

Therapeutic Class Overview

Irritable Bowel Syndrome and Constipation Agents

INTRODUCTION

Irritable bowel syndrome (IBS)

- 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 2019, Wald 2020*).
- IBS may consist of diarrhea-predominant (IBS-D; abnormal BMs are usually diarrhea), constipation-predominant (IBS-C; abnormal BMs are usually constipation), IBS with a mixed symptomatology (IBS-M), or unclassified IBS (IBS-U). Switching between the subtypes of IBS is also possible (*Wald 2019, Wald 2020*).
- IBS is a functional disorder of the gastrointestinal tract characterized by symptoms of abdominal pain, discomfort and bloating, and abnormal bowel habits with bouts of diarrhea and/or constipation. 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, Quigley et al 2012, World Gastroenterology Organization [WGO] 2015*).
- Prevalence estimates of IBS range from 10 to 12%, and it typically occurs in young adulthood (*Ford et al 2018*). IBS-D is more common in men, and IBS-C is more common in women (*WGO 2015*).
- Symptoms of IBS often interfere with daily life and social functioning (*WGO 2015*).
- The general goals of therapy in IBS 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 (*Ford et al 2018*).
- Non-pharmacological interventions to combat IBS symptoms include dietary modifications such as exclusion of gas-producing foods (eg, beans, prunes, Brussel sprouts, bagels, etc.), and consumption of probiotics, as well as psychosocial therapies (eg, hypnosis, biofeedback, etc.) (*Ford et al 2018*).
- 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 selective chloride channel activators (eg, Amitiza [lubiprostone]); guanylate cyclase-C agonists (eg, Linzess [linaclotide], Trulance [plecanatide]); mu-opioid receptor agonists (eg, Viberzi [eluxadoline]); poorly absorbable antibiotics (eg, Xifaxan [rifaximin]); serotonin-3 receptor antagonists (eg, Lotronex [alosetron]); antidepressants such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs); antispasmodics (eg, dicyclomine, hyoscine, etc.); select probiotics; and peppermint oil (*Ford et al 2018*).
- Amitiza (lubiprostone), Linzess (linaclotide), Trulance (plecanatide), and Zelnorm (tegaserod) are Food and Drug Administration (FDA)-approved for the treatment of IBS-C in adults. Lubiprostone is indicated in women ≥ 18 years of age; tegaserod is indicated for the treatment of IBS-C in adult women < 65 years of age.
 - Tegaserod is a serotonin type 4 (5-HT₄) agonist FDA-approved in July 2002 for the short-term treatment of IBS-C in women and in August 2004 for the treatment of chronic idiopathic constipation (CIC) in men and women < 65 years of age. In 2007, tegaserod was removed from the United States (U.S.) market due to safety concerns based on a postmarketing pooled safety analysis of 29 clinical trials, which demonstrated a higher rate of serious cardiovascular events (including angina, myocardial infarction and stroke) in patients treated with tegaserod vs placebo (*FDA Gastrointestinal Drugs Advisory Committee [Zelnorm] 2018, FDA Multi-disciplinary review [Zelnorm] 2019*).
 - In 2018, the FDA Gastrointestinal Drugs Advisory Committee evaluated the safety and efficacy of tegaserod and recommended approval of tegaserod for the treatment of female patients < 65 years of age with IBS-C at a low cardiovascular risk; tegaserod was re-introduced in March 2019 (*Drugs@FDA 2021, FDA Gastrointestinal Drugs Advisory Committee [Zelnorm] 2018, FDA Multi-disciplinary review [Zelnorm] 2019*).
- Viberzi (eluxadoline) and Xifaxan (rifaximin) are FDA-approved for the treatment of IBS-D. Viberzi is a schedule IV controlled substance. Lotronex (alosetron) is FDA-approved with restrictions for the treatment of women who exhibit severe IBS-D and have failed conventional therapy.

Chronic idiopathic constipation (CIC)

- Amitiza (lubiprostone), Linzess (linaclotide), Motegrity (prucalopride), and Trulance (plecanatide) are indicated for the treatment of 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 < 3 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*).
 - Prucalopride, a selective 5-HT₄ receptor agonist, is a gastrointestinal prokinetic agent that stimulates colonic peristalsis (high-amplitude propagating contractions [HAPCs]), which increases bowel motility (*Shin et al 2014*).
 - The intestinal secretagogues, ie, lubiprostone, linaclotide, and plecanatide, exert their effects by increasing intestinal and colonic secretion of chloride-rich fluid into the intestinal lumen. There is no reported evidence indicating that these agents induce HAPCs.

Opioid-induced constipation (OIC)

- 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*). There are 4 products approved for use in OIC:
 - Amitiza (lubiprostone) is FDA-approved for the treatment of OIC in adults with chronic, non-cancer related pain.
 - 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 (PAMORAs) indicated for the treatment of OIC in adult patients with chronic non-cancer pain.
- For management of OIC, the AGA recommends laxatives as a first-line treatment (*Crockett et al 2019*). For patients with laxative-refractory OIC, naldemedine or naloxegol are recommended over no treatment, methylnaltrexone is suggested over no treatment, and there are no recommendations for the use of lubiprostone or prucalopride.

