Therapeutic Class Overview
Irritable Bowel Syndrome and Constipation Agents

INTRODUCTION

- Irritable bowel syndrome (IBS) is a gastrointestinal disorder that most commonly manifests as chronic abdominal pain and altered bowel habits in the absence of any organic disorder (*Wald 2017*).
- IBS may consist of diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), IBS with a mixed symptomatology (IBS-M), or unclassified IBS (IBS-U). Switching between the subtypes of IBS is also possible (*Ford et al 2014*).
- IBS is a functional disorder of the gastrointestinal tract characterized by abdominal pain, discomfort, and bloating, as well as disturbed bowel habit. The exact pathogenesis of the disorder is unknown; however, it is believed that altered gastrointestinal tract motility, visceral hypersensitivity, autonomic dysfunction, and psychological factors indicate disturbances within the enteric nervous system, which controls the gastrointestinal system (*Andresen et al 2008, Ford et al 2009*).
- Prevalence estimates of IBS range from 5 to 15%, and it typically occurs in young adulthood (*Ford et al 2014*). IBS-D is more common in men, and IBS-C is more common in women (*World Gastroenterology Organization [WGO], 2015*).
- Symptoms of IBS often interfere with daily life and social functioning (*WGO 2015*).
- The general goals of therapy are to alleviate the patient's symptoms and to target any specific exacerbating factors (eg, medications, dietary changes), concerns about serious illness, stressors, or potential psychiatric comorbidities that may exist (*Wald 2015*).
- Non-pharmacological interventions to combat IBS symptoms include dietary modifications such as exclusion of gas-producing foods (eg, beans, prunes, Brussel sprouts, bagels, etc.), trials of gluten avoidance, and consumption of probiotics, as well as psychosocial therapies (eg, hypnosis, biofeedback, etc.) (*Ford et al 2014*).
- Depending upon the clinical presentation of an individual's IBS condition, a number of therapies exist to help alleviate the constellation of disease symptoms. Commonly used agents that are often initiated for disease control include poorly absorbable antibiotics such as rifaximin; laxative agents, including stimulant laxatives (bisacodyl, etc.) and osmotic laxatives (polyethylene glycol [PEG], lactulose, etc.); antispasmodics (eg, dicyclomine, hyoscine, etc.); selective chloride channel activators (eg lubiprostone); serotonin-3 receptor antagonists (eg, alosetron); guanylate cyclase-c agonists (eg, linaclotide); antidepressants such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs); select probiotics; and peppermint oil (*Ford et al 2014*).
- In addition to treatment of IBS-C, Amitiza (lubiprostone), Linzess (linaclotide), and Trulance (plecanatide) are indicated for the treatment of chronic idiopathic constipation (CIC). Symptoms of constipation are common with a prevalence of approximately 16% in adults overall and 33% in adults >60 years of age. Constipation is defined as fewer than three bowel movements (BMs) per week with symptoms that may include hard stools, a feeling of incomplete evacuation, abdominal discomfort, bloating, and distention. Initial treatment typically includes osmotic laxatives, stimulant laxatives, and increased fiber intake (*American Gastroenterological Association [AGA] Medical Position Statement 2013, Bharucha et al 2013*).
- Amitiza (lubiprostone) is also Food and Drug Administration (FDA)-approved for the treatment of opioid-induced constipation (OIC) in adults with chronic, non-cancer related pain. OIC is a frequent adverse event of opioid therapy. Opioids exert their action on the enteric nervous system causing dysmotility, decreased fluid secretion and sphincter dysfunction. Laxatives are typically prescribed but often are inadequate to completely relieve constipation (*Brock et al 2012*).
- Three other products are approved for use in OIC:
  - Relistor (methylnaltrexone) injection is an opioid receptor antagonist indicated for treatment of OIC in adults with chronic non-cancer pain and in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care. Relistor has also been FDA-approved in a tablet formulation, which is indicated for the treatment of OIC in adults with chronic non-cancer pain.
  - Movantik (naloxegol) and Symproic (naldemedine) are once-daily oral peripherally acting mu-opioid receptor antagonists (PAMORA) indicated for the treatment of OIC in adult patients with chronic non-cancer pain.

- Zelnorm (tegaserod) was approved in July 2002 for short-term treatment of IBS-C in women and in August 2004 for treatment of CIC in men and women <65 years of age. In March 2007, the FDA requested the manufacturer to discontinue the marketing of Zelnorm due to safety concerns related to increased rate of heart attack, stroke, and worsening heart-related chest pain. In July 2007, Zelnorm became available for use as a treatment investigational new drug (IND) protocol for IBS-C and CIC in women <55 years of age meeting specific guidelines; however, in April 2008, the manufacturer discontinued the availability as a treatment IND. Zelnorm is currently available for use only in emergency situations with FDA authorization (*Clinical Pharmacology 2018*).
- IBS-D is an IBS subtype characterized mainly by loose or watery stools at least 25% of the time. Viberzi (eluxadoline) and Xifaxan (rifaximin) are both FDA-approved for the treatment of IBS-D. Viberzi is a mu-opioid receptor agonist and a schedule IV controlled substance; Xifaxan is a rifamycin antibacterial. Lotronex (alosetron) is FDA-approved with restrictions for the treatment of women who exhibit severe IBS-D and have failed conventional therapy.
- The scope of this review will focus upon Amitiza (lubiprostone), Linzess (linaclotide), Lotronex (alosetron), Movantik (naloxegol), Relistor (methylnaltrexone bromide), Symproic (naldemedine), Trulance (plecanatide), Viberzi (eluxadoline), and Xifaxan (rifaximin) for their respective FDA-approved indications, which are outlined in Table 2.
- Medispan Classes: Agents for CIC (Trulance); Gastrointestinal Chloride Channel Activators (Amitiza); IBS Agents (Lotronex, Linzess, Viberzi); Peripheral Opioid Receptor Antagonists (Movantik, Relistor, Symproic); Anti-infective Agents – Misc (Xifaxan)

