Drug Class Review

Agents Indicated in the Treatment of Irritable Bowel Syndrome

56:92 GI Drugs, Miscellaneous

Alosetron (Lotronex®)
Eluxadoline (Viberzi®)
Linaclotide (Linzess®)
Lubiprostone (Amitiza®)
Tegaserod (Zelnorm®)

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Executive Summary

Introduction: Irritable bowel syndrome (IBS) is a common, nonfatal gastrointestinal disorder associated with significant costs and impact on quality of life. Five agents labeled for use in the treatment of IBS include: alosetron, eluxadoline, linaclotide, lubiprostone and tegaserod. Linaclotide, lubiprostone and tegaserod are indicated in the treatment of constipation-predominant IBS and work primarily to increase intestinal fluid secretion and decrease gastrointestinal transit time. Alosetron and eluxadoline are indicated in the treatment of diarrhea-predominant IBS and work by increasing GI transit time. Alosetron and tegaserod are approved specifically for use in women and are only available through restricted prescribing programs.

The American College of Gastroenterology guidelines recommend linaclotide and lubiprostone as first-line treatment options in patients with constipation-predominant IBS. Alosetron is recommended in women with diarrhea-predominant IBS. Fiber supplementation and antidepressant therapy may be used for symptomatic relief and antibiotic therapy with rifamixin and anti-spasmodic agents are considered short-term targeted therapies.

Clinical Efficacy: The efficacy of the IBS-specific treatment agents has not been directly compared in any clinical trials or meta-analyses. Placebo controlled evidence suggests the agents are effective in the treatment of IBS. In clinical trials, alosetron demonstrated efficacy compared to placebo in patients with diarrhea-predominant IBS but therapy should be monitored closely for the development of constipation and, in rare cases, ischemic colitis. According to the limited evidence, linaclotide and tegaserod appear to be effective treatment options for constipation-predominant IBS but generalizability may be limited to female patients. In addition, the evidence suggests lubiprostone may also be an effective treatment option for patients with constipation-predominant IBS. Safety and efficacy associated with long-term treatment with any of the IBS-specific agents is limited.

Adverse Drug Reactions: Adverse events most frequently reported with the agents are generally limited to the gastrointestinal tract and may include cramping, nausea, diarrhea and/or constipation. Lubiprostone and linaclotide cause dose-related adverse events and initiating treatment with the lowest effective doses is recommended. The FDA has placed restrictions on the use of alosetron and tegaserod due to post-marketing reports of serious adverse effects. Eluxadoline was recently approved for use in the US and will not be available until 2016.

Summary: The exact pathophysiology of IBS is not known and the diagnosis and treatment can be challenging. In general, the goals of therapy are to provide symptom relief and improve quality of life. Overall, pharmacologic treatment should be guided by patient-specific symptoms, cost, efficacy, potential adverse effects and patient preference.

Introduction

Irritable bowel syndrome (IBS) is a chronic, relapsing gastrointestinal disease characterized by abdominal discomfort and irregular bowel habits (diarrhea, constipation or both).[1,2] The goals of IBS treatment are to provide symptom relief and improve quality of life. Pharmacologic agents used in the treatment of IBS are aimed at relieving pain and improving bowel function. For patients with diarrhea-predominant IBS, antidiarrheal agents (i.e. loperamide) may be helpful. For patients with constipation-predominant IBS, fiber supplements are recommended. Many other over-the-counter and prescription medications may be used in the symptomatic treatment of IBS including laxatives, antibiotics, probiotics, anticholinergic agents, tricyclic antidepressants, bile acid sequestrants and a number of herbal agents (melatonin, peppermint oil, etc). Several prescription agents specifically indicated in the treatment of IBS are available: alosetron, eluxadoline, linaclotide, lubiprostone and tegaserod. All of these agents are available in oral formulations and are dosed once to twice daily. Alosetron (Lotronex®) may only be prescribed through a Risk Evaluation and Mitigation Strategy (REMS) program and the provider must enroll in the Prometheus Prescribing Program. Tegaserod (Zelnorm®) is currently only available under an emergency investigational new drug (IND) process, requiring providers to contact the Food and Drug Administration's (FDA) Division of Drug Information to receive a shipment of the medication directly from the manufacturer (Novartis). This report will highlight the clinical safety and efficacy data available for the IBS-specific treatment agents. Table 1 provides a summary of the agents included in this drug class review.

Table 1. Comparison of the Agents Indicated in the Treatment of IBS[3,4]

Product	Route of Administration	Available Doses	Labeled Uses	Dose Range	Generic Available
Alosetron (Lotronex)	Oral tablet	Tablet: 0.5 mg; 1 mg	Irritable bowel syndrome	0.5-1 mg twice daily for 4 weeks	No
Eluxadoline (Viberzi)	Oral tablet	Tablet: 75 mg; 100 mg	Irritable bowel syndrome with diarrhea in adults	75-100 mg twice daily	No
Linaclotide (Linzess)	Oral capsule	Capsule: 145 mcg; 290 mcg	Chronic idiopathic constipation Irritable bowel syndrome with constipation	CIC: 145 mcg once daily IBS-C: 290 mcg once daily	No
Lubiprostone (Amitiza)	Oral capsule	Capsule: 8 mcg, 24 mcg	Chronic idiopathic constipation Irritable bowel syndrome with constipation in adult women Opioid-induced constipation for chronic non-cancer pain	CIC: 24 mcg twice daily IBS-C: 8 mcg twice daily Opioid-induced constipation: 24 mcg twice daily	No
Tegaserod (Zelnorm)	Oral tablets	Tablet: 6 mg	Emergency treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation in women less than age 55.	CIC: 6 mg twice daily before meals IBS-C: 6 mg twice daily, before meals, for 4-6 weeks. Then reassess need for continuing.	No

Key: CIC = chronic idiopathic constipation; IBS-C = irritable bowel syndrome, constipation predominant

Disease Overview

Irritable bowel syndrome (IBS) is one of the most common, nonfatal gastrointestinal disorders in the United States with significant costs and impact on quality of life.[2] Nearly 20% of Americans suffer from IBS, which is commonly described as a "motility disorder" and is separate from IBD, or inflammatory bowel disease, which includes ulcerative colitis and Crohn's disease.[5] The most common symptoms associated with IBS are abdominal pain and disruption in bowel patterns. Treatment options for IBS are guided by the primary symptoms and are delineated as IBS-C (constipation-predominant) or IBS-D (diarrhea-predominant). Direct patient costs of the disease are estimated between $1,562 to $7,547 per patient per year, with indirect costs ranging from $791 to $7,737 per patient per year.[6] Costs associated with IBS vary due to the wide range of disease severities and willingness of patients to seek medical care. Patients with IBS experiencing significant impact on quality of life (including sleep, personal relationships, work, travel, diet, etc.) are more likely to seek medical therapy.[7]

