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Class Review: Drugs for Constipation

Month/Year of Review: March 2015

Purpose for Class Review:
To identify appropriate utilization management strategies for drugs used to treat constipation, which is an unfunded condition on the Oregon Health Plan (OHP) Prioritized List of Health Services.

Research Questions:
- What is the current evidence and recommendations for the pharmacological management of constipation?
- Is there evidence of superior clinical efficacy or effectiveness for linaclotide, lubiprostone, alvimopan, methylnaltrexone or naloxegol over traditional laxatives used to manage constipation?
- Is there evidence of superior safety for linaclotide, lubiprostone, alvimopan, methylnaltrexone or naloxegol over traditional laxatives used to manage constipation?
- Are there subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications, or co-morbidities for which one treatment for constipation is more effective or associated with fewer adverse events?

Conclusions:
- There is moderate quality evidence that osmotic and stimulant laxatives are associated with greater frequency of bowel movements and softer stool in chronic constipation relative to placebo; however, there is lower quality evidence for bulk-forming laxatives, saline laxatives and stool softeners. Comparative evidence suggests superior effectiveness with osmotic and stimulant laxatives relative to other laxatives. Significant heterogeneity, small numbers of study participants and short study durations limit most evidence associated with these traditional laxatives.
- There is moderate quality evidence that linaclotide and lubiprostone are efficacious in idiopathic constipation and irritable bowel syndrome with constipation compared to placebo. In addition, there is low quality evidence that lubiprostone is efficacious for opioid-induced constipation relative to placebo. There is insufficient evidence to determine if these drugs have superior efficacy relative to any traditional laxative.
- There is moderate quality evidence that peripheral-acting opioid antagonists methylnaltrexone and naloxegol are efficacious in opioid-induced constipation relative to placebo. Evidence for alvimopan in opioid-induced constipation is more limited. Background use of laxatives or other forms of bowel care were explicitly prohibited in Phase 3 studies of methylnaltrexone and naloxegol and therefore evidence is insufficient to determine if these two drugs have superior efficacy relative to any traditional laxative.
- There is insufficient quality evidence that linaclotide, lubiprostone, methylnaltrexone and naloxegol are safer for any duration relative to traditional laxative therapies. Potential risk for myocardial infarction limits use of alvimopan to hospital use only for post-operative ileus.

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- There is insufficient evidence that one drug is more effective or associated with fewer adverse events in specific subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications (e.g., opioids), or most co-morbidities, with one exception: in patients with central neurological diseases and chronic constipation, low quality evidence suggests polyethylene glycol 3350 is effective at increasing frequency of bowel movements in patients with Parkinson's disease.

Recommendations:

- Implement prior authorization (PA) criteria for linaclotide, lubiprostone, alvimopan, methylnaltrexone and naloxegol to assure use for OHP-funded conditions. See proposed PA criteria in **appendix 5**.
- Establish a Laxatives drug class on the Preferred Drug List (PDL).
- Polyethylene glycol 3350, lactulose and senna products are preferred products based on more robust evidence for effectiveness and safety around their use.
- After comparative cost consideration in the executive session, bulk-forming laxatives and osmotic laxatives less than $1/unit are preferred and all other bulk-forming laxatives and osmotic laxatives are non-preferred. All surfactant, stimulant and saline laxatives are preferred. All lubricant laxatives are non-preferred.

Background:

Constipation is defined as unsatisfactory defecation characterized by infrequent tools, difficult stool passage, or both.[1] There are two types of constipation: primary (or idiopathic) constipation and secondary constipation. Primary constipation includes functional constipation, which includes chronic idiopathic constipation and constipation-predominant irritable bowel syndrome often associated with difficult or delayed evacuation, hard stools, abdominal bloating or discomfort.[1] Primary constipation also includes outlet obstruction (or defecatory disorder) associated with excessive straining and feeling of incomplete evacuation due to mechanical causes such as anal stricture, cancer, prolapse or pelvic floor dysfunction.[1] Secondary constipation can be due to diet, medications, lifestyle, pregnancy, advanced age or underlying medical conditions (e.g., diabetes mellitus, multiple sclerosis, Parkinson's disease or hypothyroidism, etc.).[1] Medications commonly associated with constipation are found in **appendix 1**.

The median prevalence of constipation from questionnaire-based epidemiologic studies is 16% in adults overall and 33.5% in adults aged older than 60 years.[2] Most studies suggest the prevalence of constipation is higher in females relative to males, in the nonwhite population relative to the white population, and in institutionalized persons relative to those in the community. Factors strongly associated with high risk for constipation include lower socioeconomic status and lower parental education rates, less physical activity, depression, physical and sexual abuse, stressful life events, and medications.[2] Medications most concerning for inducing constipation are opioids, in which there may be a prevalence of constipation in up to 50% of patients.[3] However, only about 20% of those suffering from constipation seek medical care; but because of its high prevalence, constipation consumes substantial health care resources.[2] In addition, women are more likely to use laxatives and seek health care for their constipation.[2]

Constipation is not currently covered under the Oregon Health Plan Prioritized List of Health Services.[4] Therefore, funding for drugs that treat constipation are dependent whether the constipation adversely affects, or is secondary to, the underlying medical condition covered by the Prioritized List.

Formulations, FDA indications and general dosing recommendations of currently available FDA-approved drugs are summarized in **table 1**. Pharmacologic treatments for constipation include several classes of medications with different mechanisms of action:

- Bulk-forming Laxatives: organic polymers that absorb water and increase stool mass, thereby making stool bulkier, softer and easier to pass.
- Stool Softeners: facilitate water interacting with the stool in order to soften the stool, make it more slippery and easier to pass.
- Osmotic Laxatives: poorly absorbed molecules that create an osmotic gradient within the intestinal lumen, drawing water into the lumen and making stool soft and loose.
- Stimulant laxatives: increase peristalsis in the colon and fluid and electrolyte secretion in the distal small bowel and colon.
- Secretagogues: increase chloride ion secretion into the intestinal lumen, thereby increasing intestinal fluid secretion and luminal water content and stool hydration. Linaclotide was already reviewed as an individual drug by the Oregon P&T committee in March 2013.[5]
- Peripheral-acting Opioid Antagonists: bind the mu-opioid receptors located within the GI tract, thereby decreasing the constipating effects of opioids.
    - Note: alvimopan is only approved to accelerate the time to GI recovery following partial bowel resection with primary anastomosis. A Risk Evaluation and Mitigation Strategy (REMS) is in place to limit its use to the labeled indication due to potential cardiac risk – in a hospital setting, for a maximum of 15 doses.[6]

Table 1. Currently Available Drugs for Constipation.[7,8]

DRUG NAME [TRADE NAME]	FDA INDICATION(S)	RX vs. OTC	FORMULATION/ ROUTE	GENERAL DOSING RECOMMENDATIONS (*refer to FDA labeling for specific dosing instructions*)
Laxatives, Bulk-forming				
Calcium Polycarbophil [FIBERCON, FIBER-LAX, etc.]	• Constipation or diarrhea	OTC	• 625 mg tab/PO	Adult, Child (≥12 y): 1250 mg up to QID Child (6-11 y): half adult dose
Methylcellulose [CITRUCEL, etc.]	• Adjunct in treatment of constipation	OTC	• Bulk pwdr/PO • 500 mg tab/PO	Powder: Adult, Child (≥12 y): 2 g (1 heaping TBSP) up to TID Child (6-11 y): half adult dose Tablet: Adult, Child (≥12 y): 2 tabs up to 6 times daily Child (6-11 y): half adult dose
Psyllium [METAMUCIL, etc.]	• Occasional constipation	OTC	• 520 mg cap/PO • Bulk pckt/PO • Bulk pwdr/PO	Supplement to general recommendations for TOTAL daily dietary fiber intake: Adults ≥51 y: males 30 g; females 21 g Adults 19-50 y: males 38 g; females 25 g Child 14-18 y: males 38 g; females 26 g Child 9-13 y: males 31 g; females 26 g Child 4-8 y: 25 g Child 1-3 y: 19 g
Laxatives, Lubricant				
Mineral Oil	• Temporary relief of occasional constipation • Temporary relief of occasional constipation • Relief of fecal impaction	OTC	• Oil/PO • Emulsion/PO • Enema/PR	Oil: Adult, Child (≥12 y): 15-45 mL/d in 1-4 divided doses Child (6-11 y): 5-15 mL/d in 1-4 divided doses Emulsion: Adult, Child (≥12 y): 30-90 mL/d in 1-4 divided doses

				Child (6-11 y): 10-30 mL/d in 1-4 divided doses. Enema: Adult, Child (≥12 y): 118 mL single dose Child (2-11 y): half adult dose
Laxatives, Saline				
Magnesium Citrate [CITROMA]	• Relief of occasional constipation	OTC	• 1.745 g/30 mL sol/PO	Adult, Child (≥12 y): 195-300 mL once or in divided doses Child (6-11 y): 90-210 mL once or in divided doses Child (2-6 y): 60-90 mL/day once or in divided doses
Magnesium Hydroxide [MILK OF MAGNESIA, PEDIA-LAX, etc.]	• Short-term relief of occasional constipation	OTC	• 400 mg/5 mL susp/PO • 800 mg/5 mL susp/PO • 400 mg tab/PO	Suspension: Adult, Child (≥12 y): 30-60 mL/d (400 mg/5 mL) or 15-30 mL/day (800 mg/5 mL) QHS or divided doses Child (6-11 y): half adult dose Child (2-5 t): 5-15 mL/d (400 mg/5 mL) QHS or divided doses Chewable Tablet: Child (6-11 y): 3-6 tab/d Child (2-5 y): 1-3 tab/d
Sodium Phosphates [FLEET ENEMA, etc.]	• Short-term relief of constipation	OTC	• Enema/PR • 2.4/0.9 g/5 mL sol/PO	Enema: Adult, Child (≥12 y): 4.5 oz enema as single dose Child (5-11 y): 2.25 oz enema as single dose Child (2-4 y): half of 2.25 oz enema as single dose Solution: Adult, Child (≥12 y): 15 mL up to TID Child (10-11 y): 15 mL/d Child (5-9 y): 7.5 mL/d
Laxatives, Surfactant (*stool softeners*)				
Docusate Calcium [KAO-TIN, etc.]	• Constipation associated with hard, dry stools • Prophylaxis for straining (valsalva) following myocardial infarction	OTC	240 mg cap/PO	Oral: Adult, Child (≥12 y): 50-500 mg/d in 1-4 divided doses Child (6-11 y): 40-150 mg/d in 1-4 divided doses Child (3-5 y): 20-60 mg/d in 1-4 divided doses Child (<3 y): 10-40 mg/d in 1-4 divided doses Rectal: Adult, Child (≥12 y): 50-100 mg as a single dose
Docusate Sodium [COLACE, etc.]		OTC	• 50-250 mg cap/PO • 100-283 mg/5 mL enema/PR • 50 mg/5 mL sol/PO • 60 mg/15 mL syrp/PO • 100 mg tab/PO	
Docusate Sodium/ Sennosides [PERI-COLACE, SENNA PLUS, etc.]	• Short-term relief of constipation	OTC	• 50/8.6 mg tab/PO	Adult, Child (≥12 y): 2 tabs daily to 4 tabs BID Child (6-11 y): half adult dose Child (2-5 y): ½ tab daily to 1 tab BID
Laxatives, Stimulant				
Bisacodyl [DULCOLAX, etc.]	• Constipation	OTC	• 10 mg supp/PR • 5 mg tab/PR	Oral: Adult: 5-15 mg as single dose