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
Amitiza (lubiprostone)	Sucampo Pharmaceuticals, Inc./Takeda	01/31/2006	-
Linzess (linaclotide)	Ironwood Pharmaceuticals/ Forest Pharmaceuticals	08/30/2012 (145 and 290 mcg capsules) 1/25/2017 (72 mcg capsule)	-
Lotronex (alosetron)	Prometheus Laboratories, Inc.	02/09/2000	✔
Movantik (naloxegol)	AstraZeneca	09/16/2014	-
Relistor (methylnaltrexone bromide)	Salix Pharmaceuticals	04/24/2008 (injection) 07/19/2016 (tablet)	-
Symproic (naldemedine)	Shionogi Inc.	3/23/2017	-
Trulance (plecanatide)	Synergy Pharmaceuticals Inc.	1/19/2017	-
Viberzi (eluxadoline)	Patheon Pharmaceuticals/Forest Pharmaceuticals (now Actavis)	05/27/2015	-
Xifaxan (rifaximin)	Salix Pharmaceuticals	05/25/2004 (200 mg tablet) 03/24/2010 (550 mg tablet)	-

(*Drugs@FDA 2018; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Amitiza (lubiprostone)	Linzess (linaclotide)	Lotronex (alosetron)	Movantik (naloxegol)	Relistor (methylnaltrexone bromide)	Symproic (naldemedine)	Trulance (plecanatide)	Viberzi (eluxadoline)	Xifaxan (rifaximin)
Treatment of CIC in adults	✔	✔					✔		
Treatment of OIC in adults with chronic, non-cancer pain	✔*			✔	✔	✔			
Treatment of OIC in patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation.	✔			✔	✔	✔			
Treatment of OIC in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care					✔†				
Treatment of IBS-C in women ≥18 years of age	✔								
Treatment of IBS-C in adults		✔					✔		
Treatment of IBS-D in adults								✔	✔‡
Women with severe IBS-D who have: • chronic IBS symptoms (generally lasting six months or longer) • had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy§			✔						

*Effectiveness of Amitiza in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids such as methadone has not been established.
†Injection formulation only. Use of Relistor beyond four months in treatment of OIC in patients with advanced illness has not been studied.
‡Xifaxan has additional indications for treatment of traveler's diarrhea (TD) caused by noninvasive strains of *Escherichia coli* in adult and pediatric patients 12 years of age and older, and reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults. Do not use Xifaxan in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.
§IBS-D is severe if it includes diarrhea and one or more of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, disability, or restriction of daily activities due to IBS.

(*Prescribing information: Amitiza 2017, Linzess 2017, Lotronex 2016, Movantik 2017, Relistor 2017, Symproic 2018, Trulance 2018, Viberzi 2017, Xifaxan 2018*)

- Lotronex was approved by the FDA in February of 2000 and was later withdrawn from the market due to numerous reports of serious and fatal gastrointestinal adverse events. Approval of a supplemental New Drug Application (sNDA) was accepted in July 2002 by the FDA to allow restricted marketing of Lotronex to treat only women with severe IBS-D. Physicians are required to complete training before prescribing alosetron to ensure that the benefits and risks of the agent are considered before administering it to patients (*Lotronex FDA press release 2016*).

- Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.

CIC

- A network meta-analysis demonstrated linaclotide and lubiprostone to be superior to placebo for the treatment of CIC. Treatment with linaclotide resulted in a significant increase in the proportion of patients with ≥3 complete spontaneous bowel movements (CSBMs)/week compared with placebo with a relative risk (RR) of 1.96 (95% confidence interval [CI], 1.12 to 3.44), and was superior vs placebo with an increase over baseline by ≥1 CSBM/week (RR 1.72; 95% CI, 1.18 to 2.52). For change from baseline in the number of SBMs/week, the weighted mean difference (WMD) with lubiprostone was 1.91 (95% CI, 1.41 to 2.41) and WMD with linaclotide was 2.11 (95% CI, 1.68 to 2.54) (*Nelson et al 2017*).
- A meta-analysis demonstrated the total pooled treatment effect of spontaneous bowel movements (SBMs)/week in patients with CIC or IBS-C was greater in lubiprostone-treated patients compared with placebo (combined standardized difference in means, 0.419; 95% CI, 0.088 to 0.750; p<0.001) (*Li et al 2016*).
- In another meta-analysis, treatment with linaclotide 145 mcg demonstrated significant improvements in the weekly frequency of CSBMs from baseline compared with placebo in patients with CIC (RR, 3.80; 95% CI, 2.20 to 6.55). Results were similar for abdominal discomfort or bloating responders for linaclotide 145 mg vs placebo, with pooled RRs of 1.57 (95% CI, 1.26 to 1.97) and 1.97 (95% CI, 1.44 to 2.69), respectively (*Videlock et al 2013*).
- Results from a long-term safety study illustrated that overall lubiprostone was well tolerated. The most commonly reported events were diarrhea, nausea, urinary tract infection, sinusitis, abdominal distension, and headache. Significant changes from baseline in hematology, laboratory values, vital signs, weight, body mass index and physical examination were not seen over the study duration (*Chey et al 2012*).
- A double-blind, placebo-controlled, multicenter, randomized controlled trial demonstrated that treatment with linaclotide 72 mcg improved the CSBM frequency over 12-weeks compared with placebo, with 13.4% of linaclotide-treated patients meeting responder requirements compared with 4.7% in the placebo group (95% CI, 1.8% to 5.2%) (*Schoenfeld et al 2018*).
- Two double-blind, placebo-controlled, multicenter, randomized controlled trials demonstrated that treatment with plecanatide 3 mg significantly increased weekly CSBM frequency as measured by the overall CSBM responder rate vs placebo (Study 1: 21.0% vs 10.2%; p<0.001; Study 2: 20.1% vs 12.8%; p=0.004) (*DeMicco et al 2017, Miner et al 2017*).