Traveler's diarrhea (TD)

- TD is a type of acute diarrhea that develops after the consumption of contaminated food or water during periods of travel. The disease is characterized by symptoms of loose stools and abdominal cramps. Although generally not serious, TD may result in inconveniences during travel, including changes to an itinerary, overseas medical encounters, and hospitalization (*Riddle et al 2017*).
 - For the prevention of TD, a 2017 guideline recommends prophylaxis with Xifaxan (rifaximin) in high-risk groups (eg, underlying health conditions); bismuth subsalicylate may be considered second-line in these situations. If rifaximin is used as prophylaxis, azithromycin should also be provided to patients in case of need for break-through therapy. For the treatment of TD, antimicrobials such as azithromycin, rifaximin, or a fluoroquinolone are recommended, with the travel destination guiding the drug(s) of choice (*Riddle et al 2017*).

Hepatic encephalopathy (HE)

- HE is a common complication of severe liver disease. Neuropsychiatric abnormalities, ranging from shortened attention span to lethargy, confusion, and coma, are all possible manifestations depending on disease severity. At this time, pharmacological treatment is only recommended for patients with overt HE, which is diagnosed based on a clinical examination and use of the West Haven Criteria and the Glasgow Coma Score. Secondary prophylaxis of HE after an overt HE episode is also recommended, as is primary prophylaxis in high-risk patients with cirrhosis (*Vilstrup et al 2014*).
 - Rifaximin is FDA-approved for the reduction in risk of overt HE recurrence in adults. A joint guideline from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (AASLD/EASL) also recommend this agent as an adjunct therapy to lactulose for the prevention of overt HE recurrence and overt HE recurrence after the second episode (*Vilstrup et al 2014*).
- The scope of this review will focus upon Amitiza (lubiprostone), Linzess (linaclotide), Lotronex (alosecron), Motegrity (prucalopride), Movantik (naloxegol), Relistor (methylnaltrexone bromide), Symproic (naldemedine), Trulance (plecanatide), Viberzi (eluxadolone), Xifaxan (rifaximin), and Zelnorm (tegaserod) for their respective FDA-approved indications, which are outlined in Table 2.
- Medispan Classes: Agents for CIC (Motegrity, Trulance); Gastrointestinal Chloride Channel Activators (Amitiza); IBS Agents (Lotronex, Linzess, Viberzi, Zelnorm); Peripheral Opioid Receptor Antagonists (Movantik, Relistor, Symproic); Anti-infective Agents – Misc (Xifaxan)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Amitiza (lubiprostone)	✓
Linzess (linaclotide)	✓
Lotronex (alosetron)	✓
Motegrity (prucalopride)	-
Movantik (naloxegol)	-
Relistor (methylnaltrexone bromide)	-
Symproic (naldemedine)	-
Trulance (plecanatide)	-
Viberzi (eluxadoline)	-
Xifaxan (rifaximin)	-
Zelnorm (tegaserod)	-

(Clinical Pharmacology Web site 2021, Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Amitiza (lubiprostone)	Linzess (linaclotide)	Lotronex (alosetron)	Motegrity (prucalopride)	Movantik (naloxegol)	Relistor (methylnaltrexone bromide)	Symproic (naldemedine)	Trulance (plecanatide)	Viberzi (eluxadoline)	Xifaxan (rifaximin)	Zelnorm (tegaserod)
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 adult women < 65 years of age											✓ ‡
Treatment of IBS-C in adults		✓						✓			
Treatment of IBS-D in adults									✓	✓	
Women with severe IBS-D who have:			✓								

Data as of February 17, 2021 MG-U/PH-U/ALS

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Indication	Amitiza (lubiprostone)	Linzess (linaclotide)	Lotronex (alosetron)	Motegrity (prucalopride)	Movantik (naloxegol)	Relistor (methylnaltrex one bromide)	Symproic (naldemedine)	Trulance (plecanatide)	Viberzi (eluxadoline)	Xifaxan (rifaximin)	Zelnorm (tegaserod)
<ul style="list-style-type: none"> chronic IBS symptoms (generally lasting 6 months or longer) had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy[§] 											
Reduction in risk of overt HE recurrence in adults										✓	
Treatment of TD caused by noninvasive strains of <i>Escherichia coli</i> in patients ≥ 12 years of age										✓	

*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 4 months in the treatment of OIC in patients with advanced illness has not been studied.

‡ The safety and efficacy of Zelnorm have not been established in men with IBS-C.

§ IBS-D is severe if it includes diarrhea and ≥ 1 of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS.

|| Xifaxan should not be used in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.

(Prescribing information: Amitiza 2020, Linzess 2020, Lotronex 2019, Motegrity 2020, Movantik 2020, Relistor 2020, Symproic 2020, Trulance 2021, Viberzi 2020, Xifaxan 2020, Zelnorm 2020)

- 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 Lotronex 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.

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 complete spontaneous bowel movement (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%; relative risk [RR] of failure to respond, 0.80; 95% CI, 0.76 to 0.85).
- A 2018 network meta-analysis compared the relative efficacy of the secretagogues linaclotide, lubiprostone, plecanatide, and tenapanor (not available in the U.S.) for the treatment of IBS-C in 15 randomized controlled trials (N = 8462).

Linaclotide 290 mg once daily was ranked first in efficacy based on the FDA-recommended endpoint for IBS-C trials, abdominal pain, and CSBMs; plecanatide 6 mg once daily was ranked highest for safety (*Black et al 2018*).

