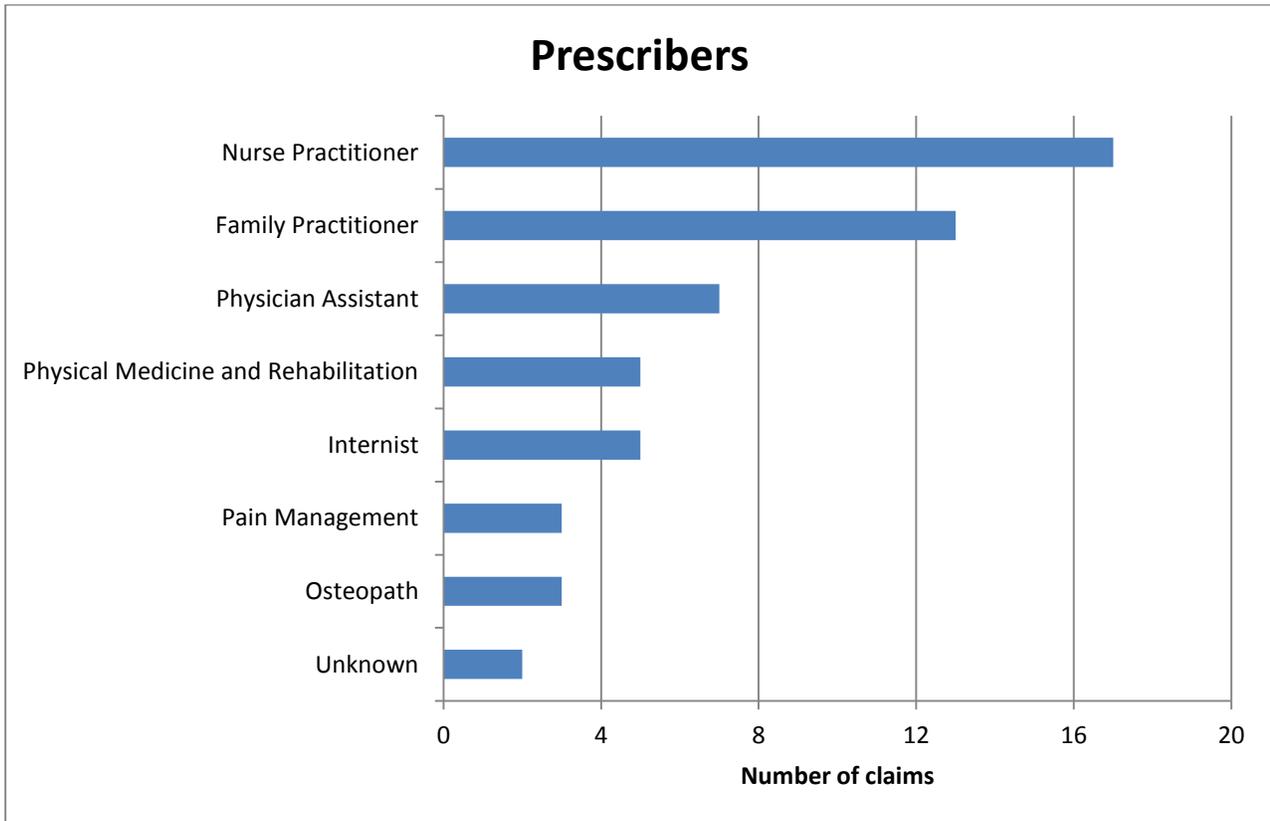
b. FFS patients (6 total; all female)



* Age at first fill.

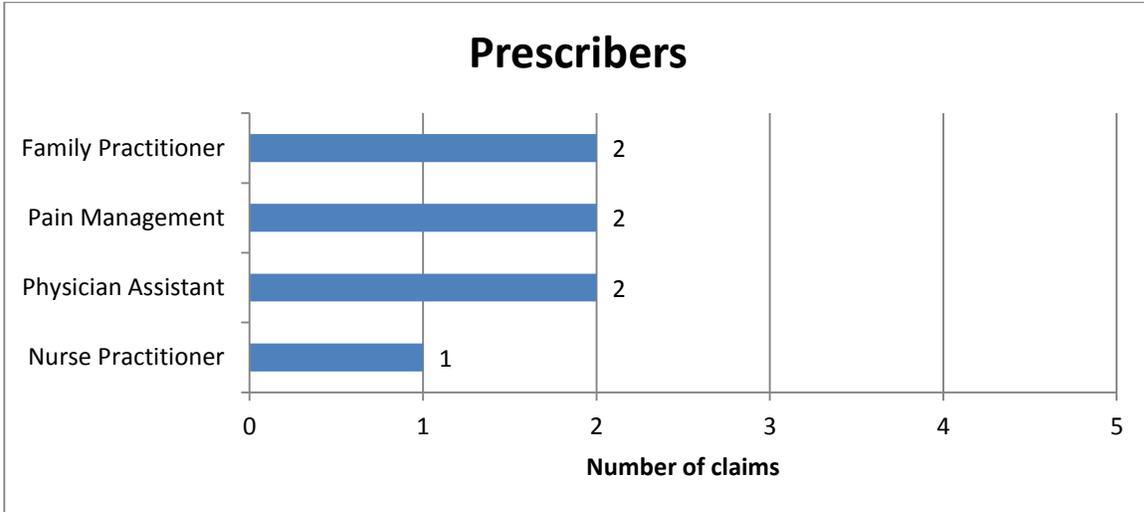
F. Prescribers of naloxegol (2012-2015)

a. All patients (55 claims in total)