IBS

- In 2 meta-analyses, linaclotide demonstrated significant improvements in the FDA-defined composite endpoint of improvement in both daily worst abdominal pain scores and CSBM frequency from baseline compared to placebo after 12 weeks and demonstrated a similar result when compared over 26 weeks (*Atluri et al 2014, Videlock et al 2013*). More patients in the placebo treatment arm failed to achieve the FDA endpoint compared with patients treated with linaclotide (82.6% vs 66%; RR of failure to respond 0.80; 95% CI, 0.76 to 0.85).
- For the treatment of IBS-C, placebo-controlled trials demonstrated that lubiprostone had a significantly higher percentage of overall responders. In multiple 12-week studies, lubiprostone-treated patients reported significant improvements in abdominal pain/discomfort, stool consistency, straining, constipation severity, and quality of life (*Drossman et al 2007, Drossman et al 2009, Johanson et al 2008b*).
- Treatment with alosetron is associated with a significantly greater proportion of patients reporting adequate relief of IBS pain and discomfort, and improvements in bowel function compared to placebo (*Camilleri et al 2000, Camilleri et al 2001, Chey et al 2004, Lembo et al 2001, Lembo et al 2004, Rahimi et al 2008, Watson et al 2001*).
- A meta-analysis concluded that the 5-hydroxytryptamine type 3 (5-HT3) antagonists as a class significantly improve symptoms of non-constipating or IBS-D in both men and women compared to placebo; however, these agents were also associated with a greater increase in the risk of causing constipation compared to placebo (*Andresen et al 2008*).
- Alosetron treatment has been shown to positively impact global symptoms, as well as pain and discomfort in non-constipated females with IBS. This analysis further supports the increased chance of developing constipation with alosetron compared to placebo (*Cremonini et al 2003*).
- The safety and efficacy of eluxadoline for treatment of IBS-D were established in two randomized, multicenter, multinational, double-blind, placebo-controlled, phase 3 clinical trials in which 2427 patients with IBS-D (meeting Rome III criteria), average abdominal pain scores greater than 3 on a 0 to 10 scale during the week prior to randomization, and a Bristol Stool Scale (BSS) of 5.5 or greater with at least five days of BSS of 5 or more during the week prior to randomization. Patients were randomly assigned to receive eluxadoline 75 mg, 100 mg, or placebo twice daily. The primary endpoint was defined by the simultaneous improvement in the daily worst abdominal pain score by 30% or more compared to the baseline weekly average and a reduction in the BSS to 5 or less on at least 50% of the days within a 12-week or 26-week time interval. From weeks 1 through 12, the primary endpoint was achieved by 23.9% of patients in the 75 mg group (p=0.01) and 25.1% of patients in the 100 mg group (p=0.004) versus 17.1% of patients in the placebo group. From weeks 1 through 26, 23.4% in the 75 mg group (p=0.11) and 29.3% in the 100 mg group (p<0.001) achieved the primary endpoint compared to 19% in the placebo group (*Lembo et al 2016a*).

- The safety and effectiveness of rifaximin for treatment of IBS-D were established in three double-blind, placebo-controlled trials.
  - In the first two trials, 1,258 patients with IBS-D (Rome II criteria) were randomly assigned to receive rifaximin 550 mg three times daily (n=624) or placebo (n=634) for 14 days, and then followed for a 10-week treatment-free period. The primary endpoint for both trials was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least two of four weeks during the month following 14 days of treatment. More rifaximin-treated patients reported improvements in abdominal pain and stool consistency than those on placebo (Trial 1: 47% vs 39%; p<0.05; Trial 2: 47% vs 36%; p<0.01 in rifaximin and placebo groups, respectively).
  - TARGET3 was the third trial, which evaluated repeat courses of rifaximin in adult patients with IBS-D (Rome III criteria) for up to 46 weeks. During a 14-day open-label phase, 1,074 patients responded to rifaximin and were evaluated over 22 weeks for continued response or recurrence of IBS symptoms. A total of 636 patients who developed recurrent signs and symptoms after a single treatment course of rifaximin were randomized to receive either rifaximin 550 mg three times daily (n=328) or placebo (n=308) for two additional 14-day courses separated by 10 weeks. More patients treated with rifaximin than placebo were responders in abdominal pain and stool consistency in this phase of the study (38% vs 31% in rifaximin and placebo groups, respectively; p<0.05) (*ClinicalTrials.gov 2018, Lembo et al 2016b*).
- In two randomized, double-blind, placebo-controlled, 12-week studies, there were significantly more overall responders (based on improved abdominal pain and weekly CSBM from baseline) with plecanatide 3 mg vs placebo in patients with IBS-C (Study 1: 30% vs 18%; Study 2: 21% vs 14%) (*Trulance prescribing information 2018*).