The pathophysiology and disease progression of IBS remain widely unknown. Abnormal gut sensory and/or motor activity, mucosal inflammation, luminal irregularities, central nervous system (CNS) dysfunction, psychological factors and stress have been implicated in the development of the disease.[8] It is theorized IBS may result from an increase in visceral sensitivity to noxious and physiological stimuli due to a transient visceral injury in genetically predisposed individuals. For these individuals, a brief visceral injury never heals properly, leading to a long-lasting hypersensitization of the neural pain circuit in the gut.[9]

The disease is more prevalent in women (2:1 ratio to men) and patients generally present between adolescence and the third and fourth decades of life.[5,10] IBS symptoms fluctuate in severity, come and go over time and are characterized by abdominal pain combined with abnormal bowel habits consisting of diarrhea or constipation or both. Other gastrointestinal (GI)-specific symptoms associated with IBS include globus sensation, dysphagia, early satiety, acid reflux, dyspepsia, nausea, abdominal bloating, flatulence and noncardiac chest pain.[11] In addition, patients may experience extraintestinal symptoms such as dysmenorrhea, urinary abnormalities, headache, backache and fibromyalgia which may significantly impact quality of life.[8,12,13]Continued advances in clinical research help to improve understanding of the disorder and advance treatment modalities available for IBS.

Five key treatment modalities available for IBS include dietary modifications, psychotherapy, probiotics, nonspecific bowel-directed therapy and IBS-specific therapy.[10] Many patients are easily managed with counseling and nonpharmacologic therapies, including avoidance of patient-specific dietary triggers and excess fats.[10] Patients who seek medical treatment are more likely to have psychological symptoms, such as stress or anxiety, associated with their condition.[10] Various methods of psychotherapy, including cognitive behavioral therapy, relaxation therapy and hypnotherapy, have proven helpful in the treatment of IBS.[14-16] Antidepressant agents may also be helpful in the treatment of IBS in this patient population. Probiotics are a controversial IBS therapy, as insufficient data exists to support or discourage use. Some clinical evidence supporting the use of specific probiotic strains, such as Bifidobacteria or the combination VSL#3 (bifidobacterium with lactobacillus), is available.[17]

Use of probiotic therapy is frequently employed in the pediatric population, where diagnosis of IBS is challenging.[18,19]

Nonspecific bowel-directed therapy is aimed at symptomatic relief and includes a variety of OTC and prescription options to alleviate gastric discomfort, constipation and diarrhea. Fiber supplementation, for example, may help some patients, although it may initially cause a worsening of symptoms and should be introduced gradually.[20,21] Other nonspecific bowel-directed therapies (including laxatives, antibiotics, anticholinergic agents, bile acid sequestrants and a number of herbal agents) may also be used in the treatment of IBS, depending on patient-specific IBS-related symptoms.[1,8,9] Treatments specifically indicated the treatment of IBS work directly in the gastrointestinal (GI) tract by regulating visceral pain, colonic transit and/or gastrointestinal secretions. Five IBS-specific therapies currently available in the US: alosetron, eluxadoline, linaclotide, lubiprostone and tegaserod.[4] Alosetron and eluxadoline are indicated in patients with diarrhea-predominant IBS. Alosetron is only available through a REMS prescribing program and eluxadoline was recently approved for use in the US (May 2015) but will not be available for use until 2016.[3,4] Linaclotide, lubiprostone and tegaserod are indicated in patients with constipation-predominant IBS. Linaclotide and lubiprostone have the highest rate of use according to Utah Medicaid utilization data and tegaserod is only available through an FDA IND program. Table 2 provides a summary of all treatment classes and therapies available for the treatment of IBS.

Table 2. Summary of IBS Treatment Options[3,4]

Class	Agents in Class	Route of Administration	Mechanism of Action	Labeled Indications	Adverse Effects	Place in Therapy
Antibiotics	Rifaximin	Oral tablet	Binds to DNA-dependent RNA polymerase and inhibits bacterial RNA synthesis. Rifamixin works to inhibit the small bowel bacterial overgrowth that is found in some IBS patients.	Treatment of traveler's diarrhea. Off-Label Uses: IBS without constipation	Peripheral edema, fatigue, dizziness, ascites, nausea	Used as a second-line agent for bloating in IBS without constipation.
Anticholinergics	Dicyclomine Hyoscyamine	Oral tablet or capsule; also available in IM formulation	Blocks the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands and the CNS. These agents help relax the smooth muscle of the intestinal tract.	Treatment of functional bowel/IBS. Hyoscamine is also indicated for anesthesia to reduce secretions, as an antidote for anticholinesterase agent poisoning, for biliary and renal colic, and for pancreatitis, Parkinsonism, partial heart block, rhinitis, urinary system disorder, and diagnostic procedures to reduce GI motility.	Dizziness, dry mouth, nausea, blurred vision	Commonly referred to as an "antispasmodic," often used to relieve intestinal cramping.
Antidiarrheals	Loperamide	Oral tablet or capsule	An opioid receptor agonist that acts in the intestine to inhibit peristalsis and increase transit time. Leads to increased viscosity, decreased fecal volume and fluid/electrolyte loss.	Control of diarrhea symptoms in traveler's diarrhea, chronic diarrhea associated with inflammatory bowel disease, and acute nonspecific diarrhea.	Abdominal cramping, nausea	Used for mild diarrhea; little effect on abdominal pain.
Antimuscarinics	Mebeverine Pinaverine	Oral tablet, granules, capsule	Inhibits gastrointestinal muscarinic receptors, which relieve muscle spasms without affecting motility.	Not currently available in the United States.	Indigestion, constipation, dizziness, insomnia, anorexia	Was used as an alternative antispasmodic for intestinal cramping.

Class	Agents in Class	Route of Administration	Mechanism of Action	Labeled Indications	Adverse Effects	Place in Therapy
Bile Acid Sequestrants	Cholestyramine Colestipol Colesevelam	Oral suspension, tablet, resin	Binds to bile acids in the intestine to form an insoluble complex that is eliminated in feces. This increased excretion of bile acids results in an increased oxidation of cholesterol to bile acid and a lowering of the serum cholesterol. Binding of bile acids results in a more solidly formed stool.	Management of elevated LDL-C in adults with primary hyperlipidemia. <u>Off-Label Uses:</u> Improve glycemic control in adults with type 2 diabetes mellitus	Constipation, bloating, dyspepsia, weakness, upper respiratory tract infection, fatigue, headache	Thought to help alleviate diarrhea, but many undesirable side effects and potential for drug interactions prevent common use.
Chloride Channel Activators	Lubiprostone	Oral capsule	Bicyclic fatty acid that acts locally at the apical portion of the intestine as a chloride channel (CIC-2) activator, which increases intestinal fluid secretion and motility.	Treatment of chronic idiopathic constipation (CIC), opioid-induced constipation with chronic non-cancer pain, and IBS-C in adult women.	Headache, nausea, diarrhea	Used for refractory IBS-C in women.
Gastrointestinal Agents	Linaclotide	Oral capsule	Guanylate cyclase-C agonist that acts on the luminal surface of intestinal epithelium. Intestinal fluid increases and GI transit time is decreased. Increased extracellular cGMP may also decrease visceral pain by reducing pain-sensing nerve activity.	Treatment of CIC and IBS-C in adults.	Diarrhea, abdominal pain, flatulence	Used for men and women with refractory IBS-C.
Laxatives	Polyethylene Glycol Fiber	Oral powder for reconstitution	An osmotic agent, polyethylene glycol 3350 causes water retention in the stool; increases stool frequency.	Treatment of occasional constipation in adults.	Urticaria, abdominal pain, cramping, flatulence.	Temporary relief of constipation, with no impact on abdominal pain or cramping. Preferred over stimulant laxatives.
Mixed Opioid Receptor Agonist/ Antagonist	Eluxadoline	Oral tablet	Mixed mu-opioid receptor agonist, delta opioid receptor antagonist and kappa opioid receptor agonist; acts locally in the gut to reduce abdominal pain and diarrhea.	Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.	Pancreatitis, sphincter of Oddi spasm, constipation, nausea and abdominal pain.	Only prescription agent specifically indicated in patients with diarrhea-predominant IBS.