				Child (>6 y): 5-10 mg (0.3 mg/kg) as single dose Rectal: Adult Child (>2 y): 10 mg as single dose Child (<2 y): 5 mg as single dose
Senna [EX-LAX; SENNA-GEN, SENOKOT, etc.]	• Short-term relief of constipation	OTC	• Bulk leaves/PO • 8.8 mg/5 mL syrp/PO • 8.6-25 mg tab/PO • 15 mg chew tab/PO	Adult, Child (≥12 y): initial sennosides 15 mg once daily (max 70-100 mg/d divided BID) Child (6-11 y): initial sennosides 8.6 mg once daily (max 50 mg/d, divided BID) Child (2-5 y): initial sennosides 3.75 mg once daily (max 15 mg/d, divided BID)
Laxatives, Osmotic				
Glycerin	• Constipation	OTC	• 1-2 g supp/PR	Adult, Child (≥6 y): one adult suppository once Child (2-5 y): one pediatric suppository once
Lactulose (CONSTULOSE CHOLAC; GENERLAC, etc.)	• Constipation in adults	RX	• 10 g/15 mL sol/PO	Adult: 10-20 g daily (max 40 g/d) Child (off-label): 0.7-2 g/kg/d in divided doses (max 40 g/d)
Polyethylene Glycol 3350 [GLYCOLAX, MIRALAX, etc.]	• Occasional constipation in adults	OTC	• 17 g pckt/PO • Bulk pwdr/PO	Adult: 17 g daily Child (≥6 months) (off-label): 0.5-1.5 g/kg/d (max 17 g/d)
Sorbitol	• Constipation	OTC	• 70% sol/PO or PR	Oral: Adult, Child (>12 y): 30-150 mL single dose Child (2-11 y): 2 mL/kg single dose Enema: Adult, Child (>12 y): 120 mL once as a 25-30% solution Child (2-11 y): 30-60 mL once as a 25-30% solution
Opioid Antagonists, Peripherally-Acting				
Alvimopan (ENTEREG)	• Post-operative ileus	RX	• 12 mg cap/PO	Adult: 12 mg BID for post-operative ileus beginning at surgery for max 7 days or until discharged from hospital
Methylnaltrexone (RELISTOR)	• Opioid-induced constipation with chronic non-cancer pain • Opioid-induced constipation with advanced illness	RX	• 8 mg/0.4 mL or • 12 mg/0.6 mL sol/SC	Adult w/ non-cancer pain: 12 mg daily Adult w/ advance illness: Wt <38 kg: 0.15 mg/kg QOD PRN Wt 38 to <62 kg: 8 mg QOD PRN Wt 62 to 114 kg: 12 mg QOD PRN Wt >114 kg: 0.15 mg/kg QOD PRN
Naloxegol (MOVANTIK)	• Opioid-induced constipation	RX	• 12.5 mg tab/PO • 25 mg tab/PO	Adult: 25 mg daily; reduce to 12.5 mg daily if not tolerated or if CrCl <60 mL/min
Secretagogues				
Linaclotide (LINZESS)	• Chronic idiopathic constipation • Irritable bowel syndrome with constipation	RX	• 145 mcg cap/PO • 290 mcg cap/PO	Adult w/ idiopathic constipation: 145 mcg daily Adult w/ IBS constipation: 290 mcg daily
Lubiprostone	• Chronic idiopathic constipation	RX	• 8 mcg cap/PO	Adult w/ idiopathic constipation: 24 mcg BID

(AMITIZA)	• Opioid-induced constipation with chronic non-cancer pain • Irritable bowel syndrome with constipation in adult women		• 24 mcg cap/PO	Adult w/ opioid-induced constipation: 24 mcg BID Adult Females w/ IBS constipation: 8 mcg BID

Abbreviations: BID = twice daily; CrCl = creatinine clearance; FDA = Food and Drug Administration; IBS = irritable bowel syndrome; OTC = over-the-counter; PO = oral; PR = rectal; PRN = as needed; QHS = at bedtime; QID = four times daily; QOD = every other day; SC = subcutaneous; RX = prescription only; sol = solution; TBSP = tablespoon; TID = three times daily; wt = body weight; y = years

Highlights of prescribing information for the prescription products are available in **appendix 2**, which also highlights the Black Boxed Warnings in place for alvimopan and linaclotide.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. The Medline search strategy used for this literature scan is available in **appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Evidence in systematic reviews is primarily limited to the traditional laxatives, linaclotide, lubiprostone, alvimopan and methylnaltrexone. However, methylnaltrexone data are primarily limited to palliative care. Efficacy and safety data for naloxegol and methylnaltrexone in patients with constipation due to opioids for chronic, non-malignant pain, of which both received FDA approval in 2014, are insufficiently available in systematic reviews at this time. Details of the trials reviewed by the FDA for approval are summarized in **appendix 3** along with comparative pharmacology and pharmacokinetic characteristics between these two drugs.

Included in this review are the high quality systematic reviewed performed in all forms of constipation since The Drug Effectiveness Review Project (DERP) at Oregon Health & Science University first performed their systematic review in 2007. The majority of systematic reviews assessed forms of constipation that are not covered under the OHP Prioritized List of Health Services: irritable bowel syndrome associated with constipation (IBS-C), opioid-induced constipation, and primary (idiopathic) constipation are unfunded conditions. However, these reviews are included for completeness in order to thoroughly assess how newer non-laxative drugs for different types of constipation compare to traditional laxatives.

Drug Effectiveness Review Project Review on Chronic Constipation (2007)[9]:
The Drug Effectiveness Review Project (DERP) performed a systematic review in 2007 on treatment of chronic constipation with or without IBS. All controlled, prospective studies were eligible for inclusion, regardless of sample size or study duration. The review identified seven head-to-head randomized controlled

trials, sixteen placebo-controlled trials, one observational extension of an RCT, one meta-analysis, six observational studies and two pooled data analyses. The review rated the strength of evidence in a three-part hierarch (high, moderate or low) based on an approach devised by the GRADE working group that incorporates study design, study quality consistency of results and directness (availability of data). The review found that the general efficacy for most drugs was sparse, fraught with methodological issues or entirely missing.[9]

No controlled evidence was available for docusate calcium, docusate sodium or lactulose for the treatment of chronic constipation in adults. Three short-term trials (two weeks or less) demonstrated moderate strength evidence in adults for the efficacy of polyethylene glycol 3350 (PEG) but long-term data were missing. In one fair quality double-blind RCT, use of PEG 17 g daily was associated with greater treatment success, defined as more than 3 stools during a 7-day period, than placebo after 2 weeks (65.8% vs. 47.8%; $p<0.001$). The mean number of BMs was 4.5 for patients on PEG and 2.7 for patients on placebo ($p<0.001$). Two other trials showed similar efficacy of PEG. Evidence for psyllium 10.8 g daily in adults with chronic constipation was more limited and rated as low: two studies of mixed methodological quality indicated a beneficial effect for psyllium relative to placebo at improving bowel function (stool consistency, frequency of stools, ease of defecation, abdominal pain/discomfort or straining). At the time of the review, there were insufficient data on lubiprostone in adults to draw any conclusions on its efficacy. In general, lubiprostone had a statistically significant treatment benefit compared with placebo in trials of 3-4 weeks duration with consistently higher rates of spontaneous bowel movements within 24 hours. Head-to-head evidence was limited to 3 trials in adults comparing docusate sodium versus psyllium, lactulose versus PEG and PEG versus psyllium. Of these trials, one poor quality double-blind RCT showed no difference in efficacy between docusate sodium 200 mg daily and psyllium 10.2 g daily in terms of subjective outcomes; another poor quality open-label RCT reported greater straining (score for straining: 1.2 vs. 0.5; $p=0.0001$) and fewer weekly stools (0.9 vs. 1.3; $p=0.005$) with lactulose 10-30 g daily after 4 weeks of treatment compared to PEG 13-39 g daily. In one fair quality study, there was a statistically significantly greater improvement in weekly defecation rate in patients on PEG 25 g daily than on psyllium 7 g daily. No studies on the general efficacy for the treatment of chronic constipation in children were found. The evidence on the comparative efficacy of constipation in children was limited to one head-to-head trial of PEG 2.95 g daily and lactulose 6-12 g daily, in which both treatments significantly improved weekly bowel movements compared to baseline.[9]

The evidence for general tolerability and safety of these drugs is sparse and of poor quality. Few studies used objective scales and most combined patient-reported events with a clinical examination or laboratory values. Rarely were adverse events pre-specified or defined. Data suggests that lubiprostone has higher rates of nausea in adults than placebo, whereas there were not significant differences in adults between PEG or psyllium and placebo, although the information is limiting. In head-to-head evidence, PEG may be associated with less flatus and abdominal pain in adults than lactulose but no significant differences were noted between lactulose and psyllium or between PEG and psyllium. For children, PEG was well tolerated without any significant laboratory abnormalities and tended to be more tolerable than lactulose.[9] No serious adverse events were reported in any study.

There was not enough evidence in specific subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications or co-morbidities to determine if one drug is more effective or associated with fewer adverse events than another drug for chronic constipation.

<u>Treatment for Chronic Idiopathic Constipation (2011)</u>[10]:
A meta-analysis of RCTs at least one week in duration examining the effect of laxatives, which included all available laxatives broadly categorized as either osmotic or stimulant, or pharmacological therapies (lubiprostone or linaclotide) in adult patients with chronic idiopathic constipation (CIC) was performed. Studies that recruited patients with organic constipation, drug-induced constipation, or a highly select group (e.g., elderly institutionalized patients) were excluded from the review. The primary outcomes assessed were the efficacy of laxatives or pharmacological therapies compared with placebo in CIC, in terms of failure to respond to therapy or an effect on mean number of stools per week during treatment. A total of 11,077 citations were originally identified in the

literature search, 49 of which appeared to be relevant; but upon further assessment, only 20 trials were eligible based on established inclusion and exclusion criteria for the review.[10]

Eight RCTs eligible for inclusion compared laxatives to placebo in 1442 CIC patients. Dichotomous data were reported by seven RCTs evaluating laxatives: 351 (40.1%) of 876 patients assigned to laxatives failed to respond to therapy, compared to 392 (73.3%) of 535 allocated to placebo (relative risk (RR) of failure to respond = 0.52; 95% confidence interval (CI), 0.46 to 0.60), with borderline heterogeneity between studies (I^2=42%; p=0.11). The number needed to treat (NNT) to prevent 1 patient failing to respond to therapy was 3. Sensitivity analyses did not affect the outcomes, with a NNT ranging from 3-5. There was no statistically significant funnel plot asymmetry suggesting no evidence of publication bias or other small study effects.[10] Details on these results are summarized in **table 2**.