- The network meta-analysis was updated in 2019 to include three 12-week Phase 3 randomized controlled trials evaluating the efficacy of tegaserod in 2472 female patients with IBS-C. For the FDA-recommended endpoint, all agents, including tegaserod, were significantly more effective than placebo, but linaclotide 290 mcg daily was ranked as the most effective for achieving at least a 30% improvement in abdominal pain along with an increase of at least 1 CSBM/week from baseline for at least 50% of treatment-weeks; tegaserod 6 mg twice a day was ranked third. Indirect comparison of active treatments showed no significant differences between individual drugs and dosages (*Black et al 2019*).
- A network meta-analysis published in 2020 included 18 randomized controlled trials (N = 9844) and compared the efficacy of alosetron, eluxadoline, ramosetron, and rifaximin in patients with IBS-D or IBS-M. All agents were found to be more effective than placebo. In an analysis that ranked agents based on their efficacy in improving both abdominal pain and stool consistency, effect on global symptoms of IBS, and effect on stool consistency, alosetron 1 mg twice daily was ranked highest (ie, most effective). Ramosetron 2.5 mcg once daily was ranked highest for relief from abdominal pain (*Black et al 2020*). 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 2004, Johanson et al 2005, Johanson et al 2007, Johanson et al 2008a, Johanson et al 2008b*).
- In 2 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 and 6 mg vs placebo in patients with IBS-C (Study 1: 30.2% vs 29.5% vs 17.8%, respectively; Study 2: 21.5% vs 24.0% vs 14.2%) (*Brenner et al 2018*).
- Three Phase 3 double-blind, placebo-controlled, multicenter, randomized controlled trials (301, 358, and 307) of similar design in 2470 adults patients evaluated the efficacy and safety of tegaserod vs placebo. In trial 301, treatment with tegaserod resulted in a statistically significant improvement in response rate vs placebo with a difference of 11.4% (95% CI, 3 to 30; $p < 0.005$). Trials 358 and 307 demonstrated treatment differences vs placebo of 4.7% and 5.3%, respectively, but results were not statistically significant. (*FDA Medical review(s) [Zelnorm] 2002, FDA Multi-disciplinary review [Zelnorm] 2019, Müller-Lissner et al 2001, Novick et al 2002*).
- A systematic review of various therapies for the treatment of IBS included 11 RCTs (n = 9242) evaluating tegaserod vs placebo for the treatment of IBS-C. The outcome of proportion of patients with persistent IBS-C symptoms with tegaserod was 55% (3301/6041) vs 64% (2032/3201) with placebo. Treatment with tegaserod was shown to be superior vs placebo with an RR of 0.85 (95% CI, 0.80 to 0.90) with a number needed to treat (NNT) of 10 (95% CI, 8 to 14) (*Ford et al 2009, Ford and Vandvik 2012*).
- A 2004 systematic review and meta-analysis included 4 double-blind controlled trials (n = 3564) evaluating tegaserod in the treatment of IBS-C. In each trial, a statistically significant effect on constipation, abdominal pain/discomfort, bloating and global relief with tegaserod treatment was demonstrated in women, with the difference between placebo and tegaserod of 10 to 15%, primarily due to a high placebo response (*Lesbros-Pantoflickova et al 2004*).
- 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 2 randomized, multicenter, multinational, double-blind, placebo-controlled, Phase 3 clinical trials in which 2427 patients with IBS-D (meeting Rome III criteria) had 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 5 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 ($p = 0.004$) vs 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 efficacy of eluxadoline for the treatment of IBS-D were also studied in patients with an inadequate response to loperamide in a randomized, multicenter, multinational, double-blind, placebo-controlled, Phase 4 trial ($n = 346$). Patients with IBS-D (meeting Rome III criteria), average abdominal pain scores > 3 on a 0 to 10 scale during the week prior to randomization, a BSS of ≥ 5.5 with at least 5 days of BSS ≥ 5 during the week prior to randomization, and a self-reported inadequate response to loperamide within the previous year were randomized to eluxadoline 100 mg or placebo twice daily. The primary endpoint was the proportion of composite responders, defined as improvement in the daily worst abdominal pain score by 40% and < 5 BSS score for at least 50% of treatment days. Over the 12-week treatment period, significantly more eluxadoline- vs placebo-treated patients achieved the primary composite endpoint (22.7% vs 10.3%; $p = 0.002$) as well as the individual components of the endpoint (improvement in stool consistency [27.9% vs 16.7%; $p = 0.01$] and improvement in the daily worst abdominal pain score by 40% [43.6% vs 31.0%; $p = 0.02$]) (*Brenner et al 2019*).
- The safety and effectiveness of rifaximin for treatment of IBS-D were established in 3 double-blind, placebo-controlled trials.
 - In the first 2 trials, 1,258 patients with IBS-D (Rome II criteria) were randomly assigned to receive rifaximin 550 mg 3 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 2 of 4 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 3 times daily ($n = 328$) or placebo ($n = 308$) for 2 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; $p < 0.05$) (*Lembo et al 2016b*).

