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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (4): Irritable bowel syndrome

Constipation-predominant irritable bowel syndrome: A review of current and emerging drug therapies

Khaled A Jadallah, Susan M Kullab, David S Sanders

Khaled A Jadallah, Susan M Kullab, Department of Internal Medicine, King Abdullah University Hospital, Faculty of Medicine, Jordan University of Science and Technology, Irbid 22110, Jordan
David S Sanders, Department of Gastroenterology and Liver Unit, Royal Hallamshire Hospital, Sheffield, South Yorkshire S102JF, United Kingdom
Author contributions: Jadallah KA and Sanders DS conceived and designed the study; Jadallah KA and Kullab SM performed the literature search and wrote the manuscript; all authors revised and approved the final version.
Correspondence to: Khaled A Jadallah, MD, Assistant Professor of Medicine, Department of Internal Medicine, King Abdullah University Hospital, Faculty of Medicine, Jordan University of Science and Technology, Irbid 22110, Jordan. khaled-j@just.edu.jo
Telephone: +962-79-6673884 Fax: +962-2-7200624
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Abstract

Irritable bowel syndrome (IBS) is a highly prevalent medical condition that adversely affects patient quality of life and constitutes a significant economic burden on healthcare resources. A large proportion of patients suffer from the constipation subtype of IBS (IBS-C), most commonly afflicting older individuals and those with a lower socioeconomic status. Conventional pharmacologic and nonpharmacologic treatment options have limited efficacies and/or significant adverse events, which lead to increased long-term health care expenditures. Failure to effectively treat IBS-C patients over the past decades has largely been due to a poor understanding of disease pathophysiology, lack of a global view of the patient, and an inappropriate selection of patients and treatment endpoints in clinical trials. In recent years, however, more effective and safer drugs have been developed for the treatment of IBS-C. The advancement in the area of pharmacologic treatment is based on new knowledge of the pathophysiologic basis of IBS-C and the development of drugs with increased selectivity within pharmacologic classes with recognized efficacies. This narrative review covers the spectrum of available drugs and their mechanisms of action, as well as the efficacy and safety profiles of each as determined in relevant clinical trials that have investigated treatment options for IBS-C and chronic constipation. A brief summary of laxative-based treatment options is presented, followed by up-to-date assessments for three classes of drugs: prokinetics, prosecretory agents, and bile acid modulators.

Key words: Constipation; Irritable bowel syndrome; Drug therapy; Serotonergic agents; Prokinetics; 5-hydroxytryptamine type 4 agonists; Secretagogues; Prosecretory agents; Bile acid modulators

Core tip: Constipation-predominant irritable bowel syndrome (IBS-C) is one of the most common disorders seen by gastroenterologists worldwide, and is associated with a substantial burden on health care resources. Pharmacologic treatments for IBS-C have largely been unsatisfactory, mainly due to the multifaceted and poorly understood pathophysiology of this disorder. Recently approved drugs and novel investigational compounds are expected to streamline the management of IBS-C. This narrative review covers the mechanisms, clinical trial efficacies, and safety profiles of these pharmacologic agents, in order to help practicing physicians keep up with the rapidly developing field of IBS-C therapy.

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INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal (GI) disorders across all ages and ethnicities, with a worldwide prevalence ranging between 5% and 20%[1-4]. The majority of individuals with IBS experience impairments to their performance of daily activities and decreased health-related quality of life, for which conventional treatments provide limited resolutions[5,6]. For some IBS sufferers, substantial psychologic and psychiatric disturbances develop over time, leading to polypharmacy accompanied by the inherent risk of drug interactions, further deterioration of health status, and increased health care expenditures[6,7].

The constipation-predominant subtype of IBS (IBS-C), defined by constipation associated with abdominal pain that is generally relieved by defecation[8], affects about 34% of the IBS population[9], of which a substantial fraction are of older age and lower socioeconomic status[3]. Recent evidence suggests that IBS-C is associated with higher rates of functional impairment, as compared to other subtypes of IBS[10-12]. Conventional laxative-based pharmacologic treatment of IBS-C, which is mostly symptom-based, is largely unsatisfactory[13,14]. Yet, despite the substantial burden of IBS-C-associated ailments and the well-recognized need for more efficacious and safer treatments, few novel treatment compounds have been approved for clinical use. The need for a drug therapy that effectively treats all of the symptoms of IBS-C (abdominal pain, constipation, and secondary symptoms of constipation), improves the patient's health-related quality of life, and can be used safely on a chronic basis remains unfulfilled.