PRESCRIBER TYPE	NALOXEGOL ALL CLAIMS 2012-15	
Unknown	2	3.64%
Osteopath	3	5.45%
Pain Management	3	5.45%
Internist	5	9.09%
Physical Medicine and Rehabilitation	5	9.09%
Physician Assistant	7	12.73%
Family Practitioner	13	23.64%
Nurse Practitioner	17	30.91%

b. FFS patients (7 claims in total)



**NALOXEGOL
FFS CLAIMS
2012-15**

PRESCRIBER TYPE		
Nurse Practitioner	1	14.29%
Physician Assistant	2	28.57%
Pain Management	2	28.57%
Family Practitioner	2	28.57%

Conclusions

Preventing and managing OIC properly will improve effectiveness of pain management (compliance), quality of life, work productivity, and reduce healthcare costs including hospital and ER visits (e.g. due to pain associated with OIC or severe consequences including fecal impaction, bowel obstruction, and bowel perforation).^{6,15,27,34,47}

According to a multidisciplinary consensus panel (Recommendations of the American Academy of Pain Medicine on Initiating Prescription Therapies for Opioid-Induced Constipation; Nov 2015⁶; Endorsed by the American Gastroenterological Association⁶), prophylactic and other first-line treatment options (such as opioid rotation, increased fluid and fiber intake, exercise, and OTC stool softeners, natural dietary supplements, and laxatives) are existing treatment standards of care that should be considered before evaluating a patient's need for prescription medications.⁶ It is also important to evaluate and eliminate other drugs that could cause constipation (where appropriate). First-line treatments are well-tolerated and readily available (low cost).^{6,12}

According to the Panel⁶, after prophylactic and first-line interventions have been evaluated, A BFI score of ≥ 30 points should prompt consideration of prescription OIC medications such as PAMORAs or lubiprostone (BFI results can be supplemented with other appropriate assessments if necessary).

Currently, there is insufficient evidence that naloxegol is safer for any duration relative to traditional laxative therapies.²

According to Utah Medicaid Utilization Data:

- Some patients (5/27) did not have a fill history for an opioid within 30 days of receiving naloxegol
- Few patients had diagnosis codes submitted for constipation whilst filling naloxegol
- Prescribers of naloxegol do not include gastroenterologists.

Naloxegol is an additional treatment option for opioid-induced constipation, but it is important to monitor its use and to ensure that it is being used appropriately through prior authorization (PA) criteria as suggested by the Utah Medicaid P&T Committee.

Potential clinical criteria

- Minimum age requirement 18 years old
- Diagnosis code for opioid-induced constipation which could include confirmation of the definition (page 11) and use of the BFI (page 8 & 9) and a score of ≥ 30 points on the BFI
- Rule out mechanical GI obstruction, and other comorbid or underlying conditions - a consultation with a gastroenterologist may be useful.
- Confirmation that patient is not taking other drugs that may cause or contribute to constipation, and that they have been reduced or discontinued if possible.
- Patient must be receiving opioids
- Step therapy: Trial with a stimulant-based bowel regimen (stimulant and stool softener, and general lifestyle changes including increased dietary fiber and fluid intake and regular exercise)
- Quantity limits based on FDA-approved labeling:
 - Movantik (naloxegol): 1 tablet per day => 30 tablets per 30 days

Authorization: 4 months

Re-authorization: Updated letter of medical necessity

Appendix 1 – Drug information

Table 1: Prescribed medications used for the treatment of constipation

Drug information for adults from product labeling^{41,43,44,109-112} and Lexicomp^{45,113-121}

Drug	Brand	Generic	Mechanism of Action	Indications	Dosing	Onset of Action	Adverse Effects	Warnings and Contraindications	Special Considerations										
Peripheral Acting Mu-opioid Antagonists																			
Naloxegol*	Movantik	No	Peripheral acting mu-opioid antagonist; limited BBB permeability	Opioid-induced constipation in chronic non-cancer pain	Oral 25 mg once daily on an empty stomach If not tolerated, reduce dose to 12.5 mg once daily	6 – 12 h	Abdominal pain (12-21%) Diarrhea (6-9%) Nausea (7-8%) Flatulence (3-6%) Vomiting (5%) Headache (4%) Hyperhidrosis (<3%)	-Concomitant use with strong CYP3A4 inhibitors - Gastrointestinal perforations have been reported. Not to be used in patients with known or suspected obstruction -Potential for precipitating opioid withdrawal in patients with disruptions in their blood-brain barrier. Use with caution.	-Not to be used with severe hepatic impairment -Initial dose is 12.5 mg in patients with a CrCl <60 mL/min -Pregnancy risk category C -May precipitate opioid withdrawal in a fetus -Discontinue drug or evaluate risks and benefits with nursing -Potential for additive effects with other opioid antagonists										
Methylnaltrexone	Relistor	No	Peripheral acting mu-opioid antagonist; restricted BBB permeability	Opioid-induced constipation in chronic non-cancer pain -Opioid-induced constipation in patients receiving palliative care and are not responsive to laxative therapy	Subcutaneous Inject one dose every other day as needed in upper arm, abdomen, or thigh Not to exceed more than one dose in a 24-h period <table border="1"> <tr> <td>Weight of adult patient</td> <td>SubQ dose</td> </tr> <tr> <td><38 kg</td> <td>0.15 mg/kg</td> </tr> <tr> <td>38-62 kg</td> <td>8 mg</td> </tr> <tr> <td>62-114 kg</td> <td>12 mg</td> </tr> <tr> <td>>114 kg</td> <td>0.15 mg/kg</td> </tr> </table>	Weight of adult patient	SubQ dose	<38 kg	0.15 mg/kg	38-62 kg	8 mg	62-114 kg	12 mg	>114 kg	0.15 mg/kg	30 min – 1 h	Abdominal pain (21-29%) Flatulence (13%) Nausea (9-12%) Dizziness (7%) Hyperhidrosis (6%) Diarrhea (6%) Hot flash (3%) Tremor (1%)	-Gastrointestinal perforations have been reported. Not to be used in patients with known or suspected obstruction -Discontinue with severe or persistent diarrhea -Symptoms consistent with opiate withdrawal have occurred. Consider risk-benefit profile in patients with disruptions to the blood-brain barrier	-Administer 50% of normal dose in patients with a CrCl <30mL/min -Pregnancy risk category C
Weight of adult patient	SubQ dose																		
<38 kg	0.15 mg/kg																		
38-62 kg	8 mg																		
62-114 kg	12 mg																		
>114 kg	0.15 mg/kg																		
Alvimopan	Entereg	No	Peripheral acting mu-opioid	Post-operative ileus (To accelerate the	Oral Initial: 12 mg administered 0.5-5 h before surgery	Unknown	Hypokalemia (10%) Dyspepsia (2-7%) Anemia (5%)	Black Box Warning For short term hospital use only. Increased incidence	-Pregnancy risk category B -Use with caution in patients recently exposed to opioids.										