IBS and CIC

- A 2018 systematic review and meta-analysis compared the efficacy of intestinal secretagogues (ie, linaclotide, lubiprostone, plecanatide, and tenapanor [not available in the U.S.]) for the treatment of chronic constipation or IBS-C (*Lasa et al 2018*). For patients with chronic constipation, intestinal secretagogues were superior to placebo for increasing the number of CSBMs per week (RR, 1.87; 95% CI, 1.24 to 2.83 [analysis included linaclotide, lubiprostone, and plecanatide]) and for achieving ≥ 3 SBMs per week (RR, 1.56; 95% CI, 1.31 to 1.85 [analysis included linaclotide and lubiprostone]). For those with IBS-C, intestinal secretagogues were superior to placebo for increase in CSBMs per week (RR, 2.44; 95% CI, 1.51 to 3.93 [analysis included linaclotide and tenapanor]) and for achieving ≥ 3 SBMs per week (RR, 1.97; 95% CI, 1.74 to 2.24 [analysis included linaclotide only]).
- 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 2 agents for efficacy in CIC, efficacy in IBS-C, frequency of diarrhea, or study withdrawal due to diarrhea (*Shah et al 2018*).
- A network meta-analysis of 13 RCTs evaluated the efficacy and tolerability of tegaserod for the treatment of IBS and chronic constipation in patients, predominantly women, ≥ 12 years of age (*Evans et al 2007*).
 - In patients with IBS-C, for the Subject Global Assessment (SGA) of relief in patients, tegaserod resulted in a statistically significant benefit in 2 trials, compared with a nonsignificant trend for benefit in the remaining 2 studies. For abdominal pain and discomfort, the RR for being a responder with tegaserod vs placebo was non-significant; for bowel habits (as measured by responder rate), 1 trial did not suggest a benefit with tegaserod, and 2 trials showed a nonsignificant trend in favor of tegaserod.
 - For patients with chronic constipation, the RR of being a responder in terms of CSBMs/week with tegaserod 12 mg vs placebo was 1.54 (95% CI, 1.35 to 1.75), with a weighted mean difference (WMD) of 0.6 (95% CI, 0.42 to 0.78). Differences between tegaserod and placebo in increases in BM frequency were small (< 1 /week).

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 CSBMs/week compared with placebo with an 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).
- A meta-analysis of 16 randomized controlled trials evaluated the safety and efficacy of prucalopride in the management of CIC (Sajid et al 2016). The primary outcome measure was the incidence of SBMs per week, and the secondary outcome measure was adverse events.
 - Based on data from 9 trials, prucalopride 2 mg significantly increased the frequency of SBMs per week compared with placebo (standardized mean difference [SMD] 0.34; 95% CI, 0.11 to 0.56; $I^2 = 78\%$; $p = 0.003$).
 - The risk of developing adverse events (eg, headache, abdominal cramps, excessive flatulence, dizziness, diarrhea, rash) was higher in the prucalopride 2 mg group (odds ratio [OR], 1.76; 95% CI, 1.33 to 2.34; $I^2 = 53\%$; $p < 0.0001$). The majority of adverse events were reported within the first 24 hours of initiation of therapy and were transient.
- A systematic review and meta-analysis evaluated the efficacy of serotonin type 4 (5-HT₄) agonists, including prucalopride, velusetrag, and naronapride (not approved in the U.S.) for the treatment of CIC. 5-HT₄ agonists were superior to control for all measured outcomes (Shin et al 2014).
 - The proportion of patients randomized to a 5-HT₄ agonist who achieved a mean of ≥ 3 CSBMs per week was 27.5% vs 17.2% of patients randomized to control (RR, 1.85; 95% CI, 1.23 to 2.79; $I^2 = 89\%$; $p < 0.001$).
 - Overall, 46.7% of patients randomized to a 5-HT₄ agonist achieved a mean increase of ≥ 1 CSBM per week over baseline vs 30.8% of control patients (RR, 1.57; 95% CI, 1.19 to 2.06; $I^2 = 89\%$; $p < 0.001$).
 - 5-HT₄ agonists also showed significant improvement over control for patient-reported quality of life (QOL) measures.
 - Adverse events were more common with 5-HT₄ agonists than with control (RR, 1.25; 95% CI, 1.14 to 1.38) and included headache, diarrhea, nausea, and abdominal pain.
- 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 (Vidlock et al 2013).
- A network meta-analysis of 33 randomized controlled trials involving 17,214 adult patients with CIC ranked prucalopride 2 mg once daily first for efficacy among other agents used for CIC (RR, 0.82; 95% CI, 0.78 to 0.86), when the endpoint was defined as failure for achieving ≥ 3 CSBMs/week at 12 weeks (Luthra et al 2019).
- 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 (OR 3.0; 95% CI, 1.8% to 5.2%) (Schoenfeld et al 2018).
- 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).
- 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,).
- Six double-blind, placebo-controlled, multicenter, randomized controlled trials of similar design in adults (N = 2484) evaluated the safety and efficacy of prucalopride for the treatment of CIC in an integrated analysis of the results (Camilleri et al 2016, FDA briefing document [Prucalopride] 2018).
 - The percentage of patients with a mean frequency of ≥ 3 CSBMs/week over a 12-week treatment period was significantly higher with prucalopride 2 mg/day (27.8%) vs placebo (13.2%) (OR, 2.68; 95% CI, 2.16 to 3.33; $p < 0.001$); the NNT with prucalopride was 8.8 (95% CI, 7.1 to 11.6). Efficacy and safety outcomes were not significantly different between men and women.

- The proportion of patients with a mean increase of ≥ 1 CSBM/week was 47.0% with prucalopride vs 29.9% with placebo ($p < 0.001$).
- Out of the 6 trials, the 24-week trial failed to demonstrate statistical significance for the primary endpoint after both 12 and 24 weeks, causing moderate heterogeneity. The reasons for the smaller treatment effect in this study remain unclear.
- Due to its differing mode of action, prucalopride may be beneficial for patients with CIC who have an insufficient quantity of high-amplitude propagating contractions (HAPCs) or in those who do not respond to other medications (Camilleri et al 2016).