Class	Agents in Class	Route of Administration	Mechanism of Action	Labeled Indications	Adverse Effects	Place in Therapy
Selective 5-HT_3 Receptor Antagonist	Alosetron Ondansetron	Oral tablet, solution	Selective serotonin 5-HT_3 receptor antagonist. Activation of 5-HT_3 channels affects the regulation of visceral pain, colonic transit, and gastrointestinal secretions.	Treatment of women with chronic severe IBS-D who have not responded adequately to conventional therapy.	Constipation, abdominal discomfort and pain, nausea, flatulence, hemorrhoids	Severe, chronic refractory IBS-D in women.
Serotonin 5-HT_4 Receptor Agonist	Tegaserod	Oral tablet	Partial neuronal 5-HT4 receptor agonist, which stimulates the peristaltic reflex and intestinal secretion and moderates visceral sensitivity.	Emergency treatment of IBS-C and CIC in women (<55 years of age) in which no alternative therapy exists.	Headache, abdominal pain, dizziness, diarrhea, flatulence, migraine, nausea, back pain	Was removed from market due to associated risk of cardiovascular events; currently only available for emergency treatment with FDA prior authorization.
Tricyclic Antidepressants	Amitriptyline Nortriptyline Imipramine Desipramine	Oral tablet, capsule	Inhibition of serotonin and norepinephrine reuptake in the presynaptic neuronal membrane, desensitization of adenyl cyclase, down regulation of beta-adrenergic receptors, and down regulation of serotonin receptors. Modulation of these receptors is thought to alleviate visceral intestinal pain.	Treatment of symptoms of depression. Off-Label Uses: IBS-D May also be used for postherpetic neuralgia, chronic pain, and smoking cessation.	Increased suicidality (especially in children and adolescents), dizziness, lethargy, chest pain, seizures, confusion, photosensitivity	Used for treatment of IBS-D symptoms, especially pain, that have not responded to antispasmodics, laxatives, or loperamide.

Key: cGMP = cyclic guanosine monophosphate; CIC = chronic idiopathic constipation; CNS = central nervous system; GI = gastrointestinal; IBS = irritable bowel syndrome; IBS-D = Diarrhea-predominant irritable bowel syndrome; IBS-C = Constipation-predominant irritable bowel syndrome; IM = intramuscular; LDL-C = low-density lipoprotein cholesterol; HT = Hydroxytryptamine

Because the exact pathophysiology of IBS is not known, diagnosis and treatment is challenging. Physical exam, blood tests, stool tests, flexible sigmoidoscopy, colonoscopy and lower GI series are used to confirm or rule-out an IBS diagnosis.[2] IBS is considered a "diagnosis of exclusion" and presence of blood in the stool, fever or anatomical abnormality, for example, rules-out a diagnosis of IBS. Once an accurate IBS diagnosis is made, choice of pharmacological treatment is guided by patient-specific symptoms, cost, efficacy, potential adverse effects and patient preference and the goals of therapy are to provide symptom relief and improve quality of life. A number of tools may be used to identify patient-specific factors and guide therapy. The Bristol Stool Scale, for example, is a tool used to describe stool consistency, to differentiate between constipation and diarrhea and to monitor response to therapy.[22] The Rome Criteria is another tool used to identify bowel patterns as well as characterize abdominal pain associated with IBS.[11] The Functional Bowel Disorder Severity Index calculates severity of pain by visual analog scale (0-100) and number of physician visits to determine severity of IBS symptoms over time.[23] The IBS Severity Scoring System is a validated measure to assess the severity of IBS symptoms with quality of life measures taken into account.[24] The Table 3 provides an overview of disease staging systems used in the diagnosis and treatment of IBS.

Table 3. IBS Disease Staging System

Classification System	Description
Bristol Stool Scale[22]	*A tool to identify stool form as a predictor of intestinal transit time, rather than defecation frequency, used to identify disease severity and monitor response to treatment.* Type 1- Separate hard lumps, like nuts Type 2- Sausage-shaped but lumpy Type 3- Like a sausage or snake but with cracks on its surface Type 4- Like a sausage or snake, smooth and soft Type 5- Soft blobs with clear cut edges Type 6- Fluffy pieces with ragged edges, a mushy stool Type 7- Watery, no solid pieces
Rome III Diagnostic Criteria[11]	Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months (with symptom onset at least 6 months prior to diagnosis) associated with 2 or more of the following: • Improvement with defecation • Onset associated with a change in frequency of stool • Onset associated with a change in form (appearance) of stool
IBS Severity Scoring System[24]	*A form to be filled out by the patient to record and monitor patient-specific characteristics to identify severity of disease.* 1. Abdominal pain severity and frequency 2. Abdominal distention severity 3. Satisfaction with bowel habit 4. IBS effect on life 5. Frequency of bowel movements 6. Stool characteristics 7. Defecation characteristics 8. Site and characteristic of Pain 9. Impact on work

Classification System	Description
Functional Bowel Disorder Severity Index (FBDSI)[23]	*FBDS Score = [Current pain by visual analog scale (0-100)] + [Diagnosis of chronic functional abdominal pain (0 if absent and 106 if present)] + [number of physicians visits over previous six months x 11]* Disease Severity: 0= none 1-36= mild 37-110= moderate >110= severe

Key: IBS = irritable bowel syndrome

The American College of Gastroenterology guidelines (2014) are considered the gold standard for treatment of IBS in the United States.[25] According to the guidelines, linaclotide and lubiprostone are recommended as first-line treatment options in patients with constipation-predominant IBS. Alosetron is recommended in women with diarrhea-predominant IBS. Fiber supplementation and antidepressant therapy are recommended for symptomatic relief. Antibiotic therapy with rifamixin and anti-spasmodic agents are recommended as short-term targeted therapies. Table 3 provides a summary of all current clinical practice guidelines available for the treatment of IBS.