	Oral capsule: 12 mg		antagonist; restricted BBB permeability	time to upper and lower GI recovery following surgeries including partial bowel resection with primary anastomosis)	Maintenance: 12 mg twice daily beginning the day after surgery. Not to exceed 15 doses.		Urinary retention (3%) Back pain (3%)	of myocardial infarction seen in a long term clinical trial. -Avoid use in patients who have received therapeutic opioids for >7 consecutive days immediately before use	May be more sensitive to GI adverse effects -Patients of Japanese descent should be more closely monitored for GI-related adverse effects -Use not recommended in patients having gastric or pancreatic anastomosis or complete bowel obstruction -Use not recommended with severe renal or hepatic impairment
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Pure Opioid Antagonists

Naloxone (oral formulation not available) Only for informational purposes – not indicated for OIC	Evzio (injectable)	Yes	Central and peripheral opioid antagonist	-Opioid overdose -Septic shock	Oral Oral doses between 9-24 mg/day (divided) have been used for the treatment of OIC ¹²² IV, IM, SubQ Opioid overdose (with standard ACLS protocols): 0.4 to 2 mg; may need to repeat every 2-3 min. If no response after 10 mg, consider other causes of respiratory depression.	Constipation: Unknown Opioid overdose: 2 min – 1 h depending on route	Observed adverse reactions identified during post-approval use: Hypertension, hypotension, ventricular tachycardia and fibrillation, cardiac arrest, pulmonary edema, dyspnea, opioid-withdrawal syndrome	-Due to a short duration of action relative to opioids, continually monitor the patient and repeat doses as needed -Use in patients who are opioid dependent may precipitate opioid-withdrawal syndrome -In neonates, opioid withdrawal syndrome may be life-threatening -Patients with cardiovascular risk should be monitored in an appropriate healthcare facility	-Pregnancy risk category B -May precipitate opioid withdrawal in a fetus
Oxycodone and Naloxone (Not approved in the US)	Targin	No	Opioid agonist (oxycodone) combined with opioid antagonist (naloxone)	-Management of moderate to severe around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate -Relief of opioid-induced constipation in patients who require an opioid	Oral Oxycodone 5 mg/naloxone 2.5 mg for use in titration or dose adjustments Opioid-experienced patients: Discontinue other opioids and initiate equivalent dose of oxycodone administered equally every 12 hours Opioid-naïve patients: oxycodone 10mg/naloxone 5 mg every 12 hours	Unknown	Withdrawal syndrome (7%) Anorexia (<1-8%) Nausea (3-8%) Hyperhidrosis (7%) Weakness (7%) Vomiting (1-7%) Constipation (3-7%) Fatigue (5%) Headache (5%) Anemia (5%) Decreased hemoglobin (<5%) Peripheral edema (2-5%) Urinary tract infection (4%) Xerostomia (3%)	Black Box Warning May cause serious or life-threatening respiratory depression. Monitor for respiratory depression, particularly at initiation or with a dose increase. -Contraindicated with moderate to severe hepatic impairment, significant respiratory depression, known or suspected paralytic ileus and GI obstruction -May cause CNS depression	-Oxycodone 40 mg/naloxone 20 mg tablets should only be used in opioid-tolerant patients -Do not exceed oxycodone 40 mg/naloxone 20 mg as a single dose or oxycodone 80 mg/naloxone 40 mg as a daily dose -Use with caution with renal impairment -Use with caution in patients with a history of seizure disorders -Use with extreme caution in patients with head injuries -Use with caution in patients with biliary tract dysfunction,