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 ≥ 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).
- In a 2019 meta-analysis of 6 randomized controlled trials ($N = 2762$), naldemedine was superior to placebo in SBM response rate (OR, 3.00; 95% CI, 1.93 to 4.65), change in SBM frequency (OR, 6.46; 95% CI, 4.73 to 8.20), and change in complete SBM frequency (OR, 5.93; 95% CI, 4.90 to 6.96) (Esmadi et al 2019).
- A total of 1,300 patients were enrolled in 3, 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 9 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 8. 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 (Amitiza prescribing information 2019). 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 < 3 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 8. Changes from baseline in SBM frequency rates were significantly higher at week 8 ($p = 0.005$) 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 7 pharmacological treatments for OIC. Efficacy assessment was based on objective outcome measures (OOMs): BM frequency, BM within 4 hours, and time to first BM. Methylnaltrexone showed improvements in all 3 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. CB-5945 (not

FDA-approved) and prucalopride (not FDA-approved for OIC) 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, 2 replicate Phase 3 clinical trials with a total of 1,352 participants with OIC who had taken opioids for at least 4 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 4 weeks followed by as-needed dosing for 8 weeks. A responder to methylnaltrexone treatment was defined as a patient with ≥ 3 SBMs per week, with an increase of ≥ 1 SBMs per week over baseline, for at least 3 weeks in the 4-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 prucalopride (not FDA-approved for OIC) and alvimopan (not FDA-approved for OIC) (*Sridharan and Sivaramakrishan 2018*). Observations from 16 randomized controlled trials with 4048 patients demonstrated that lubiprostone, naldemedine, naloxegol, and SC and oral methylnaltrexone 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*).
- A systematic review and network meta-analysis of 27 studies compared the efficacy and safety of methylnaltrexone, naloxone, naldemedine, naloxegol, lubiprostone, linaclotide, plecanatide, and several agents that are not currently approved in the U.S. in OIC. The authors found that when non-response was defined as a failure to achieve an average of ≥ 3 BMs per week with an increase of ≥ 1 BM per week from baseline or an average of ≥ 3 BMs per week, naloxone was the most efficacious treatment for OIC (RR, 0.65; 95% CI, 0.52 to 0.80) and the safest when ranked against other agents. When non-response was defined as only failure to achieve an average of ≥ 3 BMs per week with an increase of ≥ 1 BM per week from baseline, naldemedine was found to be the most efficacious (RR, 0.66; 95% CI, 0.56 to 0.77), followed by alvimopan (RR, 0.74; 95% CI; 0.57 to 0.94) (*Luthra et al 2018*).
- A systematic review and meta-analysis of 35 randomized controlled trials examined the efficacy and safety of alvimopan, linaclotide, lubiprostone, methylnaltrexone, naldemedine, naloxegol, naloxone, and prucalopride in OIC. In this analysis, naldemedine, methylnaltrexone, naloxegol 25 mg and naloxegol 12.5 mg had the highest odds of meeting

the FDA endpoint of SBMs (defined as > 3 SBMs per week plus an increase of 1 SBM per week compared to baseline). The odds ratio for lubiprostone was still significant vs placebo, but the odds ratios for linaclotide and alvimopan were not significant vs placebo. Only naloxegol 25 mg and lubiprostone demonstrated an increased risk of treatment-emergent adverse events compared to placebo (*Vijayvargiya et al 2020*).

TD

- Both a 2012 and 2017 meta-analysis including 4 and 5 randomized, placebo-controlled trials, respectively, demonstrated the superiority of rifaximin in preventing TD. In the 2012 analysis by *Alajbegovic et al*, rifaximin reduced the risk of disease by 67% (RR, 0.33; 95% CI, 0.24 to 0.45), while the 2017 analysis by *Ng et al* showed a 52.2% RR reduction (RR, 0.478; 95% CI, 0.375 to 0.610). Neither analysis reported any new safety signals (*Alajbegovic et al 2012, Ng et al 2017*).

HE

- Interventions for the treatment of overt HE were compared in a 2014 network meta-analysis of 20 randomized controlled trials (N = 10,007). Results showed no significant difference between neomycin and rifaximin when considering the outcomes of clinical improvement, blood ammonia concentration, and mental status. However, neomycin demonstrated an increased risk of adverse events when compared to rifaximin (OR, 14.03; 95% CI, 0.06 to 3035.53) (*Zhu et al 2015*).
- A 2019 meta-analysis evaluated whether the addition of rifaximin to lactulose improved outcomes in patients with overt HE. A total of 2276 patients were included across 5 randomized controlled trials and 5 observational studies. In a pooled analysis of data from all 10 studies, combination therapy improved efficacy (risk difference [RD], 0.26; 95% CI, 0.19 to 0.32) and reduced the risk of death (RD, -0.11; 95% CI, -0.19 to -0.03). Similar trends were seen in separate analyses that included only data from the randomized controlled trials. The risk of adverse events was similar between combination therapy and lactulose alone (RD, -0.06; 95% CI, -0.24 to 0.13) (*Wang et al 2019*).
- A meta-analysis of 25 randomized controlled trials involving 1564 patients with cirrhosis and minimal HE revealed that rifaximin (OR, 7.53; 95% predictive interval [PrI], 4.45 to 12.73) and lactulose (OR, 5.39; 95% PrI, 3.60 to 8.0) are more effective agents to reverse minimal HE compared with placebo or no treatment (*Dhiman et al 2019*).