OIC

- Two randomized, double-blind, placebo-controlled trials, COMPOSE-1 and COMPOSE-2, were conducted in adult patients with chronic non-cancer pain and OIC to assess the efficacy and safety of naldemedine. The primary endpoint was the proportion of responders, where response was defined as at ≥3 SBMs per week. Patients in COMPOSE-1 and COMPOSE-2 were randomized to receive naldemedine 0.2 mg (n=274; n=277) or placebo (n=273; n=276) once daily for 12 weeks. Results from both COMPOSE-1 and COMPOSE-2 showed that participants receiving naldemedine 0.2 mg experienced a significantly higher response compared to patients receiving placebo in both studies (COMPOSE-1 responders: 47.6% vs 34.6%; p=0.002 and COMPOSE-2 responders: 52.5% vs 33.6%; p<0.0001, respectively). Treatment-related adverse events due to gastrointestinal disorders were more common with naldemedine than with placebo in both studies (15% vs 7% and 16% and 7%, respectively) (*Hale et al 2017*).
- COMPOSE-4 was a 2-week randomized, double-blind, placebo-controlled trial of naldemedine 0.2 mg in patients with OIC and cancer, and COMPOSE-5 was a 12-week, open-label extension study. In COMPOSE-4, there were significantly more SBM responders in the naldemedine group compared to placebo (71.1% vs 34.4%; p<0.0001). Treatment-emergent adverse events were also higher with naldemedine vs placebo (44.3% vs 26.0%; p=0.01). In the extension study, 80.2% of patients experienced a treatment-emergent adverse event, most commonly gastrointestinal adverse events (*Katakami et al 2017*).
- A total of 1300 patients were enrolled in three, double-blind, randomized controlled trials evaluating lubiprostone compared to placebo in patients with chronic, non-cancer related pain on stable opioid therapy and constipation. In Study 1, overall responder rate, the primary outcome, was defined as ≥1 SBM improvement over baseline for all treatment weeks and ≥3 SBMs per week for at least nine weeks of the 12-week study period. Lubiprostone (27.1%) had a significantly higher “overall responder rate” than placebo (18.9%; p=0.03) (*Jamal et al 2015*). The primary outcome parameter for Study 2 and 3 was the mean change from baseline in SBM frequency at week eight. In Study 2, lubiprostone significantly increased the mean change from baseline in SBM frequency compared to placebo (p=0.004). In Study 3, the difference was not statistically significant; however, Study 3 was the only study that enrolled patients who received diphenylheptane opioids such as methadone. Studies 2 and 3 have not been published in a peer-reviewed journal at this time.
- A prospective, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of lubiprostone for relieving symptoms of OIC in adult patients with chronic non-cancer pain. OIC was defined as less than three SBMs per week. Patients were randomized to receive lubiprostone 24 mcg (n=210) or placebo (n=218) twice daily for 12 weeks. The primary endpoint was change from baseline in SBM frequency at week eight. Changes from baseline in SBM frequency rates were significantly higher at week eight (p=0.005) and overall (p=0.004) in patients treated with lubiprostone compared with placebo. The most common treatment-related adverse events with lubiprostone and placebo were nausea (16.8% vs 5.8%, respectively), diarrhea (9.6% vs 2.9%, respectively), and abdominal distention (8.2% vs 2.4%, respectively). No lubiprostone-related serious adverse events occurred (*Cryer et al 2014*).
- A 2013 systematic review evaluated pharmacological therapies for the treatment of OIC. A total of 14 randomized clinical trials of mu-opioid receptor antagonists were included. All treatments, including methylnaltrexone, naloxone, and

alvimopan, were superior to placebo for the treatment of OIC. Lubiprostone was included in the review; however, the reporting of data precluded meta-analysis (*Ford et al 2013*).