							Depression (2%) Dizziness (2%) Bronchitis (2%) Hyperglycemia (1-2%) Abdominal distention (2%) Gastroenteritis (2%) Viral infection (2%) Influenza (1%) Sinusitis (1%) Migraine (1%) Drowsiness (1%) Increased gamma-glutamyl transferase (1%)	-Patients should report severe or persistent diarrhea lasting >3 days -May cause severe hypotension	including with acute pancreatitis -Use caution with patients with thyroid disorders -Use with caution with adrenocortical deficiency -Pregnancy risk category C -Concomitant use with CYP3A4 inhibitors can increase plasma concentrations. Use with caution.
Prokinetic Agents									
Lubiprostone	Amitiza Oral capsule: 8 mcg 24 mcg	No	Chloride channel activator	-Chronic idiopathic constipation -Irritable bowel syndrome with constipation in women >18 years old -Opioid induced constipation	Oral Chronic idiopathic constipation: 24 mcg twice daily Irritable bowel syndrome: 8 mcg twice daily Opioid induced constipation: 24 mcg twice daily	28 – 48 h	Nausea (8-29%) Diarrhea (7-12%) Headache (2-11%) Abdominal pain (4-8%) Flatulence (4-6%) Abdominal distention (3-6%) Vomiting (3%) Edema (3%) Dizziness (3%) Dyspnea (<1-3%) Fatigue (2%)	-Avoid use in patients with severe diarrhea -Avoid use in patients with bowel obstruction -Dose adjustment should be considered with moderate and severe hepatic impairment	-Dose reductions with moderate and severe hepatic impairment -Pregnancy risk category C -Only approved for irritable bowel syndrome in females >18 years old -Administer with food to decrease nausea
Linacotide	Linzess	No	Guanylate cyclase-C agonist	-Chronic idiopathic constipation -Irritable bowel syndrome with constipation	Oral Chronic idiopathic constipation: 145 mcg once daily Irritable bowel syndrome: 290 mcg once daily	Within one week following consistent use	Diarrhea (16-20%; severe diarrhea: 2%) Abdominal pain (7%) Flatulence (4-6%) Upper respiratory tract infection (5%) Headache (4%) Sinusitis (3%) Abdominal distention (2-3%) Viral gastroenteritis (<3%) Dyspepsia (<2%) Fecal incontinence (<2%)	Black Box Warning -Use is contraindicated in patients <6 years of age. Avoid use in patients 6-17 years of age. Deaths due to dehydration was observed in juvenile animals in nonclinical studies. -May cause diarrhea. Patients should contact their provider if severe diarrhea occurs. Administration with a high-fat meal may worsen diarrhea.	-Contraindicated in patients < 6 years old -Avoid use in patients 6-17 years of age -Pregnancy risk category C

							Gastroesophageal reflux disease (<2%) Vomiting (<2%)		
Tegaserod (Not available in the US since 2015) ¹²³	Zelnorm	No	Serotonin 5-HT4 receptor agonist	-Chronic idiopathic constipation -Irritable bowel syndrome	Oral Chronic idiopathic constipation: 6 mg twice daily before meals Irritable bowel syndrome: 6 mg twice daily before meals	Unknown	Headache (15%) Abdominal pain (12%) Diarrhea (9%; severe <1%) Nausea (8%) Flatulence (6%) Back pain (5%) Dizziness (4%) Migraine (2%) Arthropathy (2%) Leg pain (1%)	-Use in women ≥55 years of age is contraindicated -Use with severe hepatic or renal impairment is contraindicated -Can cause serious cardiovascular events (eg, MI, stroke, or unstable angina).	-Not approved for use in men -Take on an empty stomach 30 min before meals -Pregnancy risk category B
Prucalopride ^{119,124} (Not approved in the US)	Resotran (Canada)	No	Serotonin 5-HT4 receptor agonist	-Chronic idiopathic constipation	Oral Females ≥ 18 years: 2 mg once daily Females >18 years: 1 mg once daily; may increase to 2 mg once daily if necessary	Unknown	Headache (22%) Nausea (17%) Abdominal pain (12%) Diarrhea (12%) Upper abdominal pain (5%) Flatulence (5%) Vomiting (5%) Dyspepsia (3%) Fatigue (3%) Abnormal bowel sounds (2%) Muscle spasm (2%) Palpitation (1%-similar to placebo) Pollakiuria (1%) Anorexia (1%) Gastroenteritis (1%)	-Use with caution in the elderly -Dizziness and fatigue have been observed with initiation of therapy -Consult your provider with severe or persistent diarrhea -Discontinue therapy and consult your provider with severe or worsening of GI symptoms, bloody diarrhea or rectal bleeding -Use with caution in patients with a history of cardiovascular disease	-If no bowel movement within 3-4 days, consider adjunctive laxative therapy -Discontinue use if therapy is not effective within 4 weeks of initiation -Use during pregnancy is not recommended

Other agents evaluated for constipation: misoprostol¹²⁵, colchicine¹²⁶, probiotics^{124,127}, and antidepressants (irritable bowel syndrome-related constipation)^{124,128}

*Naloxegol was previously a DEA schedule II medication due to structure similarities to noroxymorphone despite it having no abuse potential.⁸³ Naloxegol was removed as a DEA controlled medication on January 23, 2015.¹²⁹

Table 2: Common OTC products for the treatment of constipation available in the US

Drug information for adults from Tack and Muller-Lissner (2009)¹³⁰, Lexicomp,¹²¹ and the Handbook of Nonprescription Drugs, 17th Edition¹³¹

Class	Drug	Onset of Action	Adverse Effects
Fiber/Bulking Agents*	Methylcellulose Psyllium Wheat bran	12 – 24 h 24 – 48 h	Abdominal distension, cramping, flatulence
Osmotic Laxatives	Lactulose	24 – 48 h	Bloating, cramping, diarrhea

	Polyethylene glycol	48 h	
	Sorbitol	24 – 48 h	
Saline Laxatives	Magnesium hydroxide Magnesium citrate Oral Sodium phosphate liquid	30 min – 3 h 30 min – 3h	Cramping, dehydration, and electrolyte disturbances
Stool Softeners	Docusate	24 – 72 h	Diarrhea, abdominal cramping
Stimulant Laxatives	Bisacodyl Sennosides	15 min – 1 h 6 – 10 h	Abdominal discomfort, cramping

- *Fiber/bulking agents should be used with caution in OIC as they can cause fecal impaction and intestinal obstruction with inadequate fluid intake^{95,96}
- Phosphate enemas are contraindicated in patients with renal failure.⁷⁵
- Rectal interventions (enemas, suppositories, manual evacuation) are contraindicated when there is potential for serious infection (neutropenia) or bleeding (thrombocytopenia), or when there is rectal/anal disease.⁷⁵

Appendix 2 – Systematic review(s), other reviews, and trials

Cochrane Systematic Review(s)

McNicol ED, Boyce D, Schumann R, Carr DB. Mu-opioid antagonists for opioid-induced bowel dysfunction. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD006332. DOI: 10.1002/14651858.CD006332.pub2.⁷⁶

“Background

Opioid-induced bowel dysfunction (OBD) is characterized by constipation, incomplete evacuation, bloating, and increased gastric reflux. OBD occurs both acutely and chronically, in multiple disease states, resulting in increased morbidity and reduced quality of life.