Table 4. Most Current Clinical Practice Guidelines for the Treatment of IBS

Guideline	Recommendations for IBS-C	Recommendations for IBS-D	General Recommendations
American College of Gastroenterology Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation, 2014[25]	Lubiprostone and linaclotide are effective for treatment of IBS-C. Mixed 5-HT_4 agonists / 5-HT_3 antagonists are not more effective than placebo at improving symptoms of IBS-C.	Alosetron is effective for women, but has concerns of ischemic colitis. Rifamixin should only be used for nonresponsive bloating for short courses of therapy. Insufficient evidence to recommend loperamide.	Fiber provides overall symptom relief. Certain antispasmodics provide short-term relief. As a class, antidepressants are effective in symptomatic relief. Insufficient evidence to recommend polyethylene glycol.
American Gastroenterological Association Institute Guideline on the Pharmacological Management of Irritable Bowel Syndrome, 2014[26]	Recommended: Linaclotide Lubiprostone (conditional recommendation due to high out-of-pocket costs) PEG Laxatives (conditional recommendation; useful for symptom relief or as adjunctive treatment)	Recommended: Alosetron (conditional recommendation; is only approved for use in women and may cause ischemic colitis) Loperamide (conditional recommendation; limited evidence but may be useful as adjunctive therapy)	Recommended: Tricyclic antidepressants (conditional recommendation due to potential increased risk of QT interval prolongation) Antispasmodics (conditional recommendation; limited evidence and medications should be taken regularly, not as needed) Not Recommended: SSRIs
The British Society of Gastroenterology: Guidelines on the Irritable Bowel Syndrome, 2007	First Line - psyllium Second Line - 5-HT_4 agonist	First Line - loperamide Second Line - 5-HT_3 antagonist	*For Symptoms of Pain:* First Line - Antispasmodic agents Second Line - tricyclic antidepressants, hypnosis, psychological treatments *For Bloating with Distention:* First Line - dietary manipulation, polyethylene glycol Second Line - probiotics, 5-HT_4 agonist *For Bloating without Distention:* First Line - antispasmodic agents Second Line - probiotic, tricyclic antidepressants

Guideline	Recommendations for IBS-C	Recommendations for IBS-D	General Recommendations
World Gastroenterology Organisation Global Guideline Irritable bowel syndrome: a global perspective, 2009[27]	Lubiprostone is recommended for adult women The probiotic strain *Bifidobacterium lactis* DN-173 010 accelerates gastric transit and increases stool frequency. Osmotic laxatives are often useful Insufficient evidence to support a fiber-rich diet or bulk-forming agent like psyllium.	Alosetron is recommended for women who have had severe symptoms for >6 months with no relief from other antidiarrheal agents. Loperamide is effective for treatment of diarrhea, with insufficient evidence to assess impact on pain, bloating, and other symptoms	*For Pain:* • Acetaminophen (paracetamol) is preferred over NSAIDs and opioids due to negative impact on intestinal tract and dependence. • Antispasmodics, tricyclic antidepressants, and SSRIs are effective. Avoid TCAs in constipated patients. *For Bloating:* • Diets that produce less gas may be helpful for some patients. • Some specific strains, such as Bifidobacterium lactis DN-173 010 and the probiotic cocktail VSL#3, have clinical trial evidence of efficacy for bloating, distension, and flatulence. Others, such as Bifidobacterium infantis 35624, reduce bloating as well as the other cardinal symptoms of IBS. • Antibiotic treatment with rifaximin 3 × 400 mg/day has been shown to reduce bloating in some IBS patients. • No evidence to support the use of "antiflatulents," such as simethicone or activated charcoal.
National Institute for Health and Care Excellence (NICE) Guidelines on the Treatment of Irritable Bowel Syndrome, 2015[28]	First Line - laxatives Avoid lactulose. Second Line - Consider linaclotide for people with IBS only if optimal or maximum tolerated doses of previous laxatives from different classes have not helped and they have had constipation for at least 12 months.	First Line - loperamide	First Line - antispasmodics Second Line - tricyclic antidepressants Consider SSRIs only if TCAs are ineffective. Discourage the use of aloe vera. Review fiber intake, and encourage avoidance of insoluble fiber.

Key: 5-HT = 5-Hydroxytryptamine receptor; CIC = chronic idiopathic constipation; IBS = irritable bowel syndrome; IBS-D = Diarrhea-predominant irritable bowel syndrome; IBS-C = Constipation-predominant irritable bowel syndrome; IM = intramuscular; LDL-C = low-density lipoprotein cholesterol, NSAIDs = nonsteroidal anti-inflammatory drugs; PEG = polyethylene glycol; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants

Pharmacology

Linaclotide, lubiprostone and tegaserod are indicated for the treatment of constipation-predominant IBS and work primarily to increase intestinal fluid secretion and decrease gastrointestinal transit time.[8] Alosetron, on the other hand, increases colonic transit time and is indicated in diarrhea-predominant IBS. Eluxadoline is a new mixed-opioid receptor agonist/antagonist indicated in diarrhea-predominant IBS.[4] The gastrointestinal tract is the primary site of action for the IBS-specific agents. The oral bioavailability of these agents ranges from minimal with eluxadoline, linaclotide and lubiprostone, ~10% with tegaserod and up to 60% with alosetron.[1] To improve oral bioavailability, linaclotide is typically dosed once daily on an empty stomach 30 minutes before the first meal of the day and tegaserod is dosed twice daily before meals on an empty stomach. The recommended dose for lubiprostone is reduced in severe hepatic impairment. No dose adjustments are recommended with alosetron, eluxadoline, and linaclotide or tegaserod therapy. Table 5 provides a summary of the pharmacokinetic information available for the bowel-specific therapies. Of note, both alosetron and tegaserod are approved specifically for use in women and are only available through restricted prescribing programs.

Alosetron is a highly selective serotonin 5- Hydroxytryptamine 3 (5-HT_3) receptor antagonist.[3,4,29] Many 5-HT3 receptors are located within the enteric nervous system. The ligand-gated ion channels are involved in the regulation of gut motility and peristalsis in the digestive tract.[30] Blockade of the gastrointestinal 5-HT3 receptors increases colonic transit, stimulates basal jejunal water and electrolyte absorption and improves colonic compliance.[31] Together, these actions reduce diarrhea symptoms.