- In 2014, another systematic review of 21 randomized clinical trials evaluated seven pharmacological treatments for OIC. Efficacy assessment was based on objective outcome measures (OOMs): BM frequency, BM within four hours, and time to first BM. Methylnatrexone showed improvements in all three OOMs. Randomized controlled trials with naloxone and alvimopan tended to be effective for BM frequency measures. Naloxegol (≥12.5 mg) improved all OOMs. Though effectiveness of lubiprostone was demonstrated for all OOMs, group differences were small to moderate. Although not FDA-approved, CB-5945 and prucalopride tended to increase BM frequency, especially with doses of 0.1 mg twice daily and 4 mg daily, respectively. Besides nausea and diarrhea, abdominal pain was the most frequent adverse event for all drugs except for alvimopan. Treatment-related serious adverse events were slightly higher for alvimopan (cardiac events) and prucalopride (severe abdominal pain, headache) (*Siemens et al 2015*).
- The efficacy of naloxegol has been established in K4 and K5, two replicate Phase 3 clinical trials with a total of 1,352 participants with OIC who had taken opioids for at least four weeks for non-cancer related pain. Participants were randomly assigned to receive oral naloxegol 12.5 mg or 25 mg or placebo once daily for 12 weeks. The trials were designed to measure a response rate, defined as ≥3 SBMs per week and an increase of ≥1 SBM from baseline.
  - Results from K4 showed that participants receiving naloxegol 25 mg or naloxegol 12.5 mg both experienced a significantly higher response rate compared to participants receiving placebo (p=0.001 and p=0.02, respectively). Results from K5 also showed significantly higher response rates in participants receiving naloxegol 25 mg vs placebo (p=0.02) but did not show a significant difference in response rate in patients receiving naloxegol 12.5 mg vs placebo (p=0.2) (*Chey et al 2014*).
  - In K4, patients with an inadequate response to laxatives achieved a significantly higher response with naloxegol 25 mg vs placebo (p=0.002) and with naloxegol 12.5 mg vs placebo (p=0.03). In K5, patients receiving naloxegol 25 mg achieved a significantly higher response rate vs placebo (p=0.01); however, patients receiving naloxegol 12.5 mg did not have a significantly higher response rate.
  - Median time to first SBM was significantly shorter with both naloxegol 12.5 mg and 25 mg compared to placebo in K4 and was significantly shorter with naloxegol 25 mg in K5 (p<0.001 for all comparisons).
  - Average pain scores and opioid use remained relatively stable in both studies for patients receiving naloxegol; thus, centrally mediated analgesia was preserved.
- Clinical trials of methylnaltrexone injection in patients with advanced illness have shown response over several months with most patients reporting laxative effects similar to SBMs and predictable timing (*Bull et al 2015, Thomas et al 2008*). Similar findings have been reported in patients with OIC with chronic non-cancer pain (*Michna et al 2011, Webster et al 2017*).
- The efficacy of methylnaltrexone tablets was demonstrated in a randomized, double-blind, placebo-controlled study in patients using opioids for chronic non-cancer pain. Patients were randomized to methylnaltrexone (150 mg, 300 mg, or 450 mg) or placebo once daily for a period of four weeks followed by as-needed dosing for 8 weeks. A responder to methylnaltrexone treatment was defined as a patient with three or more SBMs per week, with an increase of one or more SBMs per week over baseline, for at least three weeks in the four-week treatment period. The percentage of patients classified as responders was 42.8%, 49.3% (p=0.03 vs placebo), 51.5% (p=0.005 vs placebo), and 38.3% in the methylnaltrexone 150 mg, 300 mg, 450 mg and placebo groups, respectively (*Rauck et al 2017*).
- A systematic review and network analysis compared the efficacy and safety of agents for the treatment of OIC, including lubiprostone, naldemedine, naloxegol, subcutaneous (SC) and oral methylnaltrexone, and 2 agents not approved for OIC in the U.S., alvimopan and prucalopride (*Sridharan and Sivaramakrishan 2017*). Observations from 16 randomized controlled trials with 4048 patients demonstrated that lubiprostone, naldemedine, naloxegol, and subcutaneous and oral methyl naltrexone performed better vs placebo in terms of rescue-free bowel movements (RFBM). Based on the odds ratios from direct and indirect pooled estimates, treatment with SC methylnaltrexone resulted in significantly improved RFBMs vs lubiprostone, naloxegol, and oral methylnaltrexone. Lubiprostone and naldemedine were associated with increased risks of adverse events, while SC methylnaltrexone did not significantly affect the analgesia due to background opioid use. Of note, the quality of evidence for the comparisons was either low or very low.
- Another systematic review and network analysis of 27 studies found methylnaltrexone, naloxone, naloxegol, naldemedine, alvimopan, and lubiprostone significantly more efficacious than placebo for OIC (*Nee et al 2018*).

IBS and CIC

- An updated systematic review on IBS and CIC was commissioned by the American College of Gastroenterology to assess the efficacy of available therapies in treating IBS and CIC compared with placebo or no treatment (*Ford et al 2014*). The secondary objectives included assessing the efficacy of available therapies in treating IBS according to predominant stool pattern reported (IBS-C, IBS-D, and IBS-M), as well as assessing adverse events with therapies for

both IBS and CIC. Parallel-group, randomized controlled trials comparing active interventions with either placebo or no therapy were evaluated. Crossover trials were eligible for inclusion if extractable data were provided at the end of the first treatment period, before crossover. The following were identified as “strong” recommendations for IBS and CIC treatments:

- IBS
  - There is insufficient evidence to recommend loperamide for use in IBS. Quality of evidence is very low.
  - Mixed 5-HT 4 agonists/5-HT 3 antagonists are not more effective than placebo at improving symptoms of IBS-C. Quality of evidence is low.
  - Linaclotide is superior to placebo for the treatment of IBS-C. Quality of evidence is high.
  - Lubiprostone is superior to placebo for the treatment of IBS-C. Quality of evidence is moderate.
- CIC
  - Some medicinal and dietary fiber supplements increase stool frequency in patients with CIC. Quality of evidence is low.
  - PEG is effective in improving symptoms of CIC. Quality of evidence is high.
  - Lactulose is effective in improving symptoms of CIC. Quality of evidence is low.
  - Sodium picosulfate and bisacodyl are effective in CIC. Quality of evidence is moderate.
  - Prucalopride is more effective than placebo in improving symptoms of CIC. Quality of evidence is moderate.
  - Linaclotide is effective in CIC. It is generally safe, with the main adverse event being diarrhea. Quality of evidence is high.
  - Lubiprostone is effective in the treatment of CIC. Quality of evidence is high.

- In a systematic review and meta-analysis, both linaclotide and plecanatide were efficacious for IBS-C and CIC compared to placebo. Diarrhea was more frequent with both drugs compared to placebo. In an indirect comparison, there were no differences between the two agents for efficacy in CIC, efficacy in IBS-C, frequency of diarrhea, or study withdrawal due to diarrhea (*Shah et al 2018*).