Continuous data were reported in six laxative studies. Mean number of stools per week was significantly higher with laxatives compared to placebo (weighted mean difference (WMD) in number of stools per week = 2.55; 95% CI, 1.53 to 3.57) with statistically significant heterogeneity between studies (I^2=100%; p<0.001) but no evidence of funnel plot asymmetry. The beneficial effect was seen with both osmotic and stimulant laxatives.[10]

The RR of experiencing any adverse event with laxatives was 1.94 (95% CI, 1.52 to 2.47; NNH=3). No significant differences in rate of abdominal pain were observed, but diarrhea was observed significantly more frequently with laxatives (RR=13.75; 95% CI, 2.82 to 67.14; NNH=3).[10]

Three RCTs eligible for inclusion compared lubiprostone to placebo in 610 CIC patients. Only one trial was at low risk of bias. There were 151 (45.1%) of 335 patients receiving lubiprostone who failed to respond to therapy compared to 184 (66.9%) of 275 placebo patients (RR of failure to respond to therapy = 0.67; 95% CI, 0.56 to 0.80), with no significant heterogeneity between studies (I^2=30%; p=0.24). The NNT for lubiprostone was 4. Total numbers of adverse events were significantly higher with lubiprostone (RR=1.79; 95% CI 1.21 to 2.65; NNH=4), with diarrhea and nausea occurring most frequently.[10]

The 3 RCTs comparing linaclotide to placebo involved 1582 patients with CIC. All three trials were at low risk of bias. There were 860 (79.0%) of 1089 patients receiving linaclotide who failed to respond to therapy compared to 468 (94.9%) of 493 placebo patients (RR of failure to respond to therapy = 0.84; 95% CI 0.80 to 0.87), with no significant heterogeneity between studies (I^2=32%; p=0.23). The NNT for linaclotide was 6. Analyses according to dose of linaclotide used demonstrated similar efficacy for 133 mcg and 266 mcg daily (RR=0.85 and 0.84, respectively). Total numbers of adverse events with linaclotide were similar to placebo.[10]

Table 2. Failure to Respond to Therapy in Chronic Idiopathic Constipation Relative to Placebo in Randomized Controlled Trials.[10]

Therapy	Relative Risk (95% Confidence Interval) to Placebo	Number Needed to Treat
Osmotic Laxatives	0.50 (0.39 to 0.63)	3
Stimulant Laxatives	0.54 (0.42 to 0.69)	3
Lubiprostone	0.67 (0.56 to 0.80)	4
Linaclotide	0.84 (0.80 to 0.87)	6

Cochrane Review on Treatment of Constipation with Laxatives or Methylnaltrexone in Palliative Care (2011)[11]:
Palliative care patients commonly experience constipation as a result of medications, particularly opioids, for pain control, as well as disease, dietary and mobility factors. The objective of this Cochrane review was to determine the effectiveness of laxatives or methylnaltrexone for the management of constipation in palliative care patients.[11] All laxatives administered for the management of constipation in palliative care for cancer and other long-term progressive medical

conditions were eligible for inclusion. Only seven RCTs involving 616 patients met criteria for inclusion, which included studies that either compared the effectiveness of two different laxatives, compared methylnaltrexone with a placebo, or different doses of methylnaltrexone. None of the studies compared the effectiveness of methylnaltrexone with a laxative and none of the trials compared a laxative to placebo. None of the studies reported methods to conceal random allocation, and blinding was not possible in the laxative trials owing to differences in the physical characteristics of the drugs. No differences in effectiveness were found between lactulose and senna, lactulose with senna compared to magnesium hydroxide and liquid paraffin (mineral oil), or between misrakasneham (a traditional Indian herbal product) and senna. Another study found a statistically significant increase in stool frequency with those who took lactulose and senna compared to those who took co-danthramer (stimulant laxative), though there were no differences between these two groups in patient's assessment of bowel function. In general, laxatives were well tolerated in these studies with only a few patients reporting adverse effects; primarily nausea, vomiting, diarrhea and abdominal pain. Most evidence identified in this review was on the effect of methylnaltrexone, based on evidence from two studies involving 287 patients. Methylnaltrexone was statistically significantly more effective at inducing a bowel movement than placebo; and that this response was generally rapid. It is important to note that most patients received background laxative therapy and were constipated at baseline. It is unclear, however, the frequency at which patients took conventional laxative therapy in these trials. Overall, methylnaltrexone was well tolerated though flatulence and dizziness were more common with methylnaltrexone therapy than placebo. In all studies identified in this review a number of patients remained constipated and were given rescue laxatives. None of the studies explored differences in follow-up characteristics, such as disease progression or drug use, between responders and non-responders. Conclusions on the optimal laxative management of constipation in palliative care patients cannot be made from this review as research remains limited. Specifically, there have been no RCTs on any laxative that has evaluated response rate, patient tolerability and acceptability. From the available comparative data however, the review concluded that lactulose and senna had similar effectiveness in this population and methylnaltrexone demonstrated short-term efficacy relative to placebo in patients where conventional laxative therapy was sub-optimal.[11]

Cochrane Review on Management of Fecal Incontinence and Constipation in Adults with Central Neurological Diseases (2014)[12]:
People with central neurological disease or injury have a much higher risk of both fecal incontinence and constipation than the general population. There is a fine balance in managing these two symptoms, with any management intended to ameliorate one risking precipitating the other. According to the review, current pharmacological bowel management is largely empirical with research in this population limited to two laxatives: psyllium, the bulk-forming laxative, and PEG, an osmotic laxative. The evidence for these two agents come from two small trials in patients with Parkinson's disease that had a statistically significant improvement in the number of weekly BMs when 8 weeks of psyllium 5.1 g daily or PEG 7.3 to 21.9 g daily were compared to placebo (see **table 3**). In the psyllium trial, run-in periods and washout periods were appropriate, but there were only 3 patients in the psyllium group and 4 patients in the placebo group. The PEG trial was also 8 weeks in duration and was relatively larger than the psyllium trial with 57 participants. Adverse events were not reported in either trial.[12]

Table 3. Mean Difference in Weekly Bowel Movements Relative to Placebo in Patients with Parkinson's Disease.

Drug Studied	Mean Difference in Weekly Bowel Movements Relative to Placebo	Relative Risk of Failure to Respond to Therapy
Psyllium	2.2 (95% CI, 1.4 to 3.3)	n/a
Polyethylene glycol	2.9 (95% CI, 1.5 to 4.3)	0.29 (95% CI, 0.11 to 0.72)

Cochrane Review on Osmotic and Stimulant Laxatives for the Management of Childhood Constipation (2013)[13]:
Childhood constipation is a very common problem that is commonly treated with osmotic and stimulant laxatives despite a long-standing paucity of high quality evidence to support the practice. Randomized controlled trials comparing an osmotic or stimulant laxative to either placebo or another intervention with a primary outcome of frequency of BMs in patients aged 0 to 18 years were eligible for inclusion. Eighteen RCTs (1643 patients) were included in the review, nine

of which were at high risk of bias due to lack of blinding, incomplete outcome data and selective reporting. In a meta-analysis of two studies (n=101) comparing PEG with placebo, there was a significantly increased number of weekly BMs with PEG but at the cost of more flatulence, abdominal pain, nausea, diarrhea and headache. In a meta-analysis of four short-term studies (n=338), PEG also significantly increased number of weekly BMs compared to lactulose without any serious adverse events. Patients who received PEG were also significantly less likely to require additional laxative therapy versus lactulose (18% vs. 30%, respectively; odds ratio 0.49; 95% CI 0.27 to 0.89). In a meta-analysis of three studies (n=211), PEG also statistically significantly increased number of weekly BMs compared to milk of magnesia but the clinical significance of this difference is questionable. In a meta-analysis of two studies (n=287) comparing mineral oil with lactulose, mineral oil significantly increased number of weekly BMs relative to lactulose without any serious adverse events, though there were cases of abdominal pain, distention and diarrhea. The results of these studies are illustrated in **table 4**. Weekly BMs were comparable between monotherapy with PEG relative to enemas (1 study, 90 patients, MD 1.00; 95% CI, -1.58 to 3.58), dietary fiber with lactulose (1 study, 125 patients; p=0.481), senna with lactulose (1 study, 21 patients; p>0.05), lactitol with lactulose (1 study, 51 patients, MD -0.80; 95% CI, -2.63 to 1.03), and PEG with mineral oil (1 study, 158 patients, MD 0.70; 95% CI, -0.38 to 1.78). The review suggests that PEG may be superior to placebo, lactulose and milk of magnesia for childhood constipation and relatively comparable to enemas and combination therapy including lactulose. However, short follow-up, sparse data, heterogeneity between the studies, and high risk of bias limit the evidence to low or very low quality and results should be interpreted cautiously.[13]

Table 4. Mean Difference in Weekly Bowel Movements in Children Treated with Different Laxatives.

Drugs Studied	Mean Difference in Weekly Bowel Movements
Polyethylene glycol vs. Placebo	2.61 (95% CI, 1.15 to 4.08)
Polyethylene glycol vs. Lactulose	0.95 (95% CI, 0.46 to 1.44)
Polyethylene glycol vs. Milk of Magnesia	0.69 (95% CI, 0.48 to 0.89)
Mineral oil vs. Lactulose	4.94 (95% CI, 4.28 to 5.61)

An older meta-analysis with similar inclusion criteria also found PEG achieved more treatment success (RR 1.47; 95% CI, 1.23 to 1.76) compared to other laxatives. However, significant heterogeneity between PEG trials existed, and data had to be pooled comparing PEG with any laxative rather than a specific laxative. Lactulose was less than or equally effective in increasing frequency of BMs compared to other laxatives investigated. There was no difference in effect on frequency of BM between fiber and placebo in children (MD 0.35; 95% CI, -0.04 to 0.74). However, due to the insufficiency of the data, particularly around conflicting results found with the use of PEG, the authors were not able to provide recommendations to support one laxative over the other for childhood constipation.[14]

A systematic review specifically assessing PEG in children with constipation also showed similar results, but the significant heterogeneity of the studies prohibited the authors from performing a meta-analysis.[15]

Cochrane Review of Lactulose versus Polyethylene Glycol for Chronic Constipation in Adults and Children (2010)[16]:
Lactulose and PEG are both commonly used osmotic laxatives that shown to be safe and effective for the treatment of chronic constipation in children and adults. This meta-analysis identified all relevant data from ten RCTs in children and adults (n=868) to determine whether lactulose or PEG was more effective at treatment chronic constipation and fecal impaction. Four of the studies included adults and five trials reported weekly BMs. Together, these trials demonstrated statistically significant superiority with PEG compared to lactulose in mean difference of weekly BMs. In children, the difference was even more pronounced. In adults, the difference was smaller but still statistically significant though the clinical significance of this difference may not be important. Results are provided in **table 5**. In studies reporting the Bristol Stool Scale, use of PEG resulted in a higher Bristol Stool Score (softer stool) relative to lactulose. Three trials reported

relief of abdominal pain: two of the trials showed use of PEG was associated with less abdominal pain relative to lactulose and one trial showed them to be relative equal in this outcome. Together, the odds of developing abdominal pain remained significantly greater with lactulose, which was more pronounced in children relative to adults (see **table 6** for details). All three trials reporting on the use of additional laxatives or other drugs showed that lactulose was associated with significantly greater use of other drugs to manage constipation (OR 4.00; 95% CI, 2.01 to 7.95). The odds of needing additional therapy were greater in children than adults (OR 5.69, 95% CI, 2.06 to 15.68 vs. OR 2.79, 95% CI, 1.07 to 7.27, respectively). Limitations include significant heterogeneity between trials (I^2 = 77%).[16]

Table 5. Difference in Weekly Bowel Movements Between Polyethylene Glycol and Lactulose in Children and Adults.