Objectives

To compare the efficacy and safety of traditional and peripherally active opioid antagonists versus conventional interventions for OBD.

Search methods

We searched MEDLINE, the Cochrane Central Register of Controlled Trials and EMBASE in January 2007. Additional reports were identified from the reference lists of retrieved papers.

Selection criteria

Studies were included if they were randomized controlled trials that investigated the efficacy of mu-opioid antagonists for OBD.

Data collection and analysis

Data were extracted by two independent review authors and included demographic variables, diagnoses, interventions, efficacy, and adverse events.

Main results

Twenty-three studies met inclusion criteria and provided data on 2871 opioid antagonist-treated patients. The opioid antagonists investigated were alvimopan (nine studies), methylnaltrexone (six), naloxone (seven), and nalbuphine (one). Meta-analysis demonstrated that methylnaltrexone and alvimopan were better than placebo in reversing opioid-induced increased gastrointestinal transit time and constipation, and that alvimopan appears to be safe and efficacious in treating postoperative ileus. The incidence of adverse events with opioid antagonists was similar to placebo and generally reported as mild-to-moderate.

Authors' conclusions

Insufficient evidence exists for the safety or efficacy of naloxone or nalbuphine in the treatment of OBD. Long-term efficacy and safety of any of the opioid antagonists is unknown, as is the incidence or nature of rare adverse events. Alvimopan and methylnaltrexone both show promise in treating OBD, but further data will be required to fully assess their place in therapy.”

Other Reviews in Cochrane Library (Meet the criteria for DARE)

Centre for Reviews and Dissemination - Provisional abstract¹³²

Original Author(s): Ruston T , Hunter K , Cummings G and Lazarescu A. (2013) Efficacy and side-effect profiles of lactulose, docusate sodium, and sennosides compared to PEG in opioid -induced constipation : a systematic review⁷⁹

Original Review:

“Opioid-induced constipation (OIC) is a side effect of opioid therapy that can affect quality of life, adherence to treatment, and morbidity and possibly mortality.

OBJECTIVES:

To investigate whether docusate sodium, sennosides, and lactulose have equal efficacy and side effect profiles compared to PEG in the management of OIC in adults.

METHODS:

A systematic review was undertaken. Randomized controlled trials of adults taking opioids for cancer or non-cancer pain were considered if they met inclusion criteria.

CONCLUSIONS:

Statistical pooling was not possible as no studies met inclusion criteria. Large, well-powered, randomized controlled trials are feasible. Standard definitions of OIC would assist with the execution of these studies and contribute to their internal and external validity. Further research is strongly encouraged.”

Centre for Reviews and Dissemination – Structured abstract¹³³

Original Author(s): Ford AC , Brenner DM and Schoenfeld PS. (2013) Efficacy of pharmacological therapies for the treatment of opioid-induced constipation : systematic review and meta-analysis⁷⁷

“OBJECTIVES:

There has been no definitive synthesis of the evidence for any benefit of available pharmacological therapies in opioid-induced constipation (OIC). We conducted a systematic review and meta-analysis to address this deficit.

METHODS:

We searched MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials through to December 2012 to identify placebo-controlled trials of μ -opioid receptor antagonists, prucalopride, lubiprostone, and linaclotide in the treatment of adults with OIC. No minimum duration of therapy was required. Trials had to report a dichotomous assessment of overall response to therapy, and data were pooled using a random effects model. Effect of pharmacological therapies was reported as relative risk (RR) of failure to respond to therapy, with 95% confidence intervals (CIs).

RESULTS:

Fourteen eligible randomized controlled trials (RCTs) of μ -opioid receptor antagonists, containing 4,101 patients, were identified. These were superior to placebo for the treatment of OIC (RR of failure to respond to therapy=0.69; 95% CI 0.63-0.75). Methylnaltrexone (six RCTs, 1,610 patients, RR=0.66; 95% CI 0.54-0.84), naloxone (four trials, 798 patients, RR=0.64; 95% CI 0.56-0.72), and alvimopan (four RCTs, 1,693 patients, RR=0.71; 95% CI 0.65-0.78) were all superior to placebo. Total numbers of adverse events, diarrhea, and abdominal pain were significantly commoner when data from all RCTs were pooled. Reversal of analgesia did not occur more frequently with active therapy. Only one trial of prucalopride was identified, with a nonsignificant trend toward higher responder rates with active therapy. Two RCTs of lubiprostone were found, with significantly higher responder rates with lubiprostone in both, but reporting of data precluded meta-analysis.

CONCLUSIONS:

μ -Opioid receptor antagonists are safe and effective for the treatment of OIC. More data are required before the role of prucalopride or lubiprostone in the treatment of OIC are clear.”

PubMed Systematic Review(s)

Siemens W, Gaertner J, Becker G. (2015) Advances in pharmacotherapy for opioid-induced constipation - a systematic review.⁷⁸

“INTRODUCTION:

Opioid-induced constipation (OIC) is one of the most frequent and burdening adverse events (AE) of opioid therapy. This systematic review aimed to evaluate efficacy and safety of drugs in randomized controlled trials (RCTs) with adult OIC patients.