CLINICAL GUIDELINES

- Guidelines on management of constipation suggest increased fiber intake and osmotic laxatives. Stimulant laxatives are to be used as needed or as “rescue agents”. Lubiprostone and linaclotide can be considered when symptoms of constipation do not respond to laxatives (*AGA 2013, Bharucha et al 2013, Lindberg et al 2010*).
- The American College of Gastroenterology monograph on the management of IBS and CIC makes the following statements (reported with the strength of recommendation and quality of evidence, respectively) (*Ford et al 2014*):
  - Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D (weak; moderate)
  - Alosetron is effective in females with IBS-D (weak; moderate)
  - Linaclotide is superior to placebo for the treatment of IBS-C (strong; high)
  - Linaclotide is effective in CIC (strong; high)
  - Lubiprostone is superior to placebo for the treatment of IBS-C (strong; moderate)
  - Lubiprostone is effective in the treatment of CIC (strong; high)
- The AGA guideline on management of IBS makes the following statements (reported with strength of recommendation and quality of evidence, respectively) (*Weinberg et al 2014*):
  - Recommends using linaclotide (over no drug treatment) in patients with IBS-C (strong; high)
  - Suggests using lubiprostone (over no drug treatment) in patients with IBS-C (conditional; moderate)
  - Suggests using rifaximin (over no drug treatment) in patients with IBS-D (conditional; moderate)
  - Suggests using alosetron (over no drug treatment) in patients with IBS-D to improve global symptoms (conditional; moderate)
- The 2015 WGO guideline on IBS lists rifaximin and alosetron as second-line therapies for IBS-D, although it notes a risk of ischemic colitis and constipation with alosetron. Lubiprostone and linaclotide are noted to be safe and effective for the treatment of IBS-C (*WGO, 2015*).
- In the 2014 Technical Review of the Pharmacological Management of Irritable Bowel Syndrome, the AGA Institute reviewed and graded the evidence for pharmacological interventions (linaclotide, lubiprostone, PEG laxative, rifaximin, alosetron, loperamide, TCAs, SSRIs, and antispasmodics) for treatment of IBS. Review of the evidence for these pharmacological treatments showed that across all outcomes, evidence was high for linaclotide; moderate for lubiprostone, rifaximin, and alosetron; low for TCAs, SSRIs, and PEG; and very low for loperamide and antispasmodics (*Chang et al 2014*).

SAFETY SUMMARY

- Contraindications:
  - Amitiza is contraindicated with known or suspected mechanical gastrointestinal obstruction.
  - Lotronex has several contraindications, including history of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions; ischemic colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn's disease or ulcerative colitis; diverticulitis; severe hepatic impairment.
  - Linzess and Trulance are contraindicated in patients age 6 years or younger and in patients with known or suspected mechanical obstruction.
  - Movantik is contraindicated in patients with known or suspected gastrointestinal obstruction and at increased risk of recurrent obstruction, in patients with concomitant use of strong cytochrome (CYP) 3A4 inhibitors (eg, clarithromycin, ketoconazole), and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients.
  - Relistor is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction.
  - Symproic is contraindicated in patients with known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction, and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients.
  - Viberzi has several contraindications, including use in patients with the following conditions: known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction; alcoholism, alcohol abuse, alcohol addiction, or more than three alcoholic beverages daily; history of pancreatitis or structural diseases of the pancreas including known or suspected pancreatic duct obstruction; severe hepatic impairment; severe constipation or sequelae from constipation; known or suspected mechanical gastrointestinal obstruction; use in patients without a gallbladder; or known hypersensitivity to the drug.
    - On March 15, 2017, the FDA warned that Viberzi should not be used in patients who do not have a gallbladder. The safety announcement was based on an FDA review that found these patients have an increased risk of developing serious pancreatitis that could result in hospitalization or death (*FDA Drug Safety Communication 2017*). A contraindication was added to the prescribing label for patients without a gallbladder due to an increased risk of developing serious pancreatitis. Pancreatitis was reported in patients taking either the 75 mg or 100 mg dose with most of the cases of serious pancreatitis occurring within a week of starting treatment.
  - Xifaxan is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in Xifaxan.
- Boxed Warnings:
  - Linzess and Trulance are contraindicated in pediatric patients 6 years of age and younger due to the risk of serious dehydration; use should be avoided in children 6 to 17 years of age.
  - Lotronex has a Boxed Warning regarding serious gastrointestinal adverse reactions such as ischemic colitis and serious complications of constipation that may lead to hospitalization, blood transfusion, surgery, and/or death. If patients develop constipation or ischemic colitis, Lotronex should be discontinued. Lotronex should be used only in female patients with severe IBS-D who have not benefited from usual therapies.
- Risk Evaluation and Mitigation Strategy (REMS):
  - Lotronex has REMS that distributes education to providers about the risks for ischemic colitis and serious complications of constipation (*FDA REMS program 2018*).
- Drug Interactions:
  - There are no known drug interactions with Linzess.
  - Diphenylheptane opioids such as methadone may interfere with the efficacy of Amitiza.
  - Clinically significant drug interactions associated with Lotronex include CYP1A2 moderate inhibitors, CYP3A4 inhibitors, drugs that decrease gastrointestinal motility, and fluvoxamine. Concomitant use of Lotronex and fluvoxamine is contraindicated.
  - Concomitant use of Movantik should be avoided with the following drug classes: moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil) due to increased naloxegol concentrations, strong CYP3A4 inducers (eg, rifampin) due to decreased naloxegol concentrations, and other opioid antagonists due to potentially additive effects that may increase risk of opioid withdrawal. In the event concomitant use with moderate CYP3A4 inhibitors is unavoidable, a dose reduction of Movantik is warranted.