Drugs Studied	Mean Difference in Weekly Bowel Movements
Polyethylene Glycol vs. Lactulose (all)	0.65 (95% CI, 0.15 to 1.15)
Polyethylene Glycol vs. Lactulose (adults only)	0.28 (95% CI, 0.10 to 0.45)
Polyethylene Glycol vs. Lactulose (children only)	1.57 (95% CI, 0.36 to 2.77)

Table 6. Odds of Developing Abdominal Pain with Lactulose Compared to Polyethylene Glycol in Children and Adults.

Drugs Studied	Odds of Developing Abdominal Pain
Lactulose vs. Polyethylene Glycol (all)	2.09 (95% CI, 1.26 to 3.44)
Lactulose vs. Polyethylene Glycol (adults only)	0.86 (95% CI, 0.25 to 2.90)
Lactulose vs. Polyethylene Glycol (children only)	2.52 (95% CI, 1.45 to 4.40)

In a separate meta-analysis with similar inclusion criteria but restricted to adult populations, use of PEG resulted in a highly significant increase in weekly BMs compared to placebo (all studies: MD 1.98, p=0.0003; high quality studies: MD 2.34, p=0.001) and when compared to lactulose (all studies: MD 1.0, p=0.0017; high quality studies: MD 1.65, p=0.021).[17]

Cochrane Review of Mu-opioid Antagonists for Opioid-induced Bowel Dysfunction (2008)[18]:

Opioid-induced bowel dysfunction occurs both acutely and chronically, in multiple disease states, resulting in increased morbidity and reduced quality of life due to increased symptoms of constipation, incomplete evacuation, bloating and increased gastric reflux. This review and meta-analysis identified all relevant data from twenty-three RCTs (n=2871) assessing the efficacy of mu-opioid antagonists in opioid-induced bowel dysfunction. However, only four studies (n=147) investigated an opioid antagonist for treatment of OIC in patients with cancer pain, chronic non-cancer pain and methadone maintenance. Opioid antagonists included in the review for treatment of OIC were alvimopan (1 study), methylnaltrexone (1 study) and naloxone (2 studies). Of these, alvimopan and methylnaltrexone are peripheral-acting opioid antagonists and therefore specifically block receptors in the bowel without crossing the blood-brain barrier and blocking opioid receptors in the brain and reversing reduction in pain. Assessment of constipation varied between the studies and included composite scales, proportion of patients with a BM within a specified time period, small bowel transit time, stool frequency, and overall patient satisfaction, which led to significant heterogeneity (I^2 = 98%). In the alvimopan study, 54% of patients receiving alvimopan had a BM within 8 hours of administration versus 30% of those receiving placebo (NNT 5). In the methylnaltrexone study, 100% of patients receiving methylnaltrexone had an immediate BM versus none in the placebo group (NNT 1). When both studies were combined using a fixed-effects model, the use of an opioid antagonist produces a NNT of 3. However, when a random-effects model was employed to adjust for between study heterogeneity, the combined effect observed in the two studies was no longer statistically significant. In the studies assessing weekly BMs, combined data showed an opioid antagonist induced 1.4 more weekly BMs than placebo (95% CI, 0.2 to 2.5). In the 3 studies

assessing patient satisfaction, each study showed significant improvement in patient satisfaction when receiving an opioid antagonist compared to placebo, with methylnaltrexone appearing to have the greatest improvement (100% of patients satisfied vs. 22% of patient receiving placebo). Combining the data with a fixed-effect model showed 75% of patients receiving an opioid antagonist were satisfied versus 44% of those receiving placebo (NNT 4). The small sample sizes of these trials and significant heterogeneity between them may limit the interpretation of these results.[18]

Efficacy and Safety of Polyethylene Glycol compared to Lactulose, Docusate Sodium and Senna in Opioid-induced Constipation (2013)[19]:
This systematic review sought to find whether docusate sodium, sennosides and lactulose use in the prevention and management of OIC have equal efficacy and adverse effect profiles compared to PEG in adults receiving opioid treatment for a variety of outcomes. Inclusion criteria included 1) RCT study design; 2) patients 18 years of age or older with constipation associated with chronic opioid use due to chronic cancer pain, chronic non-cancer pain, or substance withdrawal; 3) a comparative trial of PEG versus either docusate sodium, sennosides or lactulose with doses described; 4) participants could be inpatients, outpatients or palliative care patients; 5) primary efficacy outcomes of frequency of bowel movements and quality of stool and secondary outcomes assessing adverse effects, drug interactions, use of additional laxatives and relief of symptoms associated with constipation. Using these criteria, none of the 2,158 citations found were eligible.[19] The review is helpful to comprehend the paucity of head-to-head comparative data for drugs commonly used to manage OIC.

Another systematic review with more lenient inclusion criteria of RCTs for management of OIC, including open-label RCTs and placebo-controlled trials, found evidence to support the use of PEG, lactulose, senna and the opioid-receptor antagonists (methylnaltrexone, naloxone, alvimopan) for the management of OIC. There was no evidence of difference between PEG, lactulose and senna, but PEG appears to be better tolerated. There is no evidence of benefit for bisacodyl (oral or rectal), docusate sodium, sodium phosphate enema, glycerin suppositories, mineral oil, magnesium salts or bulk-forming laxatives in the management of OIC.[20]

Efficacy of Pharmacological Therapies for the Treatment of Opioid-induced Constipation (2013)[3]:
Opioid-induced constipation may have significant implications. Surveys of patients receiving long-term opioid therapy reveal that OIC is associated with significant increases in physician visits and sickness-related absence from work, as well as significantly lower quality of life, compared to opioid users who do not experience constipation. This systematic review and meta-analysis assessed the efficacy of pharmacological therapies, compared with each other or with placebo, in OIC in terms of failure to respond to therapy. Of 1607 citations, 17 eligible studies, all placebo-controlled RCTs, were identified. Fourteen of the studies assessed mu-opioid receptor antagonists (4 used methylnaltrexone, 4 used naloxone and 4 used alvimopan), 2 studies assessed lubiprostone and 1 study assessed prucalopride (not approved in U.S.). No studies assessing linaclotide in OIC were identified. In total, 1261 (46.4%) of those assigned to a mu-opioid receptor antagonists failed to respond to therapy, compared to 886 (64.1%) of 1382 allocated to placebo. There was statistically significant heterogeneity between the studies (I^2=51%, p=0.01), which was confined to trials using methylnaltrexone. Patients receiving mu-opioid receptor antagonists experienced statistically significantly more adverse effects in the clinical trials than those who received placebo (60.6% vs. 53.5%, respectively; RR 1.11; 95% CI, 1.04 to 1.20; NNH 14). The primary adverse effects with these agents were diarrhea (RR 1.61; 95% CI, 1.21 to 2.13; NNH 33) and abdominal pain (RR 1.63; 95% CI, 1.06 to 2.51; NNH 20). In studies specifically evaluating methylnaltrexone, 553 (48.7%) patients who received the drug failed to respond to therapy, compared with 332 (64.5%) of 515 patients randomized to placebo. Studies ranged from 1 day to 12 weeks. There was statistically significant heterogeneity between studies (I^2=72%, p=0.003) owing to the wide range of doses studies and the disparate definitions of OIC and criteria for response utilized within each RCT. However, when only the 4 trials that used more than 2 days of therapy were analyzed, the RR of failure to respond to therapy was 0.79 (95% CI, 0.70 to 0.88) without significant heterogeneity (I^2=16%, p=0.25). In terms of individual adverse events, only diarrhea was significantly more common with methylnaltrexone (RR 1.94; 95% CI, 1.13 to 3.30; NNH 30). Studies of naloxone for OIC ranged from 3 to 12 weeks. There were 199 (44.2%) of the 450 patients assigned to naloxone who failed to respond to therapy compared to 244 (70.1%) of 348 patients allocated to placebo. Studies of alvimopan for OIC also ranged from 3 to 12 weeks. There

were 529 (45.1%) of 1174 patients receiving alvimopan who failed to respond to therapy, compared to 310 (59.7%) of 519 patients randomized to placebo with no significant heterogeneity between studies (I^2=11%, p=0.34). A formal meta-analysis could not be conducted for lubiprostone in OIC since 1 of the 2 studies was available only in abstract form and did not report raw outcomes data and multiple attempts to contact the corporate sponsor of these trials were unsuccessful. In one study, lubiprostone 24 mcg twice daily for 12 weeks was associated with a higher proportion of patients experiencing a first-dose spontaneous bowel movement within 48 hours compared to placebo (p=0.04). In the second study, 26.9% of patients receiving lubiprostone 24 mcg twice daily achieved 3 or more spontaneous bowel movements per week, for at least 9 of the 12 weeks studied, compared to 18.6% of patients who received placebo (p=0.035).[3] Relative risk of these agents are detailed in **table 7**.

Table 7. Failure to Respond to Therapy in Opioid-induced Constipation between mu-Opioid Receptor Antagonists and Placebo.

Drug	Relative Risk of Failure to Respond to Therapy vs. Placebo	Number Needed to Treat
Any mu-Opioid Receptor Antagonist*	0.69 (95% CI, 0.63 to 0.76)	4 (95% CI, 3 to 6)
Methylnaltrexone	0.67 (95% CI, 0.54 to 0.84)	3 (95% CI, 2 to 10)
Naloxone	0.64 (95% CI, 0.56 to 0.72)	4 (95% CI, 3 to 5)
Alvimopan	0.71 (95% CI, 0.65 to 0.78)	5 (95% CI, 4 to 11)

*methylnaltrexone, naloxone and alvimopan.

Treatment of Constipation in the Elderly (2013)[21]:

Consequences of constipation in older people who are frail can be substantial as excessive straining can trigger a syncope episode, or coronary or cerebral ischemia. In addition, case reports of older people identify stercoral ulceration, perforation and death as consequences of fecal impaction. Evidence from RCTs studying patients with chronic constipation and at least 65 years of age were eligible for this systematic review. Overall, evidence supports the use of osmotic laxatives as an effective treatment of chronic constipation in older people, whereas evidence supporting the use of bulk-forming laxatives, stool softeners and stimulant laxatives were lacking, limited or inconsistent. Four placebo-controlled RCTs of osmotic laxatives (n=250) all had statistically significant results favoring active treatment. One trial demonstrated PEG improved stool frequency and improvement in Rome III criteria in 57 patients with Parkinson's disease relative to placebo (80% vs. 30.4%, respectively; p=0.0012). Two trials demonstrated lactulose improved daily stool frequency over 12 weeks (0.63 ±0.31 for lactulose vs. 0.58 ±0.30 for placebo, p<0.02) and required less laxative use over 3 weeks relative to placebo (61% vs. 87%, respectively, p<0.02). The fourth trial showed that lactitol, another disaccharide similar to lactulose, increased stool frequency over 4 weeks relative to placebo (p<0.001). Bloating, flatulence, abdominal pain and diarrhea are common adverse events with osmotic laxatives, which may occur more often with lactulose because of its metabolism by colonic bacteria to carboxylic acids. Seven RCTs (n=254) were eligible in which older patients were randomly assigned to either dietary fiber or placebo. Two trials evaluating psyllium (n=20) did not show improvement in stool frequency. Two trials evaluating patients in nursing homes (n=182) compared stimulant laxatives with placebo. In one trial, senna resulted in 4.14 more BMs on average over 4 weeks versus placebo (p=0.017). The other study assessed an herbal formulation containing an anthraquinone combined with the osmotic laxative magnesium oxide. The formulation increased weekly frequency of BMs by 1 BM relative to placebo but did not affect global assessment of efficacy by caregivers. Bisacodyl has not been evaluated in RCTs in older patients. The authors also noted that regular use of stimulant laxatives may lead to decreased efficacy over time. One old trial conducted in 1968 has assessed stool softeners in older patients. In this trial, docusate sodium in 15 older patients improved constipation by increasing weekly bowel movements by 1 bowel movement relative to placebo (p<0.01). No RCTs assessing use of only enemas or suppositories to treat chronic constipation in older patients were identified.[21]