Advancement in the treatment of IBS-C requires a greater focus on the pathophysiologic abnormalities underlying each of the symptoms of this complex disorder[15], which is the scientific basis for the development of new pharmaceutical compounds. The present article reviews the current pharmacologic agents for the treatment of IBS-C, in terms of their clinical trial efficacy, tolerability, and safety. A brief description of the broad spectrum of laxative-based treatment options is also presented. In general, this review focuses on the main classes of drugs that have been the subject of active research in recent years (prokinetics, prosecretory agents or secretagogues, and bile acid modulators). Furthermore, in addition to the well-established drugs (tegaserod and lubiprostone), newly-approved drugs (prucalopride, velusetrag, linaclotide, plecanatide, chenodeoxycholate (CDC) and elobixibat) as well as drugs currently in development for the treatment of IBS-C are discussed. As there is significant overlap between IBS-C and chronic constipation (CC)[16], drugs that are currently approved or being investigated for the treatment of CC are also included in this review, according to their potential for use in the management of IBS-C; for instance, lubiprostone, which was initially developed and approved for CC, has subsequently received approval for the treatment of IBS-C. Nonpharmacologic remedies, such as fiber supplements and probiotics, however, are not discussed.

Studies included in this review were collected from a PubMed search for English-language articles published between 1980 and December 2013 using the following keywords alone or in combination: irritable bowel syndrome, constipation, constipation-predominant irritable bowel syndrome, drug therapy, laxatives, prokinetics, serotonergic agents, 5-HT$_4$ agonists, secretagogues, prosecretory agents, bile acid modulators, randomized controlled trials (RCTs), meta-analysis. Governmental websites [www.clinicaltrials.gov (United States), www.clinicaltrialsregister.eu (European Union)] were searched for data concerning ongoing clinical trials. Only high quality studies were cited and discussed in the present review.

LAXATIVE-BASED PHRARMACOLOGIC AGENTS

Conventional laxatives and stool softeners have been used for decades for the treatment of CC, and have also been used by IBS-C patients to improve their bowel habits[13,14]. Clinical experience and, to a lesser extent, evidence from the literature indicate that about half of the patients treated with laxatives are disappointed by the lack of long-term efficacy[17-19]. Despite the high prevalence and the remarkable socioeconomic burden associated with IBS-C and CC, concrete evidence from high-quality RCTs on laxative efficacy and safety is very limited[20]. In fact, only recently have well-conducted studies provided evidence for the use of bisacodyl in CC and polyethylene glycol in IBS-C[21,22].

Although laxative-based treatments provide short-term relief of constipation in many CC and IBS-C patients, there is a lack of high quality evidence to support their regular use. However, laxatives remain a suitable therapeutic option for many patients because of their relative safety, low cost, and over-the-counter availability. Well-conducted RCTs comparing the most commonly used laxatives and newer pharmacologic agents will help to identify the safest and most effective therapy for regular use. The mechanisms and most common adverse events of different types of laxatives are summarized in Table 1.

PROKINETICS

Slow colonic transit is recognized as one of the most important mechanisms underlying constipation. Prokinetics have been designed to stimulate muscle activity to counter the underlying hypomotility that is linked with slow-transit constipation[23,24]. A crucial role for 5-hydroxytryptamine (5-HT, serotonin) in normal enteric nervous system function has been documented[25-27], and the ex-

Table 1 Main types of pharmacologic laxatives

Type	Agents	Mechanism of action	Most common adverse events
Bulking agents	Psyllium Methylcellulose Calcium polycarbophil	Increase in stool bulk and reduction in consistency by luminal water binding	Bloating Flatulence
Stool softeners (surfactants)	Docusate potassium Docusate sodium Docusate calcium	Softening and lubrication of stools by increasing water secretion	Nausea Vomiting Abdominal pain/cramps Rectal urgency
Osmotic laxatives	Milk of Magnesia (magnesium hydroxide) Magnesium citrate Magnesium sulphate Sodium picosulphate/magnesium citrate (Picoprep®) Lactulose/lactilol Sorbitol Polyethylene glycol (macrogol)	Osmotic water retention, decreased stool consistency, and increase fecal volume and peristalsis	Sweet taste Nausea Bloating Flatulence Abdominal pain/cramps Electrolyte disturbances (?)
Stimulant laxatives	Anthraquinones Senna Cascara Bisacodyl Phenolphthalein	Luminal water retention through activation of CAMP, and induction of colonic contractions by acting on enteric nerves	Abdominal pain/cramps Dehydration Electrolyte disturbances Muscle cramps Melanosis coli/colonic inertia (?)

CAMP: Cyclic adenosine monophosphate.

Table 2 Chemical and clinical characteristics of discontinued/failed prokinetics

	Cisapride	Renzapride	Tegaserod
Chemical structure	Piperidinyl benzamide	Benzamide derivative	Indole carboxaldehyde derivative
Target receptors	Nonselective 5-HT$_4$ agonist and 5-HT$_3$ antagonist	Full 5-HT$_4$ agonist and antagonist of 5-HT$_3$ and 5-HT$_{2b}$	5-HT$_4$ and 5-HT$_1$ partial agonist
Mechanism of action/ pharmacodynamic effects	Local acetylcholine release; Acceleration of GI transit	Local acetylcholine release; Acceleration of GI transit	Augmentation of the peristaltic reflex; Enhanced intestinal secretion; Reduced sensitivity to rectal distension
Most common adverse events	Diarrhea Abdominal pain	Diarrhea Abdominal pain Headache Flatulence	Diarrhea Abdominal pain Headache Flatulence
Safety	Prolongation of QTc interval and fatal arrhythmias	No prolongation of QTc interval	Increased risk of serious ischemic cardiac events
Approval status	Approved in 1993; Withdrawn in 2000	Phase 3 RCTs terminated due to insufficient efficacy	Approved in 2002 for IBS-C (not in EU) and in 2004 for CC; Withdrawn in 2007

CC: Chronic constipation; EU: European Union; GI: Gastrointestinal; IBS-C: Constipation predominant-irritable bowel syndrome; QTc: Corrected QT interval; RCT: Randomized controlled trial; 5-HT: 5-hydroxytryptamine.

pression of the 5-HT type 4 (5-HT$_4$) receptor in the GI tract has been associated with intestinal motility[23,28]. In the past two decades, several prokinetic agonists of the 5-HT$_4$ receptor have been introduced in clinical practice. Table 2 presents the chemical and clinical characteristics of the older prokinetics, whereas Table 3 summarizes the characteristics of the newer prokinetics.

Cisapride

Cisapride, a non-selective 5-HT$_4$ agonist, was originally developed for the treatment of functional upper GI disorders, and later found to be efficacious for treating constipation[29]. However, its interaction with human ether-a-go-go-related gene (hERG) potassium channels leads to cardiac arrhythmias, which caused the drug to be withdrawn from the global market[29]. This "rise and fall" of cisapride underscores the importance of longitudinal safety studies for newer drugs, as well as the need for post-market monitoring.

Tegaserod

Tegaserod, a partial 5-HT$_4$ agonist devoid of the arrhythmogenic effect elicited by cisapride, was demonstrated in RCTs to be an efficacious and well-tolerated promotility agent in IBS-C patients[30,31]. The drug received approval for the treatment of women with IBS-C in July 2002 in the United States and a few other countries, but not in the European Union. In August 2004, the United States's Food and Drug Administration (FDA) also approved tegaserod for the treatment of patients with CC, and a subsequent multinational high-quality randomized controlled trial demonstrated its efficacy and tolerability in these patients[32]. Nevertheless, due to ensuing reports of ischemic cardiac events, tegaserod was withdrawn from the

Table 3 Chemical and clinical characteristics of novel prokinetic agents

	Prucalopride	Naronapride	Velusetrag	ROSE-010
Chemical structure	Dihydrobenzofuran carboxamide	Benzamide	Dihydroxyquinoline-carboxamide	Glucagon-related peptide
Target receptor/affinity	High selectivity and affinity for 5-HT$_4$ (> 150-fold)	5-HT$_4$ full agonist in the GI tract; partial agonist in the heart	Potent selective agonist of 5-HT$_4$ with high affinity (500-fold)	GLP-1 analogue
Pharmacodynamic effects	Accelerated colonic transit in health and CC	Accelerated colonic transit in health	Dose-dependent acceleration of colonic transit in health	Acceleration of colonic transit; antinociceptive effect in IBS-C
Most common adverse events	Diarrhea Nausea Headache Abdominal pain	Diarrhea Headache	Diarrhea Nausea Headache Vomiting	Nausea Headache
Approval status/stage of development	Approved for CC in EU in 2009 and in Canada in 2011	Phase 2 RCTs in CC completed	Phase 2 RCTs in CC completed	Phase 2 RCTs in IBS-C completed

CC: Chronic constipation; EU: European Union; GI: Gastrointestinal; GLP-1: Glucagon like peptide-1; IBS-C: Constipation-predominant irritable bowel syndrome; RCT: Randomized controlled trial; 5HT: 5-hydroxytryptamine.

market in March 2007, and since 2009, its use has been limited to emergency situations[33]. Although tegaserod was eventually removed from the worldwide market, it is still considered to represent an important step in the development of novel serotonergic drugs for the management of IBS-C and CC.

Prucalopride

In recent years, three highly selective 5-HT$_4$ agonists, namely prucalopride, velusetrag, and naronapride, have been investigated mainly for the treatment of CC (Table 2). In contrast to nonselective 5-HT$_4$ agonists, these pharmacologic compounds have not been associated with adverse cardiovascular events[34]. Large, multicenter RCTs have shown that prucalopride, the most extensively investigated drug of this class, is efficacious and safe for treating patients with CC[34-36]. In October 2009 the European Medicines Agency (EMA) approved prucalopride (Resolor®, 2 mg once daily) for the treatment of CC in women for whom laxative-based approaches failed to grant adequate relief[36]. In November 2011 the drug received approval in Canada (Resotran®, 1 or 2 mg once daily) for the same indication; although, to date, the drug remains unapproved by the United States FDA.

Recently, a large phase 3 RCT conducted in 46 sites from five countries of the Asia-Pacific region evaluated the efficacy and safety of a 12-wk treatment with daily prucalopride (2 mg) in CC patients[37]. In that study, significantly more patients responded to prucalopride than placebo (33.3% *vs* 10.3%), with responding patients having a weekly average of $\geqslant$ 3 spontaneous complete bowel movements (SCBMs). The most frequently reported adverse events were diarrhea, nausea, abdominal pain, and headache, all of which mainly occurred during the first and second day of drug administration. Thus, the authors concluded that daily 2 mg prucalopride was effective and well tolerated, with a favorable safety profile. Although no studies have yet addressed the efficacy of prucalopride in IBS-C, it is expected that it will also be efficacious for the disease symptoms, even though worsening of abdominal pain would limit its use in clinical practice.

Velusetrag

The second highly selective 5-HT$_4$ agonist, velusetrag (TD5108), has demonstrated stimulatory effects on colonic motility and transit in a phase 1 RCT[38]. In that trial, 60 healthy volunteers received one of four doses of velusetrag (5, 15, 30 or 50 mg) as a single dose or once daily for six days. A significant increase in the colonic transit and bowel emptying time of the descending colon was observed in participants receiving the single dose, and accelerated gastric emptying occurred in participants receiving multiple doses, with no serious adverse events. A four-week phase 2 RCT in 401 patients evaluated the efficacy, safety and tolerability of different velusetrag doses (15, 30 or 50 mg/d) in CC patients[39]. Patients treated in that study showed significant improvement in SCBMs, stool consistency, and time to achieve the first bowel movement, with adverse events, such as diarrhea, headache, nausea and vomiting, mostly occurring in the first two days of treatment. The adverse events-related discontinuation rate was 5%, and no manifestations of cardiac toxicity were noted. The results of these RCTs indicate that velusetrag is a safe drug and efficacious for the treatment of CC, though larger and longer phase 3 trials are required before robust conclusions are drawn. Furthermore, treatment of IBS-C patients with velusetrag has yet to be evaluated.

Naronapride

A third drug, naronapride (ATI-7505), is a full agonist of 5-HT$_4$ receptors in the GI tract and partial agonist of these receptors in the heart. It is structurally similar to cisapride, but without affinity for 5-HT$_3$ receptors and negligible hERG potassium channel activity[40,41]. The drug is currently being investigated for the treatment of upper and lower GI functional disorders, but only limited

Table 4 Chemical and clinical characteristics of prosecretory agents

Drug	Lubiprostone	Linaclotide	Plecanatide
Chemical structure	A prostone, bicyclic fatty acid (metabolite of prostaglandin E1)	14-amino acid peptide, analogue of guanylin	Analogue of uroguanylin
Target receptor/ mechanism of action	Activation of ClC-2 by direct action on epithelial cells provoking intestinal fluid secretion, also mediated by CFTR	Binding to GC-C with stimulation of cGMP and CFTR-mediated secretion; desensitization of afferent pain fibers mediated by production of extracellular cGMP	GC-C receptor activation with CFTR-mediated secretion
Pharmacodynamic effects	Accelerated small bowel and colonic transit	Dose-related acceleration of colonic transit	Probable acceleration of colonic transit
Most common adverse events	Nausea Diarrhea Abdominal pain	Dose-dependent diarrhea	Dose-independent diarrhea Nausea
Potential other beneficial effects	Mucosal protection	Antineoplastic	-
Cost	AWP is $296 for one month supply	AWP is $255 for 30 capsules	-
Approval status/stage of development	United States FDA-approved for women with IBS-C and men and women with CC	United States FDA-approved for both IBS-C and CC EMA-approved for IBS-C only	Phase 2b RCT in CC completed; Phase 3 RCT in CC recruiting patients; Phase 2 RCT in IBS-C recruiting patients

AWP: Average wholesale price; CC: Chronic constipation; CFTR: Cystic fibrosis transmembrane conduction regulator; cGMP: Cyclic guanosine monophosphate; ClC-2: Chloride channel-2; EMA: European Medicines Agency; FDA: Food and Drug Administration; GC-C: Guanylate cyclase-C; IBS-C: Constipation-predominant irritable bowel syndrome; RCT: Randomized controlled trial.

data are available in the literature thus far.

Renzapride, clebopride, and mosapride

Renzapride, clebopride, and mosapride are nonselective 5-HT$_4$ agonists that are no longer considered for the treatment of patients with IBS-C or CC. Though they were shown to be safe from a cardiovascular standpoint[33], they did not show significant efficacy in IBS-C clinical trials and were therefore abandoned[42,43].

ROSE-010

ROSE-010 is an experimental glucagon-like peptide-1 (GLP-1) analogue that affects the motility of and nociception in the GI tract[44]. In one RCT investigating the effect on acute abdominal pain in IBS, ROSE-010 was favored over a placebo for patient-rated pain relief[45]. More recently, a phase 2 RCT investigating the effect of ROSE-010 on GI motor functions in women with IBS-C found that although gastric emptying was delayed, colonic transit was significantly accelerated after 48 h, providing relief of constipation in these patients[46]. Although these results are encouraging, phase 3 RCTs are needed to confirm the efficacy and safety of ROSE-010.

PROSECRETORY AGENTS (SECRETAGOGUES)

In the last decade, intestinal secretion has been the subject of active research for the development of treatments for CC and IBS-C. The chemical and clinical characteristics of prosecretory agents, drugs that augment intestinal secretion, thus acting as a stool lubricant and facilitating its evacuation, are summarized in Table 4.

Lubiprostone

Lubiprostone, a chloride channel activator, was the first secretagogue to be investigated and approved for treatment of CC and IBS-C. Chloride channels have been recognized as the major effectors of fluid transport and secretion in the intestinal lumen[47]. In particular, type-2 chloride channels (ClC-2) have been explored with regard to their role in CC and IBS-C[48,49]. Lubiprostone is a highly specific activator of ClC-2 channels that leads to increased intestinal secretion[50,51], an effect that requires the cystic fibrosis transmembrane conductance regulator (CFTR)[52]. A phase 2, 12-wk double-blind RCT demonstrated that lubiprostone [8, 16 and 24 μg, twice daily (BID)] reduced abdominal pain in IBS-C patients, though higher doses were associated with more adverse events, namely nausea and diarrhea[53]. Schey and Rao demonstrated that 8 μg lubiprostone BID offered the best risk-benefit ratio for IBS-C patients[54].

The positive results from the phase 2 studies led to two phase 3, multicenter RCTs involving 1171 IBS-C patients treated for three months with 8 μg lubiprostone BID[55]. The primary efficacy endpoint was the percentage of overall responders that were at least moderately relieved for all four weeks of the month or significantly relieved for at least two weeks of the month. Patient-rated symptoms were significantly improved with lubiprostone treatment, with no increase in adverse events compared to the placebo. As the lubiprostone regimen was effective, well tolerated and safe, the long-term (up to 52 wk) efficacy, safety, and tolerability was evaluated in an extension study including 522 of these same IBS-C patients[56]. The results of this extended trial confirmed the efficacy of lubiprostone, with a favorable safety and tolerability profile for up to 13 mo. However, the absence

of a placebo arm raises some questions about the statistical validity of the data gathered.

Lubiprostone was approved by the United States FDA in April 2006 for the treatment of CC in men and women, and in April 2008 for the treatment of IBS-C in women. The recommended dose is 24 μg BID for CC and 8 μg BID for IBS-C. A four-week phase 3 RCT evaluated the efficacy and safety of 24 μg lubiprostone BID in 237 patients with CC and demonstrated significant improvement in the number of SCBMs, stool consistency, straining effort, and global bowel satisfaction[57]. Thus, lubiprostone was considered to be the "ideal" drug for IBS-C, as it was shown to be effective on all symptoms of IBS-C, including abdominal pain. However, recent data has suggested that lubiprostone may not have an anti-nociceptive effect in IBS-C. In fact, Whitehead *et al*[58] demonstrated that lubiprostone has no effect on visceral sensory thresholds in 62 IBS-C patients who completed a barostat test of pain and urge sensory thresholds. The authors concluded that lubiprostone did not relieve abdominal pain directly, but that the reduction in clinical pain in patients appeared to be secondary to changes in stool consistency.

Linaclotide

Linaclotide, a minimally absorbed first-in-class peptide agonist of guanylate cyclase C (GC-C), was recently approved for the treatment of IBS-C and CC. GC-C mediates intestinal secretion in response to heat-stable enterotoxins, the major cause of *Escherichia coli*-induced secretory diarrhea[59]. Linaclotide binds to GC-C, which is richly present on the luminal surface of the intestinal enterocytes[60], and ultimately activates CFTR, resulting in the secretion of chloride and bicarbonate into the intestinal lumen. Consequently, intestinal fluid secretion is increased, stools are softened, and colonic transit may be accelerated. The effect of linaclotide on ascending colonic transit has been demonstrated in a phase 2 RCT involving 36 women with IBS-C[61]. Additionally, unlike lubiprostone, linaclotide has been also shown to reduce visceral nociception in laboratory rodents[62]. More recently, this visceral antihyperalgesic effect has been replicated in healthy mice and those with chronic visceral hypersensitivity[63]. The dual action of linaclotide on both constipation and abdominal pain in IBS-C is likely related to its approval by both the United States FDA and the EMA.

The efficacy and safety of linaclotide for the treatment of IBS-C patients have been demonstrated in four well-conducted RCTs[61,64-66]. In a 12-wk RCT study of 420 IBS-C patients, Johnston *et al*[64] found that various doses of linaclotide (75, 150, 300 and 600 μg, once daily) were effective in improving all symptoms of IBS-C. The only observed adverse event in that trial was a dose-dependent diarrhea, whereas other adverse events were comparable between the treatment and placebo groups. A phase 3, 26-wk RCT[65] was recently conducted with linaclotide (290 μg daily) in 804 IBS-C patients according to the recommended United States FDA primary endpoints (responder: a patient who reported (1) ⩾ 30% improvement in an average daily worst abdominal pain score; and (2) an increase of ⩾ 1 average weekly SCBMs for at least half of the trial duration)[67]. The results of that trial showed that 33.7% of treated patients were United States FDA endpoint responders, compared to only 13.9% of those receiving a placebo. Specifically, 48.9% of treated patients met the criterion for pain responder, and 47.6% met the SCBM responder criterion, compared to 34.5% and 22.6% respectively of placebo-treated patients. In terms of safety and tolerability, diarrhea was the most common adverse event, occurring most often within the first four weeks of therapy, while the discontinuation rates were 10.2% and 2.5% for linaclotide and placebo, respectively. Another phase 3 RCT included a 12-wk treatment period followed by a four-week randomized withdrawal period[66]. The outcome measures of that study were the United States FDA endpoints for IBS-C and three other endpoints based on improvement in abdominal pain and SCBMs. The results of this trial also indicated that linaclotide was safe and effective in relieving IBS-C symptoms, with diarrhea being the most common adverse event and no worsening of symptoms in the withdrawal period.

Linaclotide (145 μg, once daily) was also shown by four well-conducted RCTs to be safe and effective for the treatment of CC[68-70]. Moreover, the safety and efficacy of linaclotide for the treatment of patients with IBS-C and CC has been confirmed by a recent meta-analysis study[71]. In August 2012, linaclotide (Linzess®; Ironwood Pharmaceuticals, Inc., Cambridge, MA, United States) was approved by the United States FDA for the treatment of IBS-C at a dose of 290 μg once daily and CC at a dose of 145 μg once daily[72]. In the European Union, the drug received approval for IBS-C patients but not for CC patients. The approval of linaclotide represented an important development in the treatment of IBS-C and CC, especially for those patients with poor tolerance or response to lubiprostone.

In summary, there is evidence showing that linaclotide is an effective, well tolerated, and safe therapeutic option for patients with IBS-C and CC, though the long-term safety and efficacy of linaclotide as well as a direct comparison with lubiprostone need to be investigated. Importantly, this drug has the advantage of improving both bowel symptoms and abdominal pain. However, the high cost of linaclotide and lubiprostone may limit their use in clinical practice, especially because a large proportion of IBS-C and CC patients belong to lower socioeconomic groups.

Plecanatide

Similar to linaclotide, plecanatide is a minimally absorbed GC-C agonist believed to act on both intestinal secretion and nociception. A phase 1 RCT was conduced in 72 healthy volunteers to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of various doses

Table 5 Chemical and clinical characteristics of bile acid modulators

	Chenodeoxycholate	Elobixibat
Chemical structure	Sodium chenodeoxycholic acid (primary bile acid)	Enantiomer of 1,5-benzothiazepine
Mechanism of action	Deconjugation to secondary bile acids, thus inducing colonic secretion and propulsive contractions	IBAT inhibition resulting in delivery of endogenous bile acids to the colon, thus inducing colonic secretion and propulsive contractions
Pharmacodynamic effects	Accelerated colonic transit	Dose-dependent acceleration of colonic transit
Most common adverse events	Diarrhea Abdominal cramping/pain Nausea	Diarrhea Abdominal cramping/pain
Potential other beneficial effects	Probable lowering of LDL	Lowering of LDL and cholesterol
Stage of development	Phase 3 RCT in IBS-C completed	Phase 3 RCTs in CC, completed; extended safety and tolerability RCTs enrolling

CC: Chronic constipation; IBAT: Ileal bile acid transporter; IBS-C: Constipation-predominant irritable bowel syndrome; LDL: Low-density lipoprotein; RCT: Randomized controlled trial.

(ranging from 0.1 to 48.6 mg) of oral plecanatide[73]. The study found no measurable systemic absorption of plecanatide, with adverse events similar to the placebo; thus, it was concluded that the drug acts locally in the intestine and is well tolerated and safe. However, low statistical power prevented the authors from making any conclusions with respect to the pharmacodynamic parameters. Preliminary results from a phase 2a RCT that is underway in patients with CC have suggested that plecanatide is effective, well tolerated, and safe at doses up to 9 mg[74]. Moreover, plecanatide-treated patients showed significant improvement in bowel symptoms without any observed serious adverse events. Other phase 2 RCTs using plecanatide in CC and IBS-C patients are still recruiting patients, and no results have been reported thus far.

BILE ACID MODULATORS

Bile acid modulators have been used to treat constipation disorders based on the observation of increased incidence of diarrhea in patients taking bile acids for gallstones or cholestatic liver diseases[75], and in patients with terminal ileum disease or resection[76]. The enhancement of colonic secretion and motility is caused mainly by the deconjugation of bile acids in the colon to secondary bile acids[77,78]. Thus far, two drugs, CDC and elobixibat, have been investigated for the treatment of IBS-C and CC. Their chemical and clinical characteristics are shown in Table 5.

CDC

CDC is a primary biliary acid that has been in use for many years for the dissolution of gallstones. In clinical studies, the main adverse event of CDC (Chenodal®; Manchester Pharmaceuticals, Fort Collins, CO, United States) was a dose-dependent diarrhea[77] that is of the secretory type, due mainly to intracellular activation of adenylate cyclase and increased intestinal permeability[77,79,80]. In a four-week placebo-controlled RCT of 20 gallstone patients with CC, Bazzoli *et al*[81] found that CDC significant improved bowel frequency and stool consistency. In a recent four-day double-blind RCT of 36 women with IBS-C, CDC (500 or 1000 mg, once daily) increased stool frequency, softened stools and improved straining, with lower abdominal cramping as the most commonly reported adverse event[82]. The authors concluded that the effect in these female patients was dependent on specific genetic variations in the negative feedback inhibition of bile acid synthesis. Therefore, CDC has the potential to be used as a "physiologic laxative" for the treatment of both IBS-C and CC; although, its use in IBS-C may be limited by the concern for worsening of abdominal pain.

Elobixibat

Elobixibat (formerly A3309) is a first-in-class ileal bile acid transporter inhibitor that is currently being investigated for the treatment of CC. Elobixibat has some potential advantages over currently approved drugs (prucalopride, lubiprostone, linaclotide). First, given its negligible systemic absorption, it is unlikely to induce cardiovascular toxicity, a theoretical effect of prucalopride. Second, it has a positive effect on both secretion and motility of the colon, while lubiprostone and linaclotide are only secretagogues, without any direct effect on colonic motility[77,78].

In the first human study of the pharmacokinetic and pharmacodynamic actions of elobixibat, Simrén *et al*[83] assessed the safety and tolerability of the drug in 30 patients with CC. The efficacy and metabolic parameters of patients receiving one of five elobixibat doses (from 0.1 to 10 mg, once daily) were favorable, with no significant adverse events. Two phase 2 RCTs focusing on the efficacy of elobixibat in CC patients with doses ranging from 5 to 20 mg once daily demonstrated significant improvement of all constipation parameters[84,85]. Furthermore, safety and tolerability analyses showed no serious adverse events, with lower abdominal cramping being the most common. Based on the results of these studies, elobixibat appears to be a promising pharmacologic option for patients with CC. The efficacy of elobixibat for the treatment of IBS-C has not yet been investigated, though the abdominal pain that is commonly observed might limit

Table 6 Chemical and clinical characteristics of drugs approved for other gastrointestinal indications and currently investigated for constipation-predominant irritable bowel syndrome

	Itopride	Neomycin/Rifaximin
Brand name	Ganaton®	Neomycin: Neo-Fradin® Rifaximin: Xifaxan®
Chemical structure	Benzamide derivative	Neomycin: aminoglycoside Rifaximin: semisynthetic antibiotic based on rifampicin
Mechanism of action	Dopamine D2 antagonist and acetylcholinesterase inhibitor	Neomycin: inhibition of protein synthesis Rifaximin: inhibition of bacterial RNA synthesis
Pharmacodynamic effects	Gastrokinetic; Acceleration of intestinal transit (?)	Eradication of methane; accelerated intestinal transit (?)
Most common adverse events	Diarrhea Headache Hyperprolactinemia	Neomycin: Neurotoxicity Ototoxicity Nephrotoxicity Rifaximin: Headache Nausea Dizziness Fatigue
Approval status/stage of development	Approved in Japan for functional dyspepsia; Phase 2 RCT in IBS-C completed in the United States	FDA-approved for hepatic encephalopathy and traveler's diarrhea; Phase 2 efficacy RCT in methane + IBS-C patients, comparing neomycin *vs* combination rifaximin and neomycin (completed)

FDA: Food and Drug Administration; IBS-C: Constipation-predominant irritable bowel syndrome; RCT: Randomized controlled trial.

Table 7 Quality of evidence supporting different pharmacologic agents for constipation-predominant irritable bowel syndrome and chronic constipation

Pharmacologic agent	Quality of evidence for IBS-C	Quality of evidence for CC
Laxatives		
Psyllium	No RCTs	Moderate
Docusate sodium	No RCTs	Low
Lactulose	No RCTs	Moderate
PEG	Moderate	High
Senna	No RCTs	Low
Bisacodyl	No RCTs	Moderate
Prokinetics		
Prucalopride	No RCTs	High
Naronapride	No RCTs	Low
Velusetrag	Low	Low
Rose-010	Moderate	No RCTs
Secretagogues		
Lubiprostone	High	High
Linaclotide	High	High
Plecanatide	Low	Low
Bile acid modulators		
CDC	Low	Low
Elobixibat	No RCTs	Moderate

The quality of evidence was assessed according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system[86], which defines study quality as high (further research is very unlikely to change confidence in the estimated effect); moderate (further research is likely to have an important impact on confidence in the estimated effect and may change the estimate); low (further research is very likely to have an important impact on confidence in the estimated effect and is likely to change the estimate); or very low (any estimate of effect is very uncertain). CC: Chronic constipation; CDC: Chenodeoxycholate; IBS-C: Constipation-predominant irritable bowel syndrome; PEG: Polyethylene glycol; RCT: Randomized controlled trials.

its use in clinical practice.

OTHER INVESTIGATIONAL AGENTS

The search for safer and more effective drugs for the treatment of IBS-C is ongoing, with phase 1 and phase 2 clinical trials underway to evaluate various pharmacologic options, including drugs already approved for other gastrointestinal indications [Ganaton® (Abbott India Ltd., Mumbai, India), Neo-Fradin® (X-Gen Pharmaceuticals Inc., Horseheads, NY, United States), Xifaxan® (Salix Pharmaceuticals Inc., Raleigh, NC, United States)] (Table 6), as well as novel molecules (DA6886, AZD1722, RDX5791, TC6499). Thus far, no results from completed studies are available, and other studies are still recruiting patients.

PERSPECTIVES AND CONCLUSION

IBS-C has been, and probably will remain for some time, a troubling disease for many sufferers and an enormous challenge for the treating physician. The multifactorial pathogenesis of the disease and the ill-defined drug targets make the goal of manufacturing a "universal drug" for IBS-C a hard one to attain. In recent years, new drug therapies have been added to the armamentarium for the treatment of IBS-C. The current available evidence indicates that linaclotide is the "ideal" treatment option for IBS-C patients at this time, but other investigational agents are showing promise as well. However, large scale, high quality longitudinal studies of such agents and post-

market monitoring of approved drugs are needed to confirm the efficacy, tolerability and safety of these treatments. The quality of current evidence in support of different drug classes is summarized in Table 7. However, drug choice is dictated not only by the supporting evidence, but also by the patients' and societal perspectives.

Patient-relevant symptoms in conjunction with a better understanding of the pathophysiologic mechanisms underlying IBS-C should drive the development of novel pharmacologic agents for this complex disorder. Novel drug therapies are expected to streamline the management of IBS-C, thus increasing patient satisfaction and ultimately reducing the use of healthcare resources. This could indeed compensate for the high cost of these drugs, which is one of the major concerns for many patients and insurers. Finally, since IBS-C is a spectrum disorder resulting in a broad range of responses to different drug regimens, the treatment of most IBS-C patients should be individualized. It is anticipated that in the near future, a multitude of pharmacologic agents with divergent mechanisms of action will be effective for diverse subsets of IBS-C patients, and the reconciliation of past pharmacologic treatment successes and failures will ultimately improve future management of IBS-C.

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