Eluxadoline is a mixed mu-opioid receptor agonist, delta opioid receptor antagonist and kappa opioid receptor agonist which acts on opioid receptors in the GI tract to normalize gastrointestinal transit and defecation in patients with altered GI function. Eluxadoline clinical trials demonstrate reduced abdominal pain and diarrhea in patients with diarrhea-predominant IBS without constipating side effects. Because eluxadoline works on opioid receptors, risk of abuse was also evaluated in clinical trials and was found to be the same or less than that of placebo.[3,4]

Linaclotide is a guanylate cyclase-C receptor agonist. Linaclotide is metabolized into an active metabolite (MM 419441) in the gastrointestinal tract. This active metabolite binds to guanylate cyclase-C receptors on the luminal surface of intestinal epithelium, resulting in increased concentrations of intracellular and extracellular cyclic guanosine monophosphate (c-GMP). The cystic fibrosis transmembrane conductance regulator (CFTR) is subsequently activated, stimulating the release of chloride and bicarbonate into the intestinal lumen. As a result, gastrointestinal transit time decreases and intestinal fluid secretion increases.[3,4,32]

Lubiprostone is a chloride channel activator and is rapidly metabolized in the stomach and jejunum. Its full mechanism of action in the treatment of IBS is not well understood. It is thought lubiprostone selectively activates type 2 chloride channels in the apical membrane of the gastrointestinal tract, resulting in increased intestinal fluid secretion and improved fecal transit. The activation of these chloride channels does not affect serum sodium or potassium levels.[3,4,33]

Tegaserod is a potent, partial agonist at the 5-HT4 receptor. Stimulation of 5-HT4 receptors in the GI tract results in increased intestinal secretion, peristaltic reflex and gastric motility and inhibition of visceral sensitivity. Together, these effects result in reduced constipation symptoms and relief of associated pain.[3,4,34] Tegaserod has some 5-HT2B antagonist activity which may result in abnormal cardiac function, including prolongation of the QTc interval, and clinical use is restricted to reduce this risk.[35]

Table 5. Pharmacokinetic Properties of the IBS Agents[3,4,36]

Agent	Bioavailability	Distribution	Time to Peak	Elimination Half-Life	Metabolism	Excretion
Alosetron	50-60%	Vd: 65-95 L	1 hour	Normal renal function: 1.5 hours	Extensive hepatic metabolism via CYP2C9, CYP3A4, CYP1A2 to metabolites of which biological activity is unknown	Urine (74%; 13% as unchanged drug); feces (11%; 1% as unchanged drug)
Eluxadoline	Minimal	Primarily GI tissue	With food: ~1.5 hours (range: 1-8 hrs) Without food: ~2 hours (range: 0.5-6 hrs)	3.7-6 hrs	Not clearly established; there is evidence that glucuronidation can occur to form an acyl glucuronide metabolite	Feces (82.2%); urine (<1%)
Linaclotide	Minimal (24433216, 24939497)	Minimal tissue distribution at recommended doses	Plasma concentrations following therapeutic oral doses are not measurable	Plasma concentrations following therapeutic oral doses are not measurable	Primarily within the GI tract to an active metabolite (MM-419441) (24939497) that undergoes proteolytic degradation in the intestinal lumen	Feces (3-5% as active metabolites)
Lubiprostone	Minimal	Primarily GI tissue	M3: 1 hour	M3: 0.9-1.4 hours	Extensive and rapid metabolism in the stomach and jejunum by carbonyl reductase to active metabolite (M3)	Feces (trace amounts) as parent drug and M3
Tegaserod	10% in fasting state	Vd: 368 ± 223 L	1 hour	11 ± 5 hours (IV route)	Hydrolysis in the stomach, followed by oxidation, conjugation, and glucuronidation to metabolites with negligible activity (5-methyoxyindole-3-carboxylic acid glucuronide, isomeric N-glucuronides)	Feces (~66% as unchanged drug); urine (~33% as metabolites)

Key: GI = gastrointestinal; Vd = volume of distribution; hrs = hours

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2015), the Cochrane Library and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE, evaluating efficacy of the IBS agents are included. Trials evaluating the agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Placebo-controlled trials and trials comparing monotherapy with combination regimens are excluded. The following reports were excluded (note: some were excluded for more than 1 reason, see table in appendix for additional exclusions):[37-90]

- Individual clinical trials which evaluated endpoints other than reduction of symptoms, such as: pharmacologic characteristics[91-116], safety[43,50,55,117-125], productivity[126-129], patient satisfaction[130] or cost analysis.[131-133]
- Individual trials comparing the agents in dose-finding studies or in healthy volunteers.[42,47,48,98,101,106,108,115,118,134-143]
- Individual clinical trials evaluating formulations not currently available in the US[131,144-172] or clinical trials without access to the full article.[173-176]

Clinical Efficacy

The efficacy of the IBS-specific treatment agents has not been directly compared in any clinical trials or meta-analyses. The agents have been studied in the treatment of IBS and in the treatment of chronic idiopathic constipation (CIC) in a number of placebo-controlled trials. Six meta-analyses and over 20 additional placebo controlled trials evaluating the efficacy of an IBS-specific agent in the treatment of IBS are available.

Two meta-analyses evaluating clinical trials of alosetron in the treatment of IBS are available. Andresen at al (2008)[177] conducted a systematic review to estimate the treatment efficacy and constipation rate of all 5-HT_3 antagonists in patients with diarrhea-predominant IBS. A total of 14 randomized, controlled trials of alosetron (n=3024) or cilansetron (a novel serotonin type-3 currently in trial phase; n=1116) vs. placebo or mebeverine (an antispasmodic agent, currently not available in the US) were identified for evaluation. Random effects analyses demonstrated increased rates of global improvement in IBS symptoms (pooled relative risk (RR) 1.60, 95% CI 1.49-1.72; I^2=0%) and relief of abdominal pain and discomfort (pooled RR 1.30, 95% CI 1.22-1.39, I^2=22%) with 5-HT^3 antagonist therapy compared to placebo or mebeverine. The 5-HT_3 agents were more likely to cause constipation (pooled RR 4.28, 95% CI 3.28-5.60, I^2=65%) and 9 patients (0.2%) receiving a 5-HT_3 antagonist reported a possible ischemic colitis versus zero in the control groups.

Rahimi et al (2008)[178] conducted a meta-analysis to evaluate the efficacy and tolerability of alosetron in adult patients with IBS. A total of 8 multicenter, randomized,

controlled, 12-week clinical trials with a total of 4170 patients (80% female) with IBS (97.4% diarrhea-predominant IBS; 2.6% constipation-predominant IBS) were included in the analysis. The three trials with global improvement in symptoms scores demonstrated increased improvements with alosetron therapy compared to placebo (RR 1.60; 95% CI 1.44–1.76; p <0.001) and the six trials with pain and discomfort relief data also demonstrated increased relief with alosetron therapy (RR 1.31; 95% CI 1.20–1.43; p < 0.001). Seven trials provided data on tolerability and a significant difference between alosetron therapy and placebo was reported (RR 1.19; 95% CI 1.07–1.31; p < 0.001). A significantly higher incidence of constipation (8 trials; RR 4.35; 95% CI 3.01–6.26; p < 0.001) and abdominal pain/discomfort (5 trials; RR 1.96; 95% CI, 1.46–2.64; p < 0.001) was reported in the alosetron groups. In addition, 4 cases of ischemic colitis (0.16%) and 2 cases of serious complications of constipation (0.08%) were reported in the alosetron treatment groups; no serious adverse events were reported in the placebo groups. This information suggests alosetron is an effective treatment option for patients with diarrhea-predominant IBS but therapy should be monitored closely for the development of constipation and, in rare cases, ischemic colitis.