Effects of Linaclotide in patient with Chronic Constipation or in Patients with Irritable Bowel Syndrome with Constipation (2013)[22]:
The objective of this systematic review was to assess double-blind, placebo-controlled RCTs of linaclotide assessing CIC and IBS-C and to use meta-analysis to estimate the efficacy of linaclotide in treating the individual and combined end points of bowel function and abdominal symptoms. The primary outcomes assessed were the improvement from baseline in bowel symptoms, such as complete spontaneous bowel movements per week, or abdominal symptoms. A total of 4 RCTs in IBS-C and 4 studies in CIC were eligible for inclusion. All authors on all studies included in the meta-analysis were employees or paid consultants for the developer and manufacturer of linaclotide. Heterogeneity was minimal in the CIC studies but it was significant in the IBS-C studies so a random effects model was chosen for analysis. Duration of treatment in the IBS-C trials ranged from 4 to 26 weeks. Linaclotide resulted in a pooled RR of response of 1.95 in the first 12 weeks (95% CI, 1.30 to 2.94) compared with placebo for IBS-C using the 290 mcg dose. This pooled estimate corresponded to a NNT of 7 (95% CI, 5 to 11). There were significantly more responders to linaclotide using the FDA standard definition of a responder in studies assessing constipation (≥3 SBM/week plus increase of ≥1 SBM/week from baseline in at least 75% of the weeks studied) with a RR of response of 3.20 (95% CI, 2.40 to 4.26) relative to placebo. There were also significantly more responders to linaclotide using the FDA standard definition of an abdominal pain responder in an IBS-C study (improvement in weekly average of daily worst abdominal pain of ≥30% from baseline for ≥75% of weeks) with a RR of response of 1.58 (95% CI, 1.76 to 5.49) relative to placebo. In the CIC trials, linaclotide had a RR of response of 4.26 (95% CI, 2.80 to 6.47) compared to placebo using the standard FDA definition of a responder in studies assessing constipation. This pooled estimate corresponded to a NNT of 7 (95% CI, 5 to 8). Both the 290 mcg dose and the 145 mcg dose resulted in similar efficacy. In all 8 trials, linaclotide was well tolerated with similar rates of adverse events as the placebo group. Of note, one of the authors of this review (Cremonini) was a Board member for the manufacturer of linaclotide (Ironwood/Forest) at the time of the writing.[22]

The Effects of Fiber in the Management of Chronic Idiopathic Constipation (2011)[23]:
Patients with CIC are often told to increase dietary fiber intake but the benefit if this treatment remains unclear. This systematic review identified only six RCTs out of 3146 citations assessing soluble and insoluble fiber supplementation using dichotomous data (to assess response to therapy) in the management of CIC against placebo or randomized trials comparing these therapies to no therapy. A formal meta-analysis was not performed due to concerns about the methodological quality of identified studies and risk of bias. Four eligible trials used soluble fiber; of these, three trials used psyllium and the fourth used a combination of inulin and maltodextrose. Two studies used insoluble fiber, wheat bran in one study and rye bread in the other. Duration of treatment ranged from 2 to 8 weeks. No trial was at low risk of bias, and the majority of trials were conducted in tertiary care centers and recruited mostly female patients. None of the trials allowed any active medications for the treatment of constipation to be co-administered to patients. The largest of the trials included in the review was a single-blind, placebo-controlled study (n=201) in which 86.5% of patients allocated to psyllium reported an improvement in symptoms compared to 47.4% of patients receiving placebo (P<0.001). This study also showed that psyllium reduced abdominal pain and discomfort in 80.0% of patients who reported those symptoms at baseline compared to 64.3% of those who received placebo (p=0.035). Straining on defecation was also reduced with psyllium compared to placebo (p=0.003). Smaller trials showed increased weekly bowel frequency and “normalization of evacuation” with psyllium relative to placebo. In addition, stool consistency and pain on defecation were also improved with psyllium, although straining and a sense of complete evacuation was not significantly different from placebo. Similar success relative to placebo was also observed with the soluble fiber mixture of inulin and maltodextrin when administered as a dairy preparation. When assessing insoluble fiber, bran did not have a significant impact on symptoms of constipation compared to placebo but rye bread did when compared to low fiber bread. One trial reported more abdominal pain in patients receiving psyllium compared to placebo and rye bread appeared to cause more GI side effects than low fiber bread. Otherwise, fiber was well tolerated in these studies.[23]

Guidelines:

The American Gastroenterological Association[2,24]:

The American Gastroenterological Association issued a technical statement and official recommendations on constipation in 2013.[2,24] Traditional approaches to treatment of constipation are recommended, starting with fiber supplementation, osmotic laxatives or stimulant laxatives, which are effective, safe and generally inexpensive, before newer agents are considered for management of chronic constipation.[2] The review notes that evidence shows these traditional approaches are as effective as newer agents for treating patients with chronic constipation. Grading of Recommendation Assessments, Development and Evaluation (GRADE), which is based on the quality of evidence and magnitude of benefit, graded therapies into 4 categories (i.e., high, moderate, low or very low), and are summarized as follows[24]:

> *After discontinuing medications that can cause constipation and performing the recommended tests as guided by clinical features, a therapeutic trial of fiber supplementation and/or osmotic or stimulant laxatives is advised (strong recommendation, moderate-quality evidence). In most cases, constipation can be safely managed with long-term use of laxatives (strong recommendation, moderate-quality evidence). When bowel symptoms are refractory to traditional laxatives, new agents such as lubiprostone or linaclotide should be considered (weak recommendation, moderate-quality evidence). Suppositories or enemas rather than oral laxatives alone should be considered in patients with refractory pelvic floor dysfunction (weak recommendation, low-quality evidence).*

The evidence for specific treatment of chronic constipation and IBS-C adapted from the American Gastroenterological Association is summarized in **table 8**. Note the numbers in parenthesis reflect 95% confidence intervals where available. Data for therapeutic efficacy and numbers of patients with chronic constipation are obtained from meta-analyses.

Table 8. Comparison of Efficacy of Approved Therapies for Relief of Chronic Constipation and IBS-C.[2,24]

	Chronic Constipation			**IBS-C**		
Agent	NNT	n	GRADE Evidence	NNT	n	GRADE Evidence
Soluble Fiber	NA*	368	Very low	4.5	275	Moderate
Osmotic and Stimulant Laxatives	3 (2-4)	1411	High	NA	NA	Moderate**
PEG	2.4	573	High	NA	NA	Moderate**
Lubiprostone	4 (3-7)	610	Moderate	13	1171	Moderate
Linaclotide	6 (5-8)	2858	Moderate	10	420	Moderate

Abbreviations: n = number of patients; NA = not available; NNT = number needed to treat.

*Although some trials suggest that dietary fiber is effective in patients with chronic constipation, the efficacy cannot be estimated reliably because of quality of evidence.

**Although no controlled clinical trials have been conducted in patients with IBS-C, indirect evidence from trials in chronic constipation, the mechanism of action of these agents, and clinical experience suggest they are also likely to be effective in patients with IBS-C.

Several limitations of the evidence reviewed should be noted: endpoints differ across studies so strict comparisons are not advised; peripheral-acting opioid antagonists were not reviewed in the guideline so comparisons of these agents to traditional laxatives were not made; there is more evidence of efficacy in chronic constipation compared to IBS-C; there are no large high-quality studies of PEG, osmotic or stimulant laxatives in patients with IBS-C (though these agents

are probably effective in IBS-C based on their pharmacology and clinical experience in patients with IBS-C); and the incremental utility of newer agents over traditional laxatives, which is the critical question in clinical practice, requires further study because refractoriness to traditional laxatives was not an entry criterion in most studies of newer agents. The evidence of efficacy is strongest for osmotic and stimulant laxatives but there are several well-designed clinical trials showing that lubiprostone and linaclotide are efficacious for patients with chronic constipation and in IBS-C but the upper bounds of the 95% confidence intervals, relative to placebo, were relatively low and generally imprecise.[2]

The World Gastroenterology Organization[25]:
The World Gastroenterology Organization published its Global Guideline on constipation in 2011.[25] In uncomplicated normal-transit constipation without alarm symptoms, the guidelines recommends a graded approach to treatment based on recommending changes in lifestyle and diet, stopping or reducing medications that cause constipation, and administering fiber supplementation or other bulk-forming agents. The second step is to add an osmotic laxative, of which the best evidence is for PEG, followed by lactulose. The third step in these patients should include stimulant laxatives and enemas. The guideline uses a resource-sensitive approach where recommendations are ranked according to the resources available.

If a diagnosis of slow-transit constipation has been made, an aggressive laxative program is recommended. In these patients, fiber, milk of magnesia and bisacodyl are recommended, followed by PEG, lactulose or lubiprostone if there is no improvement. **Table 9** summarizes the recommendation levels and grade of evidence of various pharmacological agents.[25]

Table 9. Recommendation Levels and Grades of Evidence for Common Treatment Modalities in Constipation.[25]

Treatment Modalities	Recommendation Level, Grade of Evidence*	Treatment Modalities	Recommendation Level and Grade of Evidence
Bulking Agents		Stimulant Laxatives	
Psyllium	Level 2, Grade B	Bisacodyl	Level 2, Grade B
Calcium polycarbophil	Level 3, Grade C	Senna	Level 3, Grade C
Methylcellulose	Level 3, Grade C		
Osmotic Laxatives		Others	
Polyethylene glycol	Level 1, Grade A	Lubiprostone	Level 1, Grade A
Lactulose	Level 2, Grade B	Linaclotide	Level 2, Grade B
Wetting Agents			
Docusate	Level 3, Grade C		

**methodology of grading the evidence and making recommendations is unclear. In short, Level 1 recommendation is higher than a Level 2 recommendation; Grade A evidence is more robust than Grade B evidence.*

National Institute for Health and Clinical Excellence (NICE)[26,27]:
The NICE recently published a quality standards for the treatment of constipation in children and young adults.[26,27] NICE recommends that children and young people with constipation receive a full assessment before a diagnosis of CIC is made to ensure that underlying causes or alarm symptoms are excluded. A diagnosis of CIC, in which the constipation cannot be explained by anatomical or physiological abnormalities, can only be made through a full assessment. Once the diagnosis of CIC has been made, NICE recommends children and young adults receive PEG as first-line treatment due to its effectiveness for treatment of constipation and ease administration at home and in the community. It is recommended to substitute a stimulant laxative with or without lactulose if PEG is not tolerated. Adding a stimulant laxative is advised if the treatment is ineffective after 2 weeks. The treatment should be reviewed by a healthcare professional

within 6 weeks of starting therapy to assess effectiveness and adverse effects such fecal impaction or diarrhea. Maintenance with the laxative for several weeks may be advised once regular bowel habit has been established and may take several months. Stopping medication abruptly is not advised; rather, gradually reducing the dose over a period of months is recommended in respond to stool frequency and consistency. Parents or caregivers of children or young people starting laxative treatment should receive written information about laxatives to help enable self-management and adherence to therapy.[26]

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Appendix 1: Medications Associated with Constipation.