- Concomitant use of Relistor with other opioid antagonists should be avoided due to potentially additive effects that may increase risk of opioid withdrawal.
- Concomitant use of Symproic should be avoided with strong CYP3A inducers (eg, rifampin, carbamazepine, phenytoin, St. John's Wort) due to a significant decrease in naldemedine concentrations, and other opioid antagonists due to potentially additive effect of opioid receptor antagonism that may increase the risk of opioid withdrawal. Moderate CYP3A inhibitors (eg, fluconazole, atazanavir, aprepitant, diltiazem, erythromycin), strong CYP3A inhibitors (eg, itraconazole, ketoconazole, clarithromycin, ritonavir, saquinavir), and P-glycoprotein inhibitors (eg, amiodarone, captopril, cyclosporine, quinidine, verapamil) can increase Symproic concentrations.
- Drug interactions with Viberzi which potentially may result in clinically relevant effects include the following drug classes: organic anion transporting polypeptide (OATP) 1B1 inhibitors (eg, cyclosporine, gemfibrozil, antiretrovirals, rifampin, eltrombopag, etc.), strong CYP inhibitors (eg, ciprofloxacin, fluconazole, clarithromycin, paroxetine, bupropion), constipation-inducing drugs (eg, alosetron, anticholinergics, opioids), OATP1B1 and breast cancer resistance protein (BCRP) substrates (eg, rosuvastatin), and CYP3A substrates (eg, alfentanil, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).
- Concomitant administration of drugs that are P-glycoprotein inhibitors with Xifaxan can substantially increase systemic exposure to rifaximin. Caution should be exercised when concomitant use of Xifaxan and a P-glycoprotein inhibitor such as cyclosporine is needed.

- The IBS agents are most commonly associated with gastrointestinal-related adverse events.

Table 3. Specific Populations

Drug	Pregnancy and nursing
Amitiza (lubiprostone)	• Pregnancy Category C* • Unknown whether excreted in breast milk; use with caution.
Linzess (linaclotide)	• Not categorized† • Unknown whether excreted in breast milk; use with caution.
Lotronex (alosetron)	• Pregnancy category B* • Unknown whether excreted in breast milk; use with caution.
Movantik (naloxegol)	• Pregnancy Category C* • Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
Relistor (methylnaltrexone bromide)	• Not categorized† • Unknown whether excreted in breast milk; breastfeeding not recommended during treatment.
Symproic (naldemedine)	• Not categorized† • Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug. If drug is discontinued, breastfeeding can be resumed 3 days after the final dose.
Trulance (plecanatide)	• Not categorized† • Unknown whether excreted in breast milk; use with caution.
Viberzi (eluxadoline)	• Not categorized†; no studies in pregnant women. • Unknown whether excreted in breast milk; use with caution.
Xifaxan (rifaximin)	• Not categorized†; no studies in pregnant women. • Unknown whether excreted in breast milk, effects on breastfed infant, or effects on milk production; use with caution.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

- Pediatric populations:
  - Safety and efficacy have not been established in pediatric patients with Amitiza, Lotronex, Movantik, Relistor, Symproic, and Viberzi.
  - For Xifaxan, safety and efficacy have not been established in pediatric patients <12 years of age with TD or patients <18 years of age for HE and IBS-D.

- Elderly populations:
  - For Lotronex, caution should be used in patients ≥65 years of age due to risk for constipation.
- Hepatic dysfunction:
  - For Lotronex, caution should be used in patients with mild or moderate impairment; use should be avoided in severe hepatic impairment.
  - For Movantik, Symproic, and Viberzi, use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C).