Two meta-analyses evaluating clinical trials of alosetron or tegaserod in the treatment of IBS are also available. Ford et al (2009)[179] conducted a systematic review to estimate the treatment efficacy of all 5-HT agents (including HT_3 antagonists and HT_4 agonists) in patients with IBS. A total of 29 randomized, controlled trials of alosetron (n=4987), cilansetron (n=2229), tegaserod (n=9242), renzapride (a mixed 5HT agent not currently available in US; n=726) or cisapride (a prokinetic agent used in the treatment of gastroesophageal reflux disease (GERD); n=317) vs. placebo were identified for evaluation. The 5-HT_3 antagonists (alosetron, cilansetron) significantly reduced IBS symptoms compared to placebo (RR 0.78, 95% CI 0.71-0.86) and tegaserod significantly reduced IBS symptoms compared to placebo (RR 0.85; 95% CI 0.80-0.90). Both renzapride and cisapride failed to demonstrate an improvement compared to placebo. Adverse event rate was 64% in the alosetron treatment group and 55% in the placebo group (RR 1.19; 95% CI 1.09-1.30, I^2 66.5%). Constipation was reported in 716 patients (25%) receiving alosetron versus 96 patients (6%) receiving placebo (RR 4.5; 95% CI 3.11-6.53, I^2 60.5%). Serious adverse events were reported in 66 patients (2.9%) receiving alosetron and 30 patients (2.4%) receiving placebo (RR 1.30; 95% CI 0.83-2.04, I^2 0%), with ischemic colitis reported in four patients receiving alosetron therapy. Adverse event rate was 51% in the tegaserod treatment group and 47% in the placebo group (RR 1.07; 95% CI 1.0-1.15, I^2 0%). Diarrhea was reported in 266 patients (6%) receiving tegaserod and 51 patients (2%) receiving placebo (RR 3.60; 95% CI 2.45-5.30, I^2 31%). Two cardiovascular events were reported in the tegaserod group and zero in the placebo group.

Lesbros-Pantoflickova et al (2004)[180] conducted a meta-analysis to evaluate therapies (including bulking agents, prokinetics, antispasmodics, alosetron, tegaserod and antidepressants) used in the treatment of irritable bowel syndrome. A total of 51 double-blind clinical trials were selected for evaluation. Alosetron (OR: 2.2; 95% CI: 1.9–2.6) and tegaserod (OR: 1.4; 95% CI: 1.2–1.5) demonstrated significant improvements in IBS symptoms in women when compared to placebo. Rate of adverse events was not

reported. This evidence suggests alosetron is an effective treatment option for patients with diarrhea-predominant IBS and tegaserod is an effective treatment option for patients with constipation-predominant IBS.

One meta-analysis evaluated the tolerability and efficacy of tegaserod in adults and adolescents (12+ years) with IBS or chronic idiopathic constipation (CIC). In total, Evens et al (2007)[181] identified 13 clinical trials for evaluation (IBS: 11 trials, n = 8,675; CIC: 2 trials, n = 2,612). The population studied was predominantly women and the mean age range was 36-48 years old. In patients with constipation-predominant IBS, global relief of GI symptoms at the end of the study period was significantly higher in the tegaserod treatment groups compared to placebo (RR 1.19, 95% CI 1.09 to 1.29). No differences in improvement of abdominal pain and discomfort symptoms were reported between the tegaserod and placebo treatment groups. Diarrhea was reported more frequently in the tegaserod treatment group compared to placebo (RR 2.80, 95% CI 2.13-3.68). According to the review, tegaserod therapy appears to improve "overall symptomatology of IBS" but efficacy in men and the effect on quality of life requires more research.

One systematic review evaluating the efficacy of linaclotide in the treatment of constipation-predominant IBS is available. Atluri et al (2014)[182] identified 5 trials (n = 1773) for analysis. The FDA endpoint (defined as both an improvement of ≥30% in abdominal pain scores and an increase of ≥1 complete spontaneous bowel movement (CSBM) from baseline) was higher in the linaclotide treatment group compared to placebo (RR 0.80; 95% CI 0.76–0.85). Adequate IBS symptom relief (defined as patient reported adequate relief from IBS symptoms for at least 9/12 weeks) was also higher in the linaclotide treatment group compared to placebo (RR 0.73; 95% CI 0.65–0.82). Discontinuation rate due to presence of diarrhea was higher with linaclotide treatment compared to placebo (RR 14.75; 95% CI 4.04–53.81). According to the limited evidence, linaclotide is an effective treatment option for constipation-predominant IBS but generalizability may be limited to female patients. Further studies are required to determine the long-term safety and efficacy of linaclotide therapy.

No meta-analyses evaluating eluxadoline or lubiprostone were identified for review. However, one placebo-controlled study evaluating the efficacy of eluxadoline and five studies evaluating the efficacy of lubiprostone are available. The singular phase-II trial evaluating eluxadoline reported improvements in abdominal pain and stool consistency with eluxadoline therapy when compared to placebo.[94] The five placebo-controlled trials of lubiprostone reported variable rates of efficacy. Whitehead et al (2011)[44] reported significantly softer stools ($p < 0.05$) with lubiprostone therapy but no differences in pain, urgency or transit time when compared to placebo. Fukudo et al (2011)[45] reported significant and dose-dependent increases in spontaneous bowel movements ($p < 0.05$) and no serious adverse events with lubiprostone therapy compared to placebo. Drossman et al (2009) reported a significantly higher responder rate (defined as patient reported IBS-symptom improvements; $p = 0.001$) and a similar rate of adverse events with lubiprostone therapy compared to placebo. Johanson et al (2008)[57] reported improvements in abdominal pain scores with lubiprostone therapy compared to placebo

in months one ($p = 0.023$) and two ($p = 0.039$) but not month three of the study (no CI provided). Throughout the trial, lubiprostone therapy was associated with significantly higher rates of GI adverse events (diarrhea, nausea) compared to placebo ($p = 0.020$). A second trial by Johanson et al (2007)[59] reported dose-related, significantly increased rates of spontaneous bowel movements throughout the 3-week study period ($p \leq 0.020$) with lubiprostone therapy compared to placebo. Increased rates of GI adverse events (nausea, headache, diarrhea) were reported with the 72mcg lubiprostone dose compared to the 48mcg dose and/or placebo. Overall, this evidence suggests lubiprostone may be an effective treatment option for patients with constipation-predominant IBS; although, the long-term safety and efficacy is unclear. Lubiprostone may also be an efficacious option for the treatment of IBS/constipation associated with Parkinson disease[183], cystic fibrosis[184] and in the pediatric population.[185]

A number of additional placebo controlled trials evaluating the IBS-specific agents are also available. Alosetron therapy was evaluated in a quality-of-life (QOL) study[42] and demonstrated significant ($p < 0.05$) improvements when compared to placebo in workplace productivity, restriction of daily activities, treatment satisfaction and IBS-QOL domains including: emotional functioning, mental health, sleep behavior, energy, physical functioning, diet and social role. Overall, the additional placebo-controlled data available for linaclotide demonstrate significant improvements ($p < 0.05$) in abdominal symptoms (discomfort, bloating, fullness and cramping)[38,39], global measures[38], QOL[38], sustained response[39] and spontaneous bowel movements[48,186] compared to placebo. In general, incidence of adverse events was similar among all study groups across the trials, with the exception of diarrhea, which was reported more frequently with linaclotide treatment compared to placebo. The additional placebo-controlled data available for tegaserod demonstrate significant improvements ($p < 0.05$) in patient's assessment of satisfactory relief[56,61,72,74] and stool frequency/consistency[61,79]. Only one trial reported significant improvements ($p < 0.05$) in abdominal pain/discomfort[79]; the other trials failed to demonstrate and improvement in pain with tegaserod therapy. Diarrhea and abdominal cramping were the most frequent adverse events reported with tegaserod therapy across the trials.