AREAS COVERED:

Efficacy assessment focused on objective outcome measures (OOMs): bowel movement (BM) frequency, BM within 4 h and time to first BM. Twenty-one studies examining seven drugs were identified. Methylnaltrexone showed improvements in all three OOMs. RCTs in naloxone and alvimopan tended to be effective for BM frequency measures. Naloxegol (≥ 12.5 mg) improved all OOMs. Though effectiveness of lubiprostone was demonstrated for all OOMs, group differences were small to moderate. CB-5945 and prucalopride tended to increase BM frequency, especially for 0.1 mg twice daily and 4 mg daily, respectively. Besides nausea and diarrhea, abdominal pain was the most frequent AE for all drugs (risk ratio, range: 1.52 - 5.06) except for alvimopan. Treatment-related serious AEs were slightly higher for alvimopan (cardiac events) and prucalopride (severe abdominal pain, headache). Pain scores for placebo and intervention groups were similar for all drugs.

EXPERT OPINION:

Finding a consensus definition and inclusion criteria for OIC plus a rational balance between efficacy and AEs of drugs remain future challenges.”

KEYWORDS:

constipation; drug; opioid; pharmacotherapy; review

Phase III Pivotal Trials

Chey WD, et al. (2014) Naloxegol for opioid-induced constipation in patients with noncancer pain.⁸⁴

“BACKGROUND:

Opioid-induced constipation is common and debilitating. We investigated the efficacy and safety of naloxegol, an oral, peripherally acting, μ -opioid receptor antagonist, for the treatment of opioid-induced constipation.

METHODS:

In two identical phase 3, double-blind studies (study 04, 652 participants; study 05, 700 participants), outpatients with noncancer pain and opioid-induced constipation were randomly assigned to receive a daily dose of 12.5 or 25 mg of naloxegol or placebo. The primary end point was the 12-week response rate (≥ 3 spontaneous bowel movements per week and an increase from baseline of ≥ 1 spontaneous bowel movements for ≥ 9 of 12 weeks and for ≥ 3 of the final 4 weeks) in the intention-to-treat population. The key secondary end points were the response rate in the subpopulation of patients with an inadequate response to laxatives before enrollment, time to first postdose spontaneous bowel movement, and mean number of days per week with one or more spontaneous bowel movements.

RESULTS:

Response rates were significantly higher with 25 mg of naloxegol than with placebo (intention-to-treat population: study 04, 44.4% vs. 29.4%, $P=0.001$; study 05, 39.7% vs. 29.3%, $P=0.02$; patients with an inadequate response to laxatives: study 04, 48.7% vs. 28.8%, $P=0.002$; study 05, 46.8% vs. 31.4%, $P=0.01$); in study 04, response rates were also higher in the group treated with 12.5 mg of naloxegol (intention-to-treat population, 40.8% vs. 29.4%, $P=0.02$; patients with an inadequate response to laxatives, 42.6% vs. 28.8%, $P=0.03$). A shorter time to the first postdose spontaneous bowel movement and a higher mean number of days per week with one or more spontaneous bowel movements were observed with 25 mg of naloxegol versus placebo in both studies ($P<0.001$) and with 12.5 mg of naloxegol in study 04 ($P<0.001$). Pain scores and daily opioid dose were similar among the three groups. Adverse events (primarily gastrointestinal) occurred most frequently in the groups treated with 25 mg of naloxegol.

CONCLUSIONS:

Treatment with naloxegol, as compared with placebo, resulted in a significantly higher rate of treatment response, without reducing opioid-mediated analgesia. (Funded by AstraZeneca; KODIAC-04 and KODIAC-05 ClinicalTrials.gov numbers, [NCT01309841](#) and [NCT01323790](#), respectively.)”

Long-term Safety Trial

Webster L, et al. (2014) Randomised clinical trial: the long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation⁸⁷

“BACKGROUND:

Opioid-induced constipation (OIC) is a common adverse effect of opioid therapy.

AIM: To evaluate the long-term safety and tolerability of naloxegol, an oral, peripherally acting μ -opioid receptor antagonist (PAMORA), in patients with noncancer pain and OIC.

METHODS:

A 52-week, multicenter, open-label, randomised, parallel-group phase 3 study was conducted in out-patients taking 30-1000 morphine-equivalent units per day for ≥ 4 weeks. Patients were randomised 2:1 to receive naloxegol 25 mg/day or usual-care (UC; investigator-chosen laxative regimen) treatment for OIC.

RESULTS:

The safety set comprised 804 patients (naloxegol, n = 534; UC, n = 270). Mean exposure duration was 268 days with naloxegol and 297 days with UC. Frequency of adverse events (AEs) was 81.8% with naloxegol and 72.2% with UC. Treatment-emergent AEs occurring more frequently for naloxegol vs. UC were abdominal pain (17.8% vs. 3.3%), diarrhoea (12.9% vs. 5.9%), nausea (9.4% vs. 4.1%), headache (9.0% vs. 4.8%), flatulence (6.9% vs. 1.1%) and upper abdominal pain (5.1% vs. 1.1%). Most naloxegol-emergent gastrointestinal AEs occurred early, resolving during or after naloxegol discontinuation and were mild or moderate in severity; 11 patients discontinued due to diarrhoea and nine patients owing to abdominal pain. Pain scores and mean daily opioid doses remained stable throughout the study; no attributable opioid withdrawal AEs were observed. Two patients in each group had an adjudicated major adverse cardiovascular event unrelated to study drug; no AEs were reported nor adjudicated as bowel perforations.

CONCLUSION:

In patients with noncancer pain and opioid-induced constipation, naloxegol 25 mg/day up to 52 weeks was generally safe and well tolerated.”