CLINICAL GUIDELINES

IBS

- In 2021, the American College of Gastroenterology (ACG) released a guideline on the management of IBS (*Lacy et al 2021*). The ACG makes the following recommendations regarding pharmacologic therapy within the guideline (reported with the strength of recommendation and quality of evidence, respectively):
 - Recommends the use of guanylate cyclase activators to treat global IBS-C symptoms (strong; high)
 - Recommends the use of rifaximin to treat global IBS-D symptoms (strong; moderate)
 - Recommends that alosetron be used to relieve global IBS-D symptoms in women with severe symptoms who have failed conventional therapy (conditional; low)
 - Suggests that mixed opioid agonists/antagonists be used to treat global IBS-D symptoms (conditional; moderate)
 - Suggests that tegaserod be used to treat IBS-C symptoms in women < 65 years of age with ≤ 1 cardiovascular risk factors who have not adequately responded to secretagogues (strong/conditional; low)
 - Recommends the use of chloride channel activators to treat global IBS-C symptoms (strong; moderate)
 - Suggests against PEG products to relieve global IBS symptoms in those with IBS-C (conditional; low)
 - Recommends against the use of antispasmodics for the treatment of global IBS symptoms (conditional; low)
 - Suggests the use of peppermint to provide relief of global IBS symptoms (conditional; low)
 - Suggests against probiotics for the treatment of global IBS symptoms (conditional; very low)
 - Suggests that soluble, but not insoluble, fiber be used to treat global IBS symptoms (strong; moderate)
 - Do not suggest the use of bile acid sequestrants to treat global IBS-D symptoms (conditional; very low)
 - Recommends that tricyclic antidepressants be used to treat global IBS symptoms (strong; moderate)
- The AGA guideline on management of IBS makes the following statements (reported with the 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).

CIC

- The 2014 ACG 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). Of note, only statements pertaining to CIC are included **as more recent guidelines on IBS management were published in 2021 (summarized above)**:
 - Linaclotide is effective in CIC (strong; high)
 - Lubiprostone is effective in the treatment of CIC (strong; high)
 - Prucalopride is more effective than placebo in improving symptoms of CIC (strong; moderate)
 - Although supported by varying levels of evidence, fiber supplements, osmotic laxatives (PEG, lactulose), and stimulant laxatives (sodium picosulfate [not available in the U.S. as a single agent], bisacodyl) are recommended for the treatment of CIC (all strong recommendations).
- Additional guidelines on the 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).

OIC

- For the management of OIC, the AGA recommends laxatives as a first-line treatment (Crockett *et al* 2019). For patients with laxative-refractory OIC, naldemedine or naloxegol are recommended over no treatment. Methylnaltrexone is suggested over no treatment, but authors note that evidence supporting the use of this agent for OIC is low and costs may be prohibitive. The AGA does not make any recommendations for the use of lubiprostone or prucalopride for OIC due to lack of evidence.

TD

- Guidelines for TD were published in 2017 and recommend rifaximin for moderate-to-severe cases of the disease. If rifaximin is used as prophylaxis, azithromycin should also be provided to patients in case of need for breakthrough therapy. For the treatment of TD, antimicrobials such as azithromycin, rifaximin, or a fluoroquinolone are recommended, with the travel destination guiding the drug(s) of choice (Riddle *et al* 2017).

HE

- A joint guideline from AASLD and EASL recommends rifaximin as an adjunct therapy to lactulose for the prevention of overt HE and recurrent episodes of HE after the second episode (Vilstrup *et al* 2014).

SAFETY SUMMARY

- Contraindications:
 - Amitiza is contraindicated with known or suspected mechanical gastrointestinal obstruction.
 - Lotronex has several contraindications, including a 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 6 years of age or younger and in patients with known or suspected mechanical gastrointestinal obstruction.
 - Motegrity is contraindicated in patients with intestinal perforation or obstruction due to a structural or functional disorder of the gut wall, obstructive ileus, and severe inflammatory conditions of the intestinal tract such as Crohn’s disease, ulcerative colitis, and toxic megacolon/megarectum; and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients.
 - Movantik is contraindicated in patients with known or suspected gastrointestinal obstruction **or in patients at 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 a 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 3 alcoholic beverages daily; history of pancreatitis or structural diseases of the pancreas including known or suspected pancreatic duct obstruction; severe hepatic impairment; history of 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.
- Zelnorm is contraindicated in patients with a history of myocardial infarction, stroke, transient ischemic attack, or angina; a history of ischemic colitis or other forms of intestinal ischemia; severe renal impairment or end-stage renal disease; moderate or severe hepatic impairment; a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions; and hypersensitivity to tegaserod.
- **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 for Linzess and Trulance.
 - 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.
- **Warnings/precautions:**
 - Amitiza: nausea (29% incidence in CIC), diarrhea (12% in CIC), syncope and hypotension, dyspnea, and bowel obstruction
 - Motegrity and Zelnorm: Worsening of depression and emergence of suicidal thoughts and behavior may occur during therapy. Patients should discontinue the drug and contact their provider if these situations occur.
 - Movantik, Relistor, Trulance, and Zelnorm: Discontinue in the event of severe, persistent, or worsening abdominal pain or diarrhea.
 - **Linzess:** Dosing should be suspended if severe diarrhea occurs.
 - Relistor, **Movantik**, and Symproic: Use with caution in patients with known or suspected lesions of the gastrointestinal tract; discontinue in the event of severe, persistent, or worsening abdominal pain.
 - Viberzi: Constipation, sometimes requiring hospitalization, has been reported following administration of Viberzi. Patients who develop severe constipation should discontinue treatment and contact their health care provider immediately.
 - Xifaxan: Use in travelers' diarrhea complicated by fever and/or blood in the stool should be avoided due to pathogens other than *E.coli*. The agent may contribute to *Clostridium difficile*-associated diarrhea.
 - Zelnorm: Avoid use in patients with severe diarrhea. Patients should contact their healthcare provider if severe diarrhea, hypotension or syncope occur. Zelnorm may increase the risk for stroke, myocardial infarction, and cardiovascular death; patients should be assessed for cardiovascular risk factors prior to therapy initiation. Patients may develop ischemic colitis, which may require hospitalization. Patients should be monitored for worsening of depression and any signs of suicide attempt and/or ideation.
- **Drug Interactions**
 - Amitiza: Diphenylheptane opioids such as methadone may interfere with the efficacy of Amitiza.
 - Lotronex: 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.
 - Motegrity: Concomitant administration of Motegrity and erythromycin may increase erythromycin concentrations via an unknown mechanism. Concomitant administration of Motegrity and ketoconazole may increase the Motegrity concentrations.
 - Movantik: Concomitant use of Movantik should be avoided with the following drug classes: moderate CYP3A4 inhibitors (eg, diltiazem, erythromycin, verapamil) due to increased Movantik concentrations, strong CYP3A4 inducers