Other agents evaluated in the treatment of IBS in clinical trials include: rifaximin[187,188], ondansetron, pregabalin, duloxetine, mesalamine, citalopram, microencapsulated sodium butyrate (MSB), GLP-1 receptor agonists, proton pump inhibitors, dronabinol, sildenafil, cannabinoid, naltrexone, leuprolide, clonidine[189], polyethylene glycol (PEG) 3350, probiotics[190], melatonin, papaya, peppermint oil, guar gum, red pepper, placebo administered without deception[191], NMDA, ketotifen, St. Johns wort, ginger, spinal orthopedic manipulation, etc.

Safety

Common side effects of alosetron, eluxadoline, linaclotide, lubiprostone and tegaserod are generally limited to the gastrointestinal tract and may include cramping, nausea, diarrhea and/or constipation. Lubiprostone and linaclotide cause dose-related adverse events and initiating treatment with the lowest effective doses is recommended.[175] One meta-analysis evaluating the safety of all IBS treatments reported increased rates of adverse events with tricyclic antidepressants and alosetron compared to rifaximin. The authors reported lubiprostone and selective serotonin reuptake inhibitors also appeared to be safe treatment options.[192] The FDA has placed restrictions on the use of alosetron and tegaserod due to post-marketing reports of serious adverse effects detailed below. In contrast, linaclotide and lubiprostone have shown favorable safety and tolerability profiles in adults suffering from constipation-predominant IBS. Table 6 summarizes adverse events and Table 7 summarizes the warnings and precautions associated with the IBS-specific agents.

Alosetron was previously withdrawn from the market in 2000 due to reports of serious gastrointestinal adverse effects, including serious complications of constipation (obstruction, perforation, impaction, secondary colonic ischemia, and toxic megacolon) and ischemic colitis. "Pooled data from clinical trials indicate an increased rate of ischemic colitis among alosetron-using patients compared to placebo-using patients (0.15%vs 0.0%, respectively, $p = 0.03$), but there was no significant difference in the rate of serious complications of constipation." All ischemic colitis episodes reported in the trials were reversible without long-term effects.[193] Alosetron was reintroduced in 2002 in conjunction with a Risk Evaluation and Mitigation Strategy (REMS) mandated by the FDA.[3,4,194] Prescribers must enroll and be certified in the Alosetron REMS Program to prescribe alosetron, and patients must sign the Alosetron Patient Acknowledgement Form. The most frequently reported adverse effect is dose-related constipation (9-20%). Geriatric patients may be more susceptible to complications associated with constipation due to reduced clearance of the drug.[3,4,111] Currently, alosetron is only approved for use in women. However, clinical trials have found similar rates of side effects in both men and women.[138,177,178]

Eluxadoline. Phase III clinical trials report constipation, nausea and abdominal pain as the most frequent adverse events reported with eluxadoline therapy. In the trials, discontinuation rates due to constipation were low for both eluxadoline and placebo. Rare adverse events reported with eluxadoline therapy include central nervous system (CNS) and respiratory effects. At a dose 10 times the maximum recommended dose (100 mg), eluxadoline not prolong the QT interval to any clinically relevant extent.[3,4]

Linaclotide. Mild-to-moderate diarrhea is the most common adverse effect reported with linaclotide therapy, affecting approximately 16-20% of patients receiving linaclotide.[3,4,32,41,195] Discontinuation rates (~4% vs. 0.5% for placebo) during clinical trials were attributed to diarrhea.[41] Adverse effects of linaclotide are generally mild and primarily limited to the gastrointestinal tract.[32,196] Linaclotide is contraindicated in patients younger than age six due to trials in which young mice were given a single adult dose and consequently suffered dehydration, resulting in death.

Lubiprostone. The most frequent adverse effects reported with lubiprostone therapy include nausea (8-29%), diarrhea (7-12%) and headache (2-11%). Diarrhea occurs in up to 19% of geriatric patients receiving lubiprostone.[3,4] In a study observing long-term safety of lubiprostone, patients treated with lubiprostone reported a high degree of tolerability over the course of 52 weeks.[43] Adverse events associated with lubiprostone tend to be mild-to-moderate in intensity and related to dose.[33,43,53] According to the packing insert, edema (3%), peripheral edema (1-3%) and chest discomfort (2%) have also been reported.[3,4]

Tegaserod is not currently available for general use due to post-marketing evidence of rare but serious cardiovascular adverse events, such as myocardial infarction, stroke and unstable angina, in patients taking tegaserod.[3,4,197] Clinical studies evaluating the cardiovascular effects related to tegaserod therapy report prolongation of the QTc interval and frequency of overall electrocardiographic abnormalities was the same for placebo and tegaserod.[122] "The adverse event profile, clinical laboratory evaluations, vital signs and electrocardiogram recordings revealed no evidence of any unexpected adverse events, and suggest that treatment is safe over a 12-month period."[123] Women under the age of 55, who have failed alternative drugs or therapies and have no known or preexisting cardiac conditions, may still receive tegaserod under a treatment investigational new drug (IND) protocol.[197] Prescribers may contact Novartis at 888-669-6682 or 800-QUI-NTILE for more information on how to obtain tegaserod for patients. The most common side effects observed in tegaserod clinical trials include abdominal pain and headache.[3,4,119,123]

Table 6. Adverse Events Reported with the IBS Agents[3,4]