Class	Example	Class	Examples
5-HT3 receptor antagonists	*Ondansetron*	Bile acid sequestrants	*Cholestyramine*
Analgesics		Chemotherapy agents	
Opiates	*Oxycodone*	Vinca alkaloids	*Vincristine*
NSAIDs	*Ibuprofen*	Alkylating agents	*Cyclophosphamide*
Anticholinergic agents		Cation-containing compounds	
Tricyclic antidepressants	*Amitriptyline*	Aluminum	*Antacids*
Antiparkinsonian drugs	*Benztropine*	Calcium	*Antacids*
Antipsychotics	*Haloperidol*	Bismuth	
Antispasmodics	*Dicylcomine*	Iron supplements	*Ferrous sulfate*
Antihistamines	*Diphenhydramine*	Lithium	
Anticonvulsants	*Carbamazepine*	Endocrine medications	*Alendronate*
Antihypertensives			
Calcium channel blockers	*Verapamil*		
Diuretics	*Furosemide*		
Centrally-acting	*Clonidine*		
Beta-blockers	*Atenolol*		
Antiarrhythmics	*Amiodarone*		

Appendix 2: Highlights of Prescribing Information for Prescription Products.[6,28–31]

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MOVANTIK safely and effectively. See full prescribing information for MOVANTIK.

MOVANTIK™ (naloxegol) tablets, for oral use
Initial US Approval: 2014

----------INDICATIONS AND USAGE----------

MOVANTIK (naloxegol) is an opioid antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain (1)

----------DOSAGE AND ADMINISTRATION----------

- Discontinue maintenance laxative therapy before starting MOVANTIK; may resume laxatives if patients have OIC symptoms after taking MOVANTIK for 3 days (2.1)
- Alteration in analgesic dosing regimen prior to starting MOVANTIK is not required (2.1)
- MOVANTIK has been shown to be efficacious in patients who have taken opioids for at least 4 weeks (2.1)
- Take on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal (2.1)
- Swallow tablets whole, do not crush or chew (2.1)
- Avoid consumption of grapefruit or grapefruit juice (2.1, 7.1)
- Discontinue if treatment with the opioid pain medication is also discontinued (2.1)

Recommended dosage:

- 25 mg once daily; if not tolerated, reduce to 12.5 mg once daily (2.2)
- Renal Impairment (CLcr < 60 mL/min): 12.5 mg once daily; increase to 25 mg once daily if tolerated and monitor for adverse reactions (2.3, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 12.5 mg and 25 mg (3)

----------CONTRAINDICATIONS----------

- Patients with known or suspected gastrointestinal obstruction and at increased risk of recurrent obstruction (4, 5.1)
- Concomitant use with strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) (4, 7.1)
- Known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients (4)

----------WARNINGS AND PRECAUTIONS----------

- Gastrointestinal perforation: Consider the overall risk benefit in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent or worsening abdominal pain; discontinue if development of symptoms (5.1)
- Opioid withdrawal: Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor for symptoms of opioid withdrawal (5.2)

----------ADVERSE REACTIONS----------

The most common adverse reactions in clinical trials (≥3%) are: abdominal pain, diarrhea, nausea, flatulence, vomiting, and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil): Increased naloxegol concentrations; avoid concomitant use; if unavoidable, reduce dosage to 12.5 mg once daily and monitor for adverse reactions (2.4, 7.1)
- Strong CYP3A4 inducers (e.g., rifampin): Decreased concentrations of naloxegol; concomitant use is not recommended (7.1)
- Other opioid antagonists: Potential for additive effect and increased risk of opioid withdrawal; avoid concomitant use (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May precipitate opioid withdrawal in a fetus (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)
- Hepatic Impairment: avoid in severe impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2015

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RELISTOR safely and effectively. See full prescribing information for RELISTOR.

RELISTOR (methylnaltrexone bromide) Subcutaneous Injection
Initial U.S. Approval: 2008

RECENT MAJOR CHANGES

Indications and Usage, Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain (1.1)	[09/2014]
Dosage and Administration, Important Administration Information (2.1)	[09/2014]
Dosage and Administration, Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain (2.2)	[09/2014]
Contraindications (4)	[09/2014]
Warnings and Precautions, Gastrointestinal Perforation (5.1)	[09/2014]
Warnings and Precautions, Opioid Withdrawal (5.3)	[09/2014]

INDICATIONS AND USAGE

RELISTOR is an opioid antagonist indicated for:

- Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain (1.1)
- Treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.

  Limitation of Use: Use beyond four months has not been studied (1.2)

DOSAGE AND ADMINISTRATION

- For subcutaneous use only (2.1)
- Inject in upper arm, abdomen or thigh. Rotate injection sites (2.1)
- Be within close proximity to toilet facilities once administered (2.1)
- Discontinue if treatment with opioid pain medication is also discontinued (2.1)

  Opioid-induced constipation in adult patients with chronic non-cancer pain:
  - RELISTOR has been shown to be efficacious in patients who have taken opioids for at least 4 weeks (2.1)
  - Discontinue maintenance laxative therapy before starting RELISTOR; may resume laxatives if patients have OIC symptoms after taking RELISTOR for 3 days (2.1)
  - Recommended dosage: 12 mg subcutaneously once daily (2.2)

  Opioid-induced constipation in adult patients with advanced illness:
  - Recommended one dose administered every other day, as needed, but no more frequently than one dose in a 24-hour period (2.1, 2.3)

Weight of Adult Patient	Subcutaneous Dose*
Less than 38 kg	0.15 mg/kg
38 kg to less than 62 kg	8 mg
62 kg to 114 kg	12 mg
More than 114 kg	0.15 mg/kg

* see full prescribing information for corresponding injection volume

- Severe renal impairment (Clcr <30 mL/min): Reduce dose by one-half (2.4)
- Prescribe pre-filled syringes only for patients requiring an 8 mg or 12 mg dose (2.5)

DOSAGE FORMS AND STRENGTHS

Single-use vial (3)
- 12 mg/0.6 mL solution for subcutaneous injection, for use with a 27 gauge x ½-inch needle and 1 mL syringe
- 12 mg/0.6 mL solution for subcutaneous injection with one 1 mL syringe with retractable 27 gauge x ½-inch needle, two alcohol swabs

Single-use pre-filled syringe (3)
- 8 mg/0.4 mL solution for subcutaneous injection
- 12 mg/0.6 mL solution for subcutaneous injection

CONTRAINDICATIONS

- Patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction (4, 5.1)

WARNINGS AND PRECAUTIONS

- Gastrointestinal perforation: Consider the overall risk benefit in patients in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent or worsening abdominal pain; discontinue if development of symptoms (5.1)
- Severe or persistent diarrhea: Discontinue if severe or persistent diarrhea occurs during treatment (5.2)
- Opioid withdrawal: Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor closely for symptoms of opioid withdrawal (5.3)

ADVERSE REACTIONS

- The most common adverse reactions (≥ 1%) in adult patients with opioid-induced constipation and chronic non-cancer pain are abdominal pain, nausea, diarrhea, hyperhidrosis, hot flush, tremor, and chills (6.1)
- The most common adverse reactions (≥ 5%) in adult patients with opioid-induced constipation and advanced illness are abdominal pain, flatulence, nausea, dizziness, and diarrhea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals Inc. at 1-800-508-0024 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Other opioid antagonists: Potential for additive effect and increased risk of opioid withdrawal; avoid concomitant use (7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May precipitate opioid withdrawal in a fetus (8.1)
- Nursing Mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2014

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMITIZA safely and effectively. See full prescribing information for AMITIZA.

AMITIZA (lubiprostone) capsules, for oral use
Initial U.S. Approval: 2006

RECENT MAJOR CHANGES

Indications and Usage (1.2)	04/2013
Dosage and Administration (2.1)	04/2013
Warnings and Precautions, Pregnancy (5.1)	removed 11/2012

INDICATIONS AND USAGE

Amitiza is a chloride channel activator indicated for:

- Treatment of chronic idiopathic constipation in adults (1.1)
- Treatment of opioid-induced constipation in adults with chronic, non-cancer pain (1.2)
- Treatment of irritable bowel syndrome with constipation in women ≥ 18 years old (1.3)

Limitations of Use:

Effectiveness of Amitiza in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids (e.g., methadone) has not been established (1) (14.2)

DOSAGE AND ADMINISTRATION

Capsules should be swallowed whole and should not be broken apart or chewed (2)

Chronic Idiopathic Constipation and Opioid-induced Constipation

- 24 mcg taken twice daily orally with food and water (2.1)

Reduce the dosage in patients with moderate and severe hepatic impairment (2.1)

Irritable Bowel Syndrome with Constipation

- 8 mcg taken twice daily orally with food and water (2.2)

Reduce the dosage in patients with severe hepatic impairment (2.2)

DOSAGE FORMS AND STRENGTHS

- Capsules: 8 mcg and 24 mcg (3)

CONTRAINDICATIONS

- Amitiza is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. (4)

WARNINGS AND PRECAUTIONS

- Patients may experience nausea; concomitant administration of food may reduce this symptom (5.1)
- Do not prescribe for patients that have severe diarrhea (5.2)
- Patients taking Amitiza may experience dyspnea within an hour of first dose. This symptom generally resolves within 3 hours, but may recur with repeat dosing (5.3)
- Evaluate patients with symptoms suggestive of mechanical gastrointestinal obstruction prior to initiating treatment with Amitiza (5.4)

ADVERSE REACTIONS

- Most common adverse reactions (incidence > 4%) in chronic idiopathic constipation are nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence (6.1)
- Most common adverse reactions (incidence > 4%) in opioid-induced constipation are nausea and diarrhea (6.1)
- Most common adverse reactions (incidence > 4%) in irritable bowel syndrome with constipation are nausea, diarrhea, and abdominal pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-825-3327 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Concomitant use of diphenylheptane opioids (e.g., methadone) may interfere with the efficacy of Amitiza (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Caution should be exercised when administering to a nursing woman (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: April 2013

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENTEREG safely and effectively. See full prescribing information for ENTEREG.

ENTEREG® (alvimopan) capsules, for oral use
Initial U.S. Approval: 2008

WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION WITH LONG-TERM USE: FOR SHORT TERM HOSPITAL USE ONLY

See full prescribing information for complete boxed warning.