QT/QTc study

Gottfridsson C, et al. (2013) Evaluation of the effect of Naloxegol on cardiac repolarization: a randomized, placebo- and positive-controlled crossover thorough QT/QTc study in healthy volunteers.⁸⁸

“BACKGROUND:

Opioid-induced constipation (OIC) is a common adverse effect associated with opioid use. Naloxegol is a PEGylated derivative of naloxone in clinical development as a once-daily oral treatment of OIC.

OBJECTIVES:

A thorough QT/QTc study was conducted, according to International Conference on Harmonisation E14 guidelines, to characterize the effect of naloxegol on cardiac repolarization.

METHODS:

In this randomized, positive- and placebo-controlled crossover study, healthy men received a single dose of naloxegol 25 mg (therapeutic dose), naloxegol 150 mg (supratherapeutic dose), moxifloxacin 400 mg (positive control), or placebo in 1 of 4 sequences (Williams Latin square design). The washout time between treatment periods was at least 5 days. Digital 12-lead ECGs were recorded at baseline and at 10 time points over 24 hours after dosing in each treatment period. QT intervals were corrected for heart rate using the Fridericia formula (QTcF) and the Bazett formula (QTcB).

RESULTS:

A total of 52 subjects were enrolled (mean age, 28 years), and 45 received all 4 treatments. The placebo-corrected, baseline-adjusted, mean increases in QTcF with naloxegol 25 and 150 mg were both <5 msec at each time point, and all upper limits of the 2-sided 90% CI were <10 msec. Similar findings were observed using QTcB; the upper limits of the 2-sided 90% CI were <10 msec at all time points after dosing with naloxegol 25 or 150 mg. With moxifloxacin 400 mg, mean QTcF was increased by a maximum of 11.1 msec (90% CI, 9.3-12.9 msec), supporting assay sensitivity.

CONCLUSION:

Naloxegol at 25 and 150 mg was not associated with QT/QTc interval prolongation in these healthy men, and at the proposed therapeutic dose of 25 mg/d, naloxegol is not expected to have a clinically relevant effect on cardiac repolarization in patients with OIC. ClinicalTrials.gov identifier: [NCT01325415](https://clinicaltrials.gov/ct2/show/study/NCT01325415).

KEYWORDS:

cardiac repolarization; electrocardiography; naloxegol; opioid antagonist; opioid-induced constipation; peripheral μ -opioid receptor antagonist”

Appendix 3 – Constipation Management

Please refer to the guidelines for complete information.

The authors of this recently published Consensus Article state that it highlights the need to consider selected factors before evaluating whether treatment with OIC prescription medication is warranted (not intended to provide specific treatment recommendations).⁶

Argoff CE, et al. Consensus Recommendations of the American Academy of Pain Medicine on Initiating Prescription Therapies for Opioid-Induced Constipation (Nov 2015)⁶

“OBJECTIVE:

Aims of this consensus panel were to determine (1) an optimal symptom-based method for assessing opioid-induced constipation in clinical practice and (2) a threshold of symptom severity to prompt consideration of prescription therapy.

METHODS:

A multidisciplinary panel of 10 experts with extensive knowledge/experience with opioid-associated adverse events convened to discuss the literature on assessment methods used for opioid-induced constipation and reach consensus on each objective using the nominal group technique.

RESULTS:

Five validated assessment tools were evaluated: the Patient Assessment of Constipation-Symptoms (PAC-SYM), Patient Assessment of Constipation-Quality of Life (PAC-QOL), Stool Symptom Screener (SSS), Bowel Function Index (BFI), and Bowel Function Diary (BF-Diary). The 3-item BFI and 4-item SSS, both clinician administered, are the shortest tools. In published trials, the BFI and 12-item PAC-SYM are most commonly used. The 11-item BF-Diary is highly relevant in opioid-induced constipation and was developed and validated in accordance with US Food and Drug Administration guidelines. However, the panel believes that the complex scoring for this tool and the SSS, PAC-SYM, and 28-item PAC-QOL may be unfeasible for clinical practice. The BFI is psychometrically validated and responsive to changes in symptom severity; scores range from 0 to 100, with higher scores indicating greater severity and scores >28.8 points indicating constipation.

CONCLUSIONS:

The BFI is a simple assessment tool with a validated threshold of clinically significant constipation. Prescription treatments for opioid-induced constipation should be considered for patients who have a BFI score of ≥ 30 points and an inadequate response to first-line interventions.”

NON-CANCER/NON-PALLIATIVE

VA/DoD clinical practice guideline for management of opioid therapy for chronic pain (2010)³⁵

The recommendations for the General Strategy for OT Initiation Phase include:

“Initiate a bowel regimen to prevent and treat constipation, which is anticipated with all opioids.”

“Adjustment of Therapy

Address Adverse Effects

Objective

Modify treatment to achieve effective pain control while minimizing adverse effects and medication intolerance.

Recommendations

A General Strategy to Minimize Adverse Effects

1. Adverse effects can usually be minimized through the use of low starting doses, slow titration rates, prophylactic and symptomatic treatments, and specific patient education provided at initiation of therapy.
2. Symptomatic treatment should be augmented with slow dosage titration, dose modification, and/or opioid rotation to minimize the adverse effects as follows:
 - a. Titrate slowly, temporarily reducing or holding doses if necessary, or modify the dosage regimen to allow the patient to develop tolerance to the adverse effects.
 - b. If these measures fail to minimize the adverse effects, consider rotating to another opioid agent.
3. If adverse effects are unmanageable and therapy is a greater detriment than benefit as determined by discussion with the patient and family, OT should be discontinued.