	Alosetron	Eluxadoline	Linaclotide	Lubiprostone	Tegaserod
Gastrointestinal (%)	Constipation (9-20%; dose-related) Abdominal discomfort and pain (1-7%) Nausea (6%) Gastrointestinal discomfort and pain (5%) Gastroenteritis (≥3%) Vomiting (≥3%) Diarrhea (2-3%) Flatulence (1-3% Hemorrhoids (1-3%) Abdominal distention (2%) Regurgitation and reflux (2%)	Sphincter of Oddi Pancreatitis Constipation Nausea Abdominal pain Vomiting Abdominal distention Flatulence Viral gastroenteritis Gastroesophageal reflux disease	Diarrhea (16-20%; severe 2%) Abdominal pain (7%) Flatulence (4-6%) Abdominal distension (2-3%) Viral gastroenteritis (≤3%) Dyspepsia (<2%) Fecal incontinence (<2%) Gastroesophageal reflux disease (<2%) Vomiting (<2%)	Nausea (8-29%; dose-related; severe 1-4%; elderly: 19%) Diarrhea (7-12%; severe <1%-2%) Abdominal pain (4-8%) Flatulence (4-6%) Abdominal distention (3-6%) Abdominal distress (3%) Loose stools (3%) Vomiting (3%) Dyspepsia (2%) Xerostomia (1%)	Abdominal pain (12%) Diarrhea (9%; severe <1%) Nausea (8%) Flatulence (6%)
Central Nervous System (%)	Fatigue (≥3%) Headache (≥3%)	Dizziness Fatigue Sedation Somnolence Euphoric mood	Headache (4%) Fatigue (<2%)	Headache (2-11%) Dizziness (3%) Fatigue (2%)	Headache (15%) Dizziness (4%) Migraine (2%)
Genitourinary (%)	Urinary tract infection (≥3%)	NR	NR	NR	NR
Neuromuscular (%)	Muscle spasm (≥3%)	NR	NR	NR	Back pain (5%) Arthropathy (2%) Leg pain (1%)
Respiratory (%)	Cough (≥3%) Nasopharyngitis (≥3%) Upper respiratory tract infection (≥3%)	Upper respiratory tract infection Nasopharyngitis Broncholitis Asthma	Upper respiratory tract infection (5%) Sinusitis (3%)	Dyspnea (<1-3%)	NR
Cardiovascular (%)	NR	NR	NR	Edema (3%) Peripheral edema (1-3%) Chest discomfort (2%)	NR
<1%, Post-marketing and/or Case Reports	GI impaction, GI perforation, GI ulceration, hepatitis, rash, small bowel mesenteric ischemia	Rash Increased liver enzymes	Hematochezia, hypersensitivity reaction, melena, rectal hemorrhage, urticaria	Anorexia, anxiety, bowel urgency, constipation, cough, decreased appetite, depression, dysgeusia, eructation, erythema, fecal incontinence, fibromyalgia syndrome, frequent bowel movements, gastritis, gastroesophageal reflux disease, gastrointestinal disease, hyperhidrosis, hypersensitivity reaction, hypokalemia, increased liver enzymes, influenza, ischemic colitis, joint swelling, lethargy, malaise, muscle cramps, muscle spasm, myalgia, pain, palpitations, pharyngolaryngeal pain, pollakiuria, rectal hemorrhage, syncope, tachycardia, tremor, urinary tract infection, weakness, weight gain	Alopecia, bile duct stone, cholecystitis, gangrenous bowel, hypersensitivity reaction, hypokalemia secondary to diarrhea, ischemic colitis, mesenteric ischemia, myocardial infarction, rectal bleeding, sphincter of Oddi spasm, stroke, unstable angina

Key: NR = Not reported, GI = gastrointestinal

Table 7. Warning and Precautions Associated with the IBS Agents[3,4]

	Alosetron	Eluxadoline	Linaclotide	Lubiprostone	Tegaserod
Pregnancy Category	B	B	C	C	B
Pediatric Use	Safety not established in <18 years of age	Safety and effectiveness in pediatric patients have not been established.	Contraindicated in <6 years of age; Avoid use in <17 years old	Safety not established in <18 years of age	Safety not established in <18 years of age
Geriatric Use	Caution; greater risk for complications of constipation	No overall differences in effectiveness were observed between older patients and younger patients.	Limited data in ≥ 65 years of age	Limited data in ≥ 65 years of age	Contraindicated in elderly women ≥ 55 years of age
Hepatic Impairment Dose Adjustment	Mild to moderate: none Severe: use is contraindicated	Mild to moderate: reduce dose Severe: contraindicated in patients with severe hepatic impairment	None	Mild to moderate: None Severe: 8 mcg once daily initially; may increase to 8 mcg twice daily if tolerated and an adequate response has not been achieved at lower doses	Mild: None Moderate to severe: use is contraindicated
Renal Impairment Dose Adjustment	None	None	None	None	Mild to moderate: None Severe: use is contraindicated
Black Box Warnings	-Discontinue medication immediately if constipation or signs of ischemic colitis develop	None	-Administration of an adult dose to young mice resulted in deaths due to dehydration	None	None
Drug-Drug Interactions	-Major CYP1A2 substrate -Strong-to-moderate inhibitors of CYP1A2 (such as fluvoxamine): may increase serum drug concentrations, half-life, and risk of adverse effects of alosetron (Lexi, Lotronex) -Apomorphine: alosetron may increase the hypotensive effects of apomorphine; caution is warranted, particularly in elderly patients at increased risk for falls (Apokyn). -Alosetron should not be used in combination with other medications associated with constipation-related side effects, as concomitant use may result in increased constipation effect (Lexi).	-The metabolism of eluxadoline by CYP pathways has not been clearly established. The potential of eluxadoline to inhibit CYP3A4 in the gut has not been established.	None	-Lubiprostone efficacy may be reduced with the concomitant use of methadone (Lexi).	None

Summary

Irritable bowel syndrome (IBS) is a common, nonfatal gastrointestinal disorder associated with significant costs and impact on quality of life. The exact pathophysiology of IBS is not known and the diagnosis and treatment can be challenging. In general, IBS is characterized by abdominal discomfort and irregular bowel habits and treatment may include alosetron, eluxadoline, linaclotide, lubiprostone, tegaserod, laxatives, antibiotics, probiotics, anticholinergic agents, tricyclic antidepressants, bile acid sequestrants and a number of herbal agents. The goals of therapy are to provide symptom relief and improve quality of life and pharmacologic treatment should be guided by patient-specific symptoms, cost, efficacy, potential adverse effects and patient preference. Linaclotide, lubiprostone and tegaserod are indicated for the treatment of constipation-predominant IBS and work primarily to increase intestinal fluid secretion and decrease gastrointestinal transit time. Alosetron and eluxadoline are indicated in diarrhea-predominant IBS and work by increasing GI transit time. Alosetron and tegaserod are approved specifically for use in women.

The American College of Gastroenterology guidelines recommend linaclotide and lubiprostone as first-line treatment options in patients with constipation-predominant IBS. Alosetron is recommended in women with diarrhea-predominant IBS. Based on a literature search of the clinical evidence, the efficacy of the IBS-specific treatment agents has not been directly compared in any clinical trials or meta-analyses. Placebo controlled evidence suggests the agents are effective in the treatment of IBS. Safety and efficacy data associated with long-term treatment with the IBS-specific agents are limited. Adverse events most frequently reported with the agents are generally limited to the gastrointestinal tract and may include cramping, nausea, diarrhea and/or constipation. Lubiprostone and linaclotide cause dose-related adverse events and initiating treatment with the lowest effective doses is recommended. The FDA has placed restrictions on the use of alosetron and tegaserod due to post-marketing reports of serious adverse effects. Eluxadoline was recently approved for use in the US and will not be available until 2016.

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