- **Increased incidence of myocardial infarction was seen in a clinical trial of patients taking alvimopan for long-term use. (5.1)**
- **ENTEREG is available only through a restricted program for short-term use (15 doses) called the ENTEREG Access Support and Education (E.A.S.E.®) Program. (5.1, 5.2)**

RECENT MAJOR CHANGES

Boxed Warning	10/2013
Indications and Usage (1)	10/2013
Warnings and Precautions (5)	10/2013

INDICATIONS AND USAGE

ENTEREG is an opioid antagonist indicated to accelerate the time to upper and lower gastrointestinal recovery following surgeries that include partial bowel resection with primary anastomosis. (1)

DOSAGE AND ADMINISTRATION

12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily beginning the day after surgery for up to 7 days for a maximum of 15 in-hospital doses. (2)

DOSAGE FORMS AND STRENGTHS

Capsules: 12 mg (3)

CONTRAINDICATIONS

Patients who have taken therapeutic doses of opioids for more than 7 consecutive days prior to taking ENTEREG (4)

WARNINGS AND PRECAUTIONS

- A higher number of myocardial infarctions was reported in patients treated with alvimopan 0.5 mg twice daily compared with placebo in a 12-month study in patients treated with opioids for chronic non-cancer pain, although a causal relationship with long-term use has not been established. (5.1)
- Patients recently exposed to opioids are expected to be more sensitive to the effects of ENTEREG and therefore may experience abdominal pain, nausea and vomiting, and diarrhea. (5.3)
- Not recommended in patients with severe hepatic impairment. (5.4)
- Not recommended in patients with end-stage renal disease. (5.5)
- Not recommended in patients with complete gastrointestinal obstruction or in patients who have surgery for correction of complete bowel obstruction. (5.6)
- Not recommended in pancreatic or gastric anastomosis. (5.7)

ADVERSE REACTIONS

The most common adverse reaction (incidence ≥1.5%) occurring with a higher frequency than placebo among ENTEREG-treated patients undergoing surgeries that included a bowel resection was dyspepsia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cubist Pharmaceuticals, Inc., at 1-877-282-4786 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Hepatic impairment:
  - Severe: ENTEREG is not recommended. (8.6)
  - Mild-to-moderate: Does not require dosage adjustment, but should monitor for adverse reactions. (8.6)
- Renal impairment:
  - End-Stage: Has not been studied and is not recommended. (8.7)
  - Mild-to-Severe: Dosage adjustment is not required, but should monitor for adverse reactions. (8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2013

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LINZESS safely and effectively. See full prescribing information for LINZESS.

LINZESS (linaclotide) capsules, for oral use
Initial U.S. Approval: 2012

WARNING: PEDIATRIC RISK
See full prescribing information for complete boxed warning.

LINZESS is contraindicated in pediatric patients up to 6 years of age; linaclotide caused deaths due to dehydration in young juvenile mice. Avoid use of LINZESS in pediatric patients 6 through 17 years of age. The safety and efficacy of LINZESS has not been established in pediatric patients under 18 years of age (4, 5.1, 8.4, 13.2).

----------RECENT MAJOR CHANGES----------

Boxed Warning	7/2014
Contraindications (4)	7/2014
Warnings and Precautions, Pediatric Risk (5.1)	7/2014
Warnings and Precautions, Diarrhea (5.2)	7/2014

----------INDICATIONS AND USAGE----------

LINZESS is a guanylate cyclase-C agonist indicated in adults for treatment of:

- Irritable bowel syndrome with constipation (IBS-C) (1.1)
- Chronic idiopathic constipation (CIC) (1.2)

----------DOSAGE AND ADMINISTRATION----------

- IBS-C: Take 290 mcg orally once daily (2.1)
- CIC: Take 145 mcg orally once daily (2.2)
- Take on empty stomach at least 30 minutes prior to first meal of the day (2.1, 2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 145 mcg and 290 mcg (3)

----------CONTRAINDICATIONS----------

- Pediatric patients under 6 years of age (4)
- Patients with known or suspected mechanical gastrointestinal obstruction (4)

---------- WARNINGS AND PRECAUTIONS----------

- *Diarrhea:* Patients may experience severe diarrhea. Hold or stop LINZESS (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence of at least 2%) reported in IBS-C or CIC patients are diarrhea, abdominal pain, flatulence and abdominal distension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Forest Pharmaceuticals, Inc., at 1- 800- 678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: July, 2014

Drug Safety:

Black Boxed Warnings:

ENTEREG (alvimopan)[6]:

WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION WITH LONG-TERM USE: FOR SHORT-TERM HOSPITAL USE ONLY

- **Increased incidence of myocardial infarction was seen in a clinical trial of patients taking alvimopan for long-term use.**
- **ENTEREG is available only through a restricted program for short-term use (15 doses) called the ENTEREG Access Support and Education Program.**

LINZESS (linaclotide)[29]:

WARNING: PEDIATRIC RISK

- **LINZESS is contraindicated in pediatric patients up to 6 years of age; linaclotide caused deaths due to dehydration in young juvenile mice. Avoid use of LINZESS in pediatric patients 6 through 17 years of age. The safety and efficacy of LINZESS has not been established in pediatric patients under 18 years of age.**

Appendix 3: Comparative Efficacy, Safety, Pharmacology and Pharmacokinetic Properties of Naloxegol and Methylnaltrexone.

Summary of Pivotal Studies for Drugs with New FDA-Approved Indications.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. Chey, et al.[32] Phase 3 (Study 04) MC, DB, PG, RCT	1. Naloxegol 25 mg once daily (N25) 2. Naloxegol 12.5 mg once daily (N12.5) 3. Placebo once daily (P) Duration: 12 weeks All laxatives and bowel therapy (e.g., prune juice, herbals) prohibited during study. Rescue laxative limited to bisacodyl 10-15 mg, followed by enema if needed, if no BM in 72 h. Stratification ensured ≥50% subjects in each arm had inadequate response to laxative(s) prior to study.	Demographics: Age: ~52 y Female: ~60% White: ~77% Opioid (morphine-equiv): ~140 mg/d Pain Type: back (56%); arthritis/joint/fibromyalgia (18.1%) Key Inclusion Criteria: ●Adults on daily stable morphine equivalent of 30-1000 mg/d for ≥4 weeks for non-cancer pain ●Opioid-induced constipation (<3 SBM/week w/ ≥1 of the following symptoms in ≥25% BMs 4 weeks before screening: hard/lumpy stool; straining; sensation of incomplete evacuation; or anorectal obstruction Key Exclusion Criteria: ●Uncontrolled pain ●Medications or medical conditions causing constipation or diarrhea ●Conditions assoc. w/ increased BBB permeability	ITT: P: 214 N12.5: 213 N25: 214 Attrition: P: 36 N12.5: 37 N25: 41	**Primary Endpoint:** Response Rate = ≥3 SBM/week and increase of ≥1 SBM/week from baseline for ≥9/12 weeks and ≥3 of final 4 weeks of study (*SBM=BM w/o use of rescue laxative in previous 24h*). P: 29.4% N12.5: 40.8% N25: 44.4% N12.5 RR 1.38 (95% CI, 1.06 to 1.80); p=0.02 N25 RR 1.51 (95% CI, 1.17 to 1.95); p=0.001 Key Secondary Endpoint: Response rate in patients with inadequate response to laxatives before study: P: 28.8% N12.5: 42.6% N25: 48.7% N12.5 RR 1.48 (95% CI, 1.04 to 2.11); p=0.03 N25 RR 1.69 (95% CI, 1.21 to 2.37); p=0.002	11.4%/9 15%/7 13.8%/8 19.9%/5	Attrition due to AE: P: 5.6% N12.5: 4.3% N25: 10.3% Abdominal pain: P: 3.3% N12.5: 8.5% N25: 12.6% MACE: P: 0 N12.5: 0.5% (n=1, MI) N25: 0.5% (n=1, MI) Mean Δ opioid dose from baseline: P: -1.8 mg/d N12.5: -2.3 mg/d N25: 0.4 mg/d Mean Δ pain score (0-10): P: -0.2 N12.5: -0.3 N25: -0.2	NA	**Quality Rating**: **FAIR** **Internal Validity (Risk of Bias)**: Selection: randomization occurred centrally w/ adequate concealment of allocation. Performance: Double-dummy design described. Detection: Data blinded from study team; imputation of missing data unclear; not truly ITT as data on some subjects not included. Attrition: twice as many patients dropped out in 25 mg group vs. 12.5 mg group due to AE. **Applicability**: Patient: age, sex and race of subjects typical for Oregon; opioid dose also typical. Intervention: prohibiting laxatives during study limit applicability and comparison to "usual care" (i.e., laxatives); short duration of study limits safety data, unclear if tachyphylaxis develops long-term. Comparator: adequate comparison groups Outcomes: clinically relevant outcomes assessed using validated tools, but limited due to short duration. Setting: outpatients only; data retrieved primarily from patient diaries. **Analysis**: Study funded, designed, monitored, and data analysis supervised by AstraZeneca. Other pre-specified secondary endpoints of unknown clinical significance included time to first post-dose SBM and number of days per week with at 1-3 SBMs during week 1-12.

2. Chey, et al.[32] Phase 3 (Study 05) MC, DB, PG, RCT	See Study 04	Demographics: Age: ~52 y Female: ~63% White: ~80% Opioid (morphine-equiv): ~136 mg/d Pain Type: back (56.8%); arthritis/joint/fibromyalgia (21.6%) Key Inclusion Criteria: See Study 04 Key Exclusion Criteria: See Study 04	ITT: P: 232 N12.5: 232 N25: 232 Attrition: P: 44 N12.5: 53 N25: 59	**Primary Endpoint:** Response Rate = ≥3 BM/week and increase of ≥1 BM/week from baseline for ≥9/12 weeks and ≥3 of final 4 weeks of study P (29.3%) N12.5 (34.9%) N25 (39.7%) N12.5 RR 1.19 (95% CI, 0.91 to 1.55); p=0.2 (NS) N25 RR 1.35 (95% CI, 1.05 to 1.74); p=0.02 Key Secondary Endpoint: Response rate in patients with inadequate response to laxatives before study: P (31.4%) N12.5 (42.4%) N25 (46.8%) N12.5 RR 1.35 (95% CI, 0.97 to 1.88); p=0.07 (NS) N25 RR 1.49 (95% CI, 1.08 to 2.06); p=0.01	NA 10.4%/10 NA 15.4%/7	Attrition due to AE: P: 5.2% N12.5: 5.2% N25: 10.3% Abdominal pain: P: 7.8% N12.5: 10.9% N25: 19.0% MACE: P: 0.9% (n=2, MI) N12.5: 0 N25: 0 Mean Δ opioid dose from baseline: P: -0.3 mg/d N12.5: -1.3 mg/d N25: 0.1 mg/d Mean Δ pain score (0-10): P: -0.1 N12.5: -0.1 N25: 0	NA	**Quality Rating**: **FAIR** **Internal Validity (Risk of Bias)**: See Study 04. **Applicability**: See Study 04. **Analysis**: Lack of statistical significance in the efficacy endpoint for the 12.5 mg dose relative to placebo suggests reserving 12.5 mg dose for patients who cannot tolerate the 25 mg dose (e.g., due to abdominal paint, etc.) See Study 04 for other comments.