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Amitiza (lubiprostone)	Capsules	Oral	Treatment of CIC in adults and OIC: twice daily Treatment of IBS-C in women ≥18 years of age: twice daily	Dose should be adjusted in moderate and severe hepatic impairment.
Linzess (linaclotide)	Capsules	Oral	IBS-C: once daily CIC: once daily	If unable to swallow, contents of capsule may be administered with applesauce or water.
Lotronex (alosetron)	Tablets		Women with severe IBS-D: twice daily	Discontinue treatment in patients who have not had adequate control of IBS symptoms after four weeks of treatment with 1 mg twice daily.
Movantik (naloxegol)	Tablets	Oral	OIC in chronic non-cancer pain: once daily	Maintenance laxative therapy should be discontinued prior to initiating therapy. Dose should be adjusted for renal Impairment (CrCl <60 mL/min). Tablet may be crushed for patients who are unable to swallow the tablet whole. Crushed tablets may also be administered via a nasogastric tube. Movantik should be discontinued when opioid pain medication is discontinued.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Relistor (methylnaltrex-one)	Single-use vials, single-use pre-filled syringes, tablets	Oral, SC injection	OIC in chronic non-cancer pain: SC injection once daily, or oral tablet(s) once daily in the morning OIC in advanced illness: Weight-based SC injection once every other day, as needed (max of once daily).	Maintenance laxative therapy should be discontinued prior to initiating therapy. Patient should be within close proximity to toilet facilities after administration. SC injection should be administered in the upper arm, abdomen, or thigh; injection sites should be rotated. Pre-filled syringes should only be used for patients taking 8 mg or 12 mg dose. Dose should be adjusted in moderate to severe renal impairment. Oral dose should be adjusted in moderate and severe hepatic impairment; adjustment of SC injection dose should be considered in severe hepatic impairment. Relistor should be discontinued when opioid pain medication is discontinued.
Symproic (naldemedine)	Tablets	Oral	OIC in chronic non-cancer pain: 0.2 mg once daily	Patients taking opioids for < 4 weeks may be less responsive to treatment. Symproic should be discontinued when opioid pain medication is discontinued.
Trulance (plecanatide)	Tablets	Oral	CIC and IBS-C: once daily	Tablet may be crushed for patients who are unable to swallow the tablet whole. Crushed tablets may also be administered via a nasogastric tube.
Viberzi (eluxadoline)	Tablets	Oral	Treatment of IBS-D in adults: twice daily	Treatment should be discontinued in patients who develop severe constipation. Dose should be adjusted in patients who are unable to tolerate the 100 mg dose, are receiving concomitant OATP1B1 inhibitors, or have mild or moderate hepatic impairment
Xifaxan (rifaximin)	Tablets	Oral	IBS-D: three times daily for 14 days TD: three times daily for three days Hepatic encephalopathy: twice daily	Patients with IBS-D who experience recurrence may be retreated up to two times with the same regimen. Do not use in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.

See the current prescribing information for full details.

CONCLUSION

- IBS is a gastrointestinal disorder with symptoms of abdominal pain, discomfort and bloating, and abnormal bowel habits with bouts of diarrhea and/or constipation (*WGO, 2015, Quigley et al 2012*).
  - IBS has four subtypes depending on the change in bowel habits: IBS-D, IBS-C, IBS-M, or IBS-U.
  - Most patients with mild disease are managed with disease state education and support, coupled with lifestyle modifications, including diet changes and stress reduction and, when possible, symptom control (*Andresen et al 2008, Ford et al 2009*).
- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.
- Guidelines on management of constipation suggest increased fiber intake and osmotic laxatives. Stimulant laxatives are to be used as needed or as "rescue agents." Lubiprostone and linaclotide can be considered when symptoms of constipation do not respond to laxatives (*AGA 2013, Bharucha et al 2013, Chang et al 2014, Lindberg et al 2010*).
- The American College of Gastroenterology monograph on the management of IBS and CIC notes that rifaximin is effective in reducing IBS symptoms and bloating in IBS-D; alosetron is effective in females with IBS-D; and linaclotide and lubiprostone are both superior to placebo for the treatment of IBS-C. In addition, linaclotide and lubiprostone are each effective for the treatment of CIC (*Ford et al 2014*).
- Amitiza (lubiprostone) is currently the only chloride channel activator commercially available. It selectively activates intestinal chloride channels, increasing intestinal fluid secretion and delaying gastric emptying.
- In clinical trials, Amitiza has demonstrated efficacy in the treatment of CIC as well as IBS-C in women, with improvement in SBMs, straining, constipation severity, stool consistency, and global assessment of constipation (*Drossman et al 2007, Drossman et al 2009, Johanson et al 2004, Johanson et al 2005, Johanson et al 2007, Johanson et al 2008a, Johanson et al 2008b*).
- Linzess (linaclotide) is a guanylate cyclase-C agonist. Linzess acts locally in the intestine to accelerate intestinal transit, increase intestinal secretions and reduce intestinal pain. Linzess has been shown in placebo-controlled studies to be effective in improving constipation related to IBS-C and CIC (*Li et al 2016, Nelson et al 2017, Videlock et al 2013*).
- Trulance (plecanatide) is approved by the FDA for treatment of CIC and IBS-C. Similar to Linzess, it is a guanylate cyclase-C agonist. In two randomized control trials, Trulance 3 mg demonstrated a significantly increased weekly CSBM frequency as measured by the overall CSBM responder rate vs placebo in patients with CIC (*DeMicco et al 2017, Miner et al 2017*). Plecanatide also improved overall responder rate (based on improved abdominal pain and weekly CSBM from baseline) vs placebo in two randomized controlled trials in patients with IBS-C (*Trulance prescribing information 2018*).
- Agents approved for use in OIC include Amitiza (lubiprostone), Movantik (naloxegol), Symproic (naldemedine), and Relistor (methylnaltrexone) in patients with chronic non-cancer pain. Relistor is also approved in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care. Symproic, Relistor, Movantik and Amitiza, are also indicated in patients with chronic pain related to prior cancer or its treatment in those who do not require frequent (eg, weekly) opioid dosage escalation.
- Lotronex (alosetron), a 5-HT receptor antagonist, has been shown to reduce pain, abdominal discomfort, urgency, and diarrhea in patients with IBS as demonstrated in several placebo-controlled trials (*Andresen et al 2008, Bardhan et al 2000, Camilleri et al 2000, Camilleri et al 2001, Chey et al 2004, Cremonini et al 2003, Ford et al 2009, Lembo et al 2001, Lembo et al 2004, Krause et al 2007, Rahimi et al 2008, Watson et al 2001*).
- Use of Lotronex is limited to female patients with chronic, severe IBS-D who have not responded to conventional therapy. Due to serious safety concerns, a boxed warning regarding gastrointestinal adverse events has been added to the alosetron prescribing information. Lotronex also has an approved REMS program.

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