(eg, rifampin) due to decreased Movantik 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.

- Relistor: Concomitant use of Relistor with other opioid antagonists should be avoided due to potentially additive effects that may increase the risk of opioid withdrawal.
- Symproic: 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 Symproic concentrations, and other opioid antagonists due to a 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.
- Viberzi: 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).
- Xifaxan: Concomitant administration of drugs that are P-glycoprotein inhibitors with Xifaxan can substantially increase systemic exposure to Xifaxan. Caution should be exercised when concomitant use of Xifaxan and a P-glycoprotein inhibitor such as cyclosporine is needed. Concomitant use with warfarin may cause changes in international normalized ratio (INR).
- Zelnorm: Co-administration with P-glycoprotein (P-gp) inhibitors (eg, ritonavir, clarithromycin, itraconazole) and quinidine may increase exposure to Zelnorm.
- 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 2021*).
- Adverse events:
 - The IBS and constipation agents are most commonly associated with gastrointestinal-related adverse events.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Amitiza (lubiprostone)	Capsules	Oral	<u>Treatment of CIC in adults and OIC: twice daily</u> <u>Treatment of IBS-C in women ≥ 18 years of age: twice daily</u>	<ul style="list-style-type: none"> ● Safety and efficacy have not been established in pediatric patients. ● Dose should be adjusted in moderate and severe hepatic impairment.
Linzess (linaclotide)	Capsules	Oral	<u>IBS-C: once daily</u> <u>CIC: once daily</u>	<ul style="list-style-type: none"> ● Safety and efficacy have not been established in pediatric patients. ● Capsule contents may be administered with applesauce or water if a patient is unable to swallow.
Lotronex (alosetron)	Tablets	Oral	<u>Women with severe IBS-D: twice daily</u>	<ul style="list-style-type: none"> ● Data in pregnant women are insufficient to determine risk for maternal or fetal outcomes. ● Safety and efficacy have not been established in pediatric patients. ● Caution should be used in patients ≥ 65 years of age due to risk for constipation. ● Caution should be used in patients with mild or moderate hepatic

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				<p>impairment; use should be avoided in severe hepatic impairment.</p> <ul style="list-style-type: none"> Treatment should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice daily.
Motegrity (prucalopride)	Tablets	Oral	<u>CIC in adults:</u> once daily	<ul style="list-style-type: none"> Safety and efficacy have not been established in pediatric patients. Dose should be adjusted for severe renal impairment (creatinine clearance [CrCl] < 30 mL/min).
Movantik (naloxegol)	Tablets	Oral	<u>OIC in chronic non-cancer pain:</u> once daily	<ul style="list-style-type: none"> Safety and efficacy have not been established in pediatric patients. Tablet may be crushed for patients who are unable to swallow the tablet whole; crushed tablets may also be administered via a nasogastric tube. Tablets should be taken 1 hour before the first meal of the day or 2 hours after the meal. Use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C). Dose should be adjusted for renal impairment (CrCl < 60 mL/min). Maintenance laxative therapy should be discontinued prior to initiating therapy. Movantik should be discontinued when opioid pain medication is discontinued.
Relistor (methylnaltrexone)	Single-use vials, single-use pre-filled syringes, tablets	Oral, SC injection	<p><u>OIC in chronic non-cancer pain:</u> SC injection once daily, or oral tablet(s) once daily in the morning</p> <p><u>OIC in advanced illness:</u> Weight-based SC injection once every other day, as needed (maximum of once daily)</p>	<ul style="list-style-type: none"> Safety and efficacy have not been established in pediatric patients. SC injection should be administered in the upper arm, abdomen, or thigh; injection sites should be rotated. Oral dose should be adjusted in moderate and severe hepatic impairment; adjustment of SC injection dose should be considered in severe hepatic impairment. Dose should be adjusted in moderate to severe renal impairment. Maintenance laxative therapy should be discontinued prior to initiating therapy. Tablets should be taken with water 30 minutes before the first meal of the day.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				<ul style="list-style-type: none"> Relistor should be discontinued when opioid pain medication is discontinued.
Symproic (naldemedine)	Tablets	Oral	<u>OIC in chronic non-cancer pain</u> : once daily	<ul style="list-style-type: none"> Safety and efficacy have not been established in pediatric patients. Use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C). Symproic should be discontinued when opioid pain medication is discontinued.
Trulance (plecanatide)	Tablets	Oral	<u>CIC and IBS-C</u> : once daily	<ul style="list-style-type: none"> 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	<u>Treatment of IBS-D in adults</u> : twice daily	<ul style="list-style-type: none"> Safety and efficacy have not been established in pediatric patients. Dose should be adjusted in patients who are unable to tolerate the 100 mg dose, are receiving concomitant OATP1B1 inhibitors, have moderate or severe renal impairment (CrCl < 60 mL/min), or have mild or moderate hepatic impairment. Use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C).
Xifaxan (rifaximin)	Tablets	Oral	<u>IBS-D</u> : 3 times daily for 14 days <u>TD</u> : 3 times daily for 3 days <u>Hepatic encephalopathy</u> : twice daily	<ul style="list-style-type: none"> Safety and efficacy have not been established in pediatric patients < 12 years of age with TD or patients < 18 years of age for hepatic encephalopathy and IBS-D. Patients with IBS-D who experience recurrence may be retreated up to 2 times with the same regimen. Should not be used in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than <i>E. coli</i>. Caution should be used in patients with severe hepatic impairment (Child-Pugh Class C).
Zelnorm (tegaserod)	Tablets	Oral	<u>IBS-C</u> : twice daily	<ul style="list-style-type: none"> Tablets should be taken 30 minutes before a meal. Zelnorm should be discontinued if no response is seen after 4 to 6 weeks of treatment.