3. Webster, et al.[33] Phase 3 MC, OL, PG, R	1. Naloxegol 25 mg once daily (N) 2. Usual Care (UC) Duration: 52 weeks Laxatives or bowel regimens prohibited in the naloxegol arm. Rescue laxative in naloxegol arm limited to bisacodyl 10-15 mg, followed by enema if needed, if no BM in 72 h. Included 90% new patients and 10% rollover patients from Study 04 and Study 05.	Demographics: Age: ~53 y Female: ~66% White: ~78% Opioid (morphine-equiv): ~146 mg/d Benzodiazepines: 41.4% Antidepressants: 31.1% Key Inclusion Criteria: ●Adults on daily stable morphine equivalent of 30-1000 mg/d for non-cancer pain ● Opioid-induced constipation (<3 SBM/week w/ ≥1 of the following symptoms in ≥25% BMs during 4-week screening: Bristol stool scale stool type 1 or 2; moderate, severe or very severe straining; or incomplete BM. Key Exclusion Criteria: ●0 BMs or uneven distribution of SBMs (0 in one week with ≥4 following week) during 2-week screening period ●Inadequate response to laxatives during screening ●Uncontrolled pain ●Medications or medical conditions causing constipation or diarrhea ●Conditions assoc. w/ increased BBB permeability	Enrolled: N: 563 UC: 281 Safety Analysis: N: 534 UC: 270 Attrition: N: 207 UC: 81	**Safety and Tolerability (all AEs assessed):** Study Completion: N 58.1% vs. UC 67.3% Any AE: N 81.8% vs. UC 72.2% Serious AE: N 9.6% vs. UC 11.1% Deaths: N (n=1) vs. UC (n=1), neither considered related to study drug AEs leading to study discontinuation of naloxegol: 10.5% Top Treatment-emergent AEs: Abdominal Pain: N 17.8% vs. UC 3.3% Diarrhea: N: 12.9% vs. UC 5.9% Nausea: N: 9.4% vs. UC 4.1% Back Pain: N 9.0% vs. UC 8.9% Headache: N 9.0% vs. UC 4.8% Flatulence: N 6.9% vs. UC 1.1% ECG Assessments: not reported in results Major Adverse Cardiovascular Events (MACE) (cardiovascular death, nonfatal MI and nonfatal stroke): N (n=2) vs. UC (n=2), neither considered related to study drug Opioid Withdrawal: N (n=2) vs. UC (n=0) Bowel Perforation: N (n=0) vs. UC (n=0) Δ Opioid Requirements (morphine equivalents): N -1.2 to -5.7 mg/d vs. UC -2.7 vs -5.3 mg/d Δ Pain Score (0-10): N ≤0.4 points vs. UC ≤0.4 points Median weekly bisacodyl dose for naloxegol patients: 1.1 mg randomization to month 1; 0 mg from month 1 to month 12.	NA	**Quality Rating**: **FAIR** **Internal Validity (Risk of Bias)**: Selection: internal computer-generated randomization scheme Performance: no blinding; no control Detection: unclear if data analyses blinded; imputation of missing data unclear Attrition: higher attrition in 52-week study vs. 12-week study more typical of real world experience. **Applicability**: Patient: subjects w/ inadequate response to laxatives not randomized. Intervention: approximates real world experience Comparator: Uncontrolled w/ usual care Outcomes: all AEs reported Setting: outpatient clinics; usual care arm was observational without intervention by investigators **Analysis**: Study funded, designed, monitored, and data analysis supervised by AstraZeneca (drug sponsor). Quality of study based on the study intent not to evaluate efficacy/effectiveness, but to assess real-world adverse effects of naloxegol (e.g., cardiovascular events). However, outcomes primarily patient-reported at monthly intervals, which are subject to recall bias. Nonetheless, serious adverse events such as rare cardiovascular signals were not observed with naloxegol.

4. Michna, et al.[34] Phase 3 MC, DB, PG, RCT	1. Methyl-naltrexone 12 mg SC once daily (QD) 2. Methyl-naltrexone 12 mg SC QOD (QOD) 3. Placebo SC once daily (P) Duration: 4 weeks DB followed by 8 weeks OL. Patients discontinued all laxatives prior to study. Only bisacodyl tablets (1 oral dose, up to 4 tablets) permitted as rescue laxative if no BM x3 d.	Demographics: Age: ~49 y Female: 60.2% White: 89.8% Opioid (morphine-equiv): ~159 mg/d Key Inclusion Criteria: ●Adults with chronic nonmalignant pain for ≥2 months on opioids for ≥1 month w/ avg morphine equivalent >50 mg/day for ≥2 weeks ●<3 BMs occurring w/o use of laxative in the prior 24 h per week w/ ≥1 of the following symptoms: hard/lumpy stool; straining; sensation of incomplete evacuation Key Exclusion Criteria: ●h/o inflammatory bowel disease in last 6 months ●Bowel impaction or bowel obstruction ●h/o rectal bleed (not hemorrhoids/fissures) ●h/o malignancy in last 5 y ●h/o chronic constipation before starting opioids	mITT: QD: 150 QOD: 148 P: 162 Attrition: QD: 28 QOD: 28 P: 16	**Primary Endpoints:** 1. Proportion of patients w/ RFBM w/i 4 h of first dose in study: QD: 33.3% (p<0.001 vs. P) QOD: 35.1% (p<0.001 vs. P) P: 9.9% *(95% CI or SD not provided)* 2. Percentage of active injections per patient resulting in RFBM w/i 4 h: QD: 28.9% (p<0.001 vs. P) QOD: 30.2% (p<0.001 vs. P) P: 9.4% *(95% CI or SD not provided)*	23.4%/5 25.2%/4 19.5%/6 20.8%/5	Attrition due to AE: QD: 6.7% QOD: 8.8% P: 2.5% Serious AE: QD: 1.7% QOD: 3.3% P: 0.7% Treatment emergent AE: QD: 49.3% QOD: 45.3% P: 38.3% Abdominal pain: QD: 19.3% QOD: 15.5% P: 3.7% Pain scores: Not reported. "No statistical or clinical significant difference" Opioid Withdrawal: Not reported. "No statistical or clinical significant difference" Rescue Laxative Use: QD: 38.7% (p<0.001 vs. P) QOD: 49.3% (p=0.03 vs. P) P: 61.7%	NA	**Quality Rating**: **FAIR** **Internal Validity (Risk of Bias)**: Selection: clear method of randomization with adequate concealment of allocation. Performance: method of double-blinding, maintaining blinding described. Detection: group allocation unblinded to investigators for data analysis; true ITT not performed but analysis methods appropriate. Attrition: overall attrition higher for treatment arms but low overall rates. **Applicability**: Patient: age, sex and race of subjects typical for Oregon; opioid dose also typical. Intervention: prohibiting laxatives during study limit applicability and comparison to "usual care" (i.e., laxatives); short duration of study limits applicability of data, unclear if tachyphylaxis develops long-term. Comparator: adequate comparison groups. Outcomes: clinical significance of primary outcomes questionable. Setting: not described, but presumed outpatient clinics. **Analysis**: Most authors employees of and stockholders of Wyeth. Study funded by drug sponsor. Quality of study based on lack of details regarding open label data assessment and questionable significance of primary outcomes. Pre-specified secondary endpoints were statistically significant for the two treatment arms relative to placebo, which included time to first RFBM after injection, change in weekly number of RFBMs, and improvement in Bristol Stool Form Scale scores, straining, and completeness of evacuation.

Abbreviations [alphabetical order]: AE = adverse event; ARR = absolute risk reduction; BB = blood brain barrier; BM = bowel movement; CI = confidence interval; d = days; DB = double-blind; h = hours; h/o = history of; ITT = intention to treat; MACE = major adverse cardiovascular events; MC = multi-centered; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; OIC = opioid-induced constipation; OL = open label; PG = parallel group; PP = per protocol; QOD = every other day; QoL = quality of life; R = randomized; RCT = randomized controlled trial; RFBM = rescue-free bowel movement; SBM = spontaneous bowel movement; SC = subcutaneously; SD = standard deviation; w/ = with; w/i = within; y = years.

*Quality of each study is ranked as "Good", "Fair" or "Poor" based on DURM Standard Methods for Quality Assessment and Grading the Evidence.
Note: number needed to treat in all cases in this review is rounded up to the next whole person.

Comparative Pharmacology and Pharmacokinetic Properties of Naloxegol and Methylnaltrexone.[30,31]

Drug Name	Naloxegol	Methylnaltrexone
Mechanism of Action	A peripheral antagonist of the mu-opioid receptor. It is a PEGylated derivative of naloxone and a substrate for P-gp transporter which reduces its passive permeability versus naloxone. Penetration into the central nervous system is thus negligible.	A peripheral antagonist of the mu-opioid receptor. It is a quaternary amine, which restricts its ability to cross the blood brain barrier and enter the central nervous system.
Pharmacokinetic Properties		
• Cmax	• <2 hours; secondary peak 0.4-3 hours later	• 30 minutes
• Dose-proportional Cmax and AUC	• Yes	• Yes
• Distribution	• 4.2% protein bound; Vd = 968-2140 L	• 11-15% protein bound; Vd = 1.1 L/kg
• Half-life	• 6-11 hours	• 8 hours
• Metabolism	• Liver via CYP3A	• 44% (not through CYP pathways)
• Renal Excretion	• 16%	• 54%
• Fecal Excretion	• 68%	• 17%

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to November Week 3 2014
1 lubiprostone.mp. 280
2 exp Constipation/ or exp Laxatives/ 13620
3 linaclotide.mp. 123
4 alvimopan.mp. 143
5 methylnaltrexone.mp. 314
6 naloxegol.mp. 5
7 1 or 2 or 3 or 4 or 5 or 6 14024
8 limit 7 to (meta analysis or systematic reviews) 380
9 limit 8 to english language 341

Appendix 5: Suggested Prior Authorization Criteria

Drugs for Constipation

Length of Authorization:

Up to 6 months

Not Covered by OHP:

- Disorders of function of stomach and other functional digestive disorders which includes constipation and Irritable Bowel Syndrome (ICD-9: 536.0-536.3, 536.8-536.9, 537.1-537.2, 537.5-537.6, 537.89-537.9, 564.0-564.6, 564.89-564.9, 787.60, 787.61, 787.63, 839.40)

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis covered by the OHP?	Yes: Go to 3	No: Pass to RPh. Deny; diagnosis not covered by OHP.
3. Will the prescriber consider a change to a preferred product? Message: preferred products do not require a PA.	Yes: Inform prescriber of covered alternatives	No: Go to 4

Approval Criteria		
4. Has the patient failed a 2-week trial of at least 3 of the following management strategies due to lack of effectiveness, contraindications or adverse effects? **A** Dietary modification—increased dietary fiber (25 g/day) **B** Bulk-forming Laxatives: (psyllium [e.g,. Metamucil],methylcellulose [e.g., Citrucel], calcium carbophil [e.g., Fibercon]) **C** Saline Laxatives: (magnesium hydroxide [e.g., Milk of Magnesia], magnesium citrate, sodium phosphate [Fleet Enema]) **D** Stimulant Laxatives: (senna or bisacodyl) **E** Osmotic Laxatives: (lactulose, sorbitol or polyethylene glycol 3350 [e.g., Miralax, Glycolax])	Yes: Approve for 6 months.	No: Pass to RPh. Go to 5.

5. RPh only:
Constipation is not covered under the OHP. Therefore, funding for drugs that treat constipation are dependent whether the constipation adversely affects, or is secondary to, the underlying medical condition covered by the Prioritized List.
   - Alvimopan (ENTEREG): FDA labeling, including a black boxed warning for risk of myocardial infarction, limit use to *in hospital use only* for a maximum of 15 doses. Evidence is primarily for the immediate post-operative period only.
   - Linaclotide (LINZESS): Constipation secondary to irritable bowel syndrome is not approvable. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4.
   - Lubiprostone (AMITIZA): Constipation secondary to irritable bowel syndrome or opioid-induced constipation is not approvable. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4.
   - Methylnaltrexone (RELISTOR): Opioid-induced constipation in patients with non-cancer pain is not approvable. Chronic constipation secondary to continuous opioid use as part of a palliative care regimen is approvable if justification is provided for not meeting criterion #4.
   - Naloxegol (MOVANTIK): Opioid-induced constipation in patients with non-cancer pain is not approvable. Justification must be provided for not meeting criterion #4.

P&T / DUR Action: 3/15 (AG); 3/09
Revisions: 3/15
Initiated: 7/09

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Date: March 2015