Constipation

1. Initial bowel regimens should generally consist of a bowel stimulant and a stool softener as well as general measures, such as increased fluid intake, increased dietary fiber, and adequate exercise.
2. Routinely initiate a stimulant-based bowel regimen at commencement of chronic OT.
3. If the initial regimen is inadequate, mild hyperosmotic, saline, and emollient laxatives may be added.
4. If possible, reduce or discontinue other drugs that may cause or contribute to constipation.
5. Bulk-producing laxatives, such as psyllium and polycarbophil, are not recommended and are relatively contraindicated as they may exacerbate constipation and lead to intestinal obstruction in patients with poor fluid intake.
6. Assess patients for constipation symptoms at every office visit.”³⁵

American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: part 2 – guidance (2012)^{71,134}

“Constipation must be closely monitored and a bowel regimen be initiated as soon as deemed necessary. (**Evidence: good**)”¹³⁴

Naloxegol for treating opioid-induced constipation

NICE technology appraisal guidance [TA345] Published date: July 2015⁷³

“Naloxegol is recommended, within its marketing authorisation, as an option for treating opioid induced constipation in adults whose constipation has not adequately responded to laxatives.

An inadequate response is defined as opioid-induced constipation symptoms of at least moderate severity in at least 1 of the 4 stool symptom domains (that is, incomplete bowel movement, hard stools, straining or false alarms) while taking at least 1 laxative class for at least 4 days during the prior 2 weeks.”

CANCER/PALLIATIVE

Palliative care for adults: strong opioids for pain relief

NICE guidelines [CG140] Published date: May 2012⁷⁴

Recommendations for management of constipation are based on clinical experience (“no evidence was identified on the effectiveness of laxative treatment with or without opioid switching in patients experiencing constipation as a side effect of strong opioid treatment”).

“Management of constipation

1.1.17 Inform patients that constipation affects nearly all patients receiving strong opioid treatment.

1.1.18 Prescribe laxative treatment (to be taken regularly at an effective dose) for all patients initiating strong opioids.

1.1.19 Inform patients that treatment for constipation takes time to work and adherence is important.

1.1.20 Optimise laxative treatment for managing constipation before considering switching strong opioids.”

Evidence update May 2014:

“The guideline does not currently recommend specific drugs for treatment of constipation.”

“Management of constipation

Evidence suggests that mu-opioid receptor antagonists appear to be safe and effective treatments for opioid-induced constipation. However, evidence of the efficacy of these drugs in a palliative care setting, particularly when compared with optimised laxative therapy, is limited.”

Methylnaltrexone for treating opioid-induced bowel dysfunction in people with advanced illness receiving palliative care (terminated appraisal)

NICE technology appraisal guidance [TA277] Published date: March 2013⁹⁸

“NICE is unable to recommend the use in the NHS of methylnaltrexone for treating opioid-induced bowel dysfunction in people with advanced illness receiving palliative care because no evidence submission was received from the manufacturer of the technology.”

Medical Services Commission. Palliative care for the patient with incurable cancer or advanced disease. Part 2: pain and symptom management. Victoria (BC): British Columbia Medical Services Commission; 2011 Sep 30.⁷⁵

“Opioid AEs

Switch if not managed symptomatically and AE persists for >1 week.

Constipation: Stepwise escalation of regular oral stimulant or osmotic laxative on opioid initiation. Consider methylnaltrexone* for refractory cases. Refer to "Constipation Management Algorithm" in the original guideline document.”

“Constipation Management (Refer to the "Constipation Management Algorithm" in the original guideline document)

Constipation Assessment

- Understand the patient's bowel habit, both current and when previously well (e.g., frequency of bowel movements [BMs], stool size and consistency, ease of evacuation).
- Goal is to restore a patient's normal BM frequency, consistency, and ease of passage.
- For lower performance status patients (e.g., reduced food intake and activity), lower BM frequency is acceptable as long as there is no associated discomfort.

Constipation Management Strategies

- There are many etiologies (e.g., reduced food/fluid/mobility and AEs of medications).
- Avoid rectal interventions (enemas, suppositories, manual evacuation) except in crisis management. Contraindicated when there is potential for serious infection (neutropenia) or bleeding (thrombocytopenia), or when there is rectal/anal disease.
- Exclude impaction when a patient presents already constipated. Abdominal X-ray can be useful when physical examination is inconclusive.
- When risk factors are ongoing, as they are in most cancer patients, suggest laxatives regularly versus prn. Adjust dose individually. Laxatives are most effective when taken via escalating dose according to response, termed "bowel protocol".
- Sennosides (e.g., Senokot®) are the first choice of laxative for prevention and treatment. Patients with irritable bowel syndrome may experience painful cramps with stimulant laxatives and often prefer osmotic laxatives such as lactulose or polyethylene glycol (PEG). There is weak evidence that lactulose and sennosides are equally effective; however lactulose can taste unpleasant and also cause bloating.
- If rectal measures are required, generally a stimulant suppository is tried first, then an enema as the next option.
- BC Palliative Care Drug Plan covers laxatives written on a prescription for eligible patients.
- For patients with opioid-induced constipation, after a trial of first-line recommended stimulant laxatives and osmotic laxatives, methylnaltrexone may be helpful. Cancer, GI malignancy, GI ulcer, Ogilvie's syndrome and concomitant use of certain medications (e.g., NSAIDs, steroids and bevacizumab) may increase the risk of GI perforation in patients receiving methylnaltrexone. (Health Canada MedEffect Notice)
- Patient handouts on constipation and bowel protocol are available from the BC Cancer Agency Web site.

See the table "Medications Used in Palliative Care for Constipation" in the original guideline document for a list of pain medications by generic and trade names, available dosage forms, standard adult doses, drug plan coverage, and approximate costs of a 30-day supply.”

Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the European Association for Palliative Care (EAPC) - 2012^{12,53}

Prophylactic laxatives are recommended for OIC in cancer patients.

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