See the current prescribing information for full details.

CONCLUSION

- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.
- IBS is a gastrointestinal disorder with symptoms of abdominal pain, discomfort and bloating, and abnormal bowel habits with bouts of diarrhea and/or constipation (*Andresen et al 2008, Quigley et al 2012, WGO 2015*). IBS has 4 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*).
 - Amitiza (lubiprostone), Linzess (linaclotide), Trulance (plecanatide), and Zelnorm (tegaserod) are indicated for the treatment of IBS-C. Amitiza is a selective chloride channel activator; Linzess and Trulance are guanylate cyclase-C agonists. Zelnorm is a 5-HT₄ agonist that was re-introduced to the market in March 2019.
 - Lotronex (alosetron), Viberzi (eluxadoline), and Xifaxan (rifaximin) are indicated for the treatment of IBS-D.
 - Viberzi is a mu-opioid receptor agonist and a schedule IV controlled substance.
 - Xifaxan is a rifamycin antibacterial. Patients with IBS-D who experience recurrence with Xifaxan treatment may be retreated up to 2 times with the same regimen.
 - Lotronex is limited to use in females with chronic, severe IBS-D who have not responded to conventional therapy. Due to serious safety concerns, Lotronex has a boxed warning regarding risk of gastrointestinal adverse events including ischemic colitis, and also has a REMS program.
- The 2021 ACG guideline on the management of IBS makes the following recommendations regarding agents within this review (*Lacy et al 2021*) (reported with the strength of recommendation and quality of evidence, respectively):
 - Recommends the use of guanylate cyclase activators to treat global IBS-C symptoms (strong; high)
 - Recommends the use of rifaximin to treat global IBS-D symptoms (strong; moderate)
 - Recommends that alosetron be used to relieve global IBS-D symptoms in women with severe symptoms who have failed conventional therapy (conditional; low)
 - Suggests that mixed opioid agonists/antagonists be used to treat global IBS-D symptoms (conditional; moderate)
 - Suggests that tegaserod be used to treat IBS-C symptoms in women < 65 years of age with ≤ 1 cardiovascular risk factors who have not adequately responded to secretagogues (strong/conditional; low)
 - Recommends the use of chloride channel activators to treat global IBS-C symptoms (strong; moderate)
- The 2014 ACG monograph on the management of CIC and IBS notes that linaclotide and lubiprostone are each effective for the treatment of CIC, and prucalopride is more effective than placebo in improving symptoms of CIC (*Ford et al 2014*).
 - Additional guidelines on management of constipation suggest increased fiber intake and osmotic laxatives (*AGA 2013, Bharucha et al 2013, Lindberg et al 2010*). Stimulant laxatives are to be used as needed or as “rescue agents.” Amitiza and Linzess can be considered when symptoms of constipation do not respond to laxatives.
 - Amitiza, Linzess, Motegrity (prucalopride), and Trulance are indicated for the treatment of CIC.
 - Motegrity is a selective 5-HT₄ receptor agonist that stimulates colonic peristalsis. Amitiza, Linzess, and Trulance are intestinal secretagogues and there is no reported evidence indicating that these agents induce peristalsis.
- For management of OIC, the AGA recommends laxatives as a first-line treatment (*Crockett et al 2019*). For patients with laxative refractory OIC, Symproic (naldemedine) or Movantik (naloxegol) are recommended over no treatment. Relistor (methylnaltrexone) is suggested over no treatment, but authors note that evidence supporting the use of this agent for OIC is low. The AGA does not make any recommendations for the use of Amitiza or Motegrity for OIC due to lack of evidence.
 - Amitiza, Movantik, Relistor, and Symproic are approved for treatment of OIC in patients with chronic non-cancer pain, and in those with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation. Relistor injection is also approved in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.
 - Movantik, Relistor, and Symproic are PAMORAs.
- TD is a type of acute diarrhea that develops after the consumption of contaminated food or water during periods of travel. For the prevention of TD, guidelines recommend prophylaxis with rifaximin in high-risk groups. If rifaximin is used as prophylaxis, azithromycin should also be provided to patients in case of need for break-through therapy. For the treatment of TD, antimicrobials such as azithromycin, rifaximin, or a fluoroquinolone are recommended, with the travel destination guiding the drug(s) of choice (*Riddle et al 2017*).

- HE is a common complication of severe liver disease characterized by neuropsychiatric abnormalities that vary in presentation based on disease severity. The AASLD and EASL recommend rifaximin as adjunct therapy to lactulose for the prevention of overt HE recurrence and overt HE recurrence after the second episode (*Vilstrup et al 2014*).

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