REVIEW

Current developments in pharmacological therapeutics for chronic constipation

Chunhuan Jiang, Qinglong Xu, Xiaoan Wen*, Hongbin Sun*

State Key Laboratory of Natural Medicines and Jiangsu Key Laboratory of Drug Discovery for Metabolic Disease, China Pharmaceutical University, Nanjing 210009, China

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Abstract Chronic constipation is a common gastrointestinal disease severely affecting the patient's quality of life. The traditional treatment of constipation is the use of laxatives. Recently, several new drugs including lubiprostone, linaclotide and prucalopride have been approved for treatment of chronic constipation. However, a significant unmet medical need still remains, particularly among those patients achieving poor results by current therapies. The 5-HT4 receptor modulators velusetrag and naronapride, the guanylate cyclase C agonist plecanatide and the ileal bile acid transporter inhibitor elobixibat are recognized as the most promising drugs under investigation. Herein, we give a comprehensive review on the pharmacological therapeutics for the treatment of chronic constipation, with the purpose of reflecting the drug development trends in this field.

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1. Introduction

Chronic constipation (CC) is a common gastrointestinal disorder in which patients have unsatisfying defaecation associated with infrequent bowel movements (<3 bowel movements per week), hard stools and straining when passing stool, even compounded with abdominal discomfort and bloating. It was estimated that constipation has a prevalence range from 8.75% in the Asian Pacific region to 27% in Western countries. Constipation in women occurs twice as frequently as in men. Severe constipation (e.g., only twice bowel movements a month) almost extensively occurs in women. Constipation heavily impacts the patient’s quality of life. In addition to the direct economic burden caused by treatment, patients may face hardships such as missing school or work. Inadequate intake of dietary fiber, lack of exercise, intestinal dysfunction, etc. can cause constipation. However, chronic primary or chronic idiopathic constipation (CIC), which is typically classified into three categories: outlet obstruction, normal-transit constipation and slow colonic transit, has no definitive cause. For the initial treatment of chronic constipation, increasing fiber intake or using laxatives is commonly recommended. Although clinical trials show that most laxatives achieve poor results, new pharmacological therapies with different mechanisms of action have been developed over the last decade for the treatment of chronic constipation.

2. Prokinetic agents

Main investigational prokinetic agents for the treatment of chronic constipation are listed in Table 1. Their mechanisms of action are illustrated in Fig. 1. 5-HT4 agonists and motilin agonists, acting on 5-HT4 receptors or motilin receptors located on epithelium, smooth muscle cells and intrinsic primary afferent neurons (IPAN), can directly or indirectly initiate the peristaltic or secretory reflex through the release of acetylcholine, resulting in decreased colonic transit time, improved bowel movement frequency and ameliorative bowel satisfaction.

2.1. 5-HT4 agonists

Serotonin (5-HT) is involved in gastrointestinal secretion, sensa-
tion and motility. It was estimated that 95% of 5-HT is distributed in the enteroendocrine cells of gastrointestinal (GI) mucosa. Among the seven subtypes of 5-HT receptors, the gastrointestinal 5-HT4 receptor is an extensively studied target for prokinetics.

Early 5-HT4 receptor agonists (e.g., tegaserod and cisapride) generally have low affinity and poor selectivity for the 5-HT4 receptor, accounting for poor efficacy and relatively serious adverse effects. More recently, many highly selective 5-HT4 receptor agonists (Fig. 2) have been investigated and may have a good profile of cardiovascular safety.

2.1.1. Prucalopride

Prucalopride (1, RO93877), initially developed by Janssen Pharmaceuticals, is presently licensed by Movetis to develop this agent as an orally administered, first-in-class drug for treatment of severe chronic constipation. As a very highly selective 5-HT4 agonist, prucalopride has no measurable affinity for other receptors. In safety evaluation tests, prucalopride showed no hERG (human ether-à-go-go-related gene) channel inhibitory activity. At dosages of 2 mg and 4 mg per day, this drug produced a low incidence of QT interval prolongation. Even up to 20 mg per day (10-fold higher than the recommended dosage), prucalopride displayed no clinically relevant effects on cardiovascular parameters in healthy volunteers. Prucalopride improved stool frequency and consistency, and dose-dependently enhanced colonic transit in healthy controls or chronic constipation patients with no negative impact on gastric emptying or small bowel transit. The patient’s quality of life was significantly improved by prucalopride treatment. Prucalopride was well absorbed from the gastrointestinal tract, with an absolute oral bioavailability of more than 90%. Its main elimination route was via the urine (60%–70% excreted unchanged in the urine). Because prucalopride has a low level of metabolism by liver, its pharmacokinetics is unlikely to be altered by hepatic impairment and no CYP3A4 drug interactions are anticipated. In Europe, 2 mg of prucalopride has been approved for the treatment of chronic constipation in women who have no adequate response to laxatives.

2.1.2. Velusetrag

Velusetrag (2, TD-5108) is an orally administrated available 5-HT4 agonist developed by Theravance. Binding affinity of this drug for the 5-HT4 receptor is over 500-fold that of other 5-HT receptor subtypes. HRX-83049, the active metabolite of velusetrag, has a similar affinity and selectivity for 5-HT4. Increased smooth muscle contractility of the antrum, fundus, duodenum and jejunum was observed in velusetrag-treated dogs. The relief of constipation by velusetrag was also confirmed in chronic constipation patients. The most common adverse

### Table 1 Prokinetic agents for the treatment of chronic constipation.

| Agent          | Class         | Company                  | Clinical consideration                                      | Status            |
|----------------|---------------|--------------------------|------------------------------------------------------------|------------------|
| Tegaserod      | 5-HT4 agonist | Novartis                 | Cardiovascular problem                                      | Withdrawn in 2007 |
| Prucalopride   | 5-HT4 agonist | Movetis, Janssen          | Accelerate colonic transit                                 | Marketed in EU, Canada |
| Velusetrag     | 5-HT4 agonist | Theravance, Alfa Wasserman | Accelerate colonic transit                                 | Phase II          |
| Naropapride    | 5-HT4 agonist | Armetheon                | Accelerate colonic transit                                 | Phase II, but not active |
| YKP1081        | 5-HT4 agonist | SK Biopharm              | Improve gastric emptying, accelerate colonic transit and reduce visceral pain | Phase I          |
| TD-8954        | 5-HT4(c) agonist | Theravance              | Increase bowel movement frequency, reduce time to first stool and cardiovascular risk | Phase II          |
| Mitemcinal fumarate | Motilin agonists | Chugai Pharma          | Strongly promote peristalsial                              | Preclinical       |
effects of velusetrag were those frequently associated with 5-HT₄ agonists, including diarrhea, headache and nausea. These dose-dependent adverse effects were mild to moderate, and usually occurred within the initial days of dosing. Clinically relevant doses of velusetrag in animals or humans did not generate severe side effects on blood pressure, heart rate or electrocardiogram. In isolated porcine or canine coronary arteries, velusetrag showed no contractile activity.

2.1.3. Naronapride

Naronapride (3, ATI-7505) activates 5-HT₄ receptors but has almost no actions on the other 5-HT subtypes. Moreover, the hERG channel inhibitory activity of this compound is negligible. A thorough QT study showed that naronapride had no obvious effect on cardiac repolarization at either therapeutic or supratherapeutic doses. ATI-7500, the main metabolite of naronapride, is 100-fold less active than the parent drug. Unlike prucalopride and velusetrag, both naronapride and ATI-7500 cannot pass the blood-brain barrier, therefore reducing the incidence of side effects. In a clinical trial Phase IIa, naronapride accelerated the stool consistency and colonic transit and promoted colonic emptying in healthy volunteers. In a 4-week Phase IIb clinical trial, 20–120 mg of naronapride twice a day led to a greater mean number of completely spontaneous bowel movements than placebo. A higher dose, 80 mg twice daily, achieved the best effect.

Figure 1  Action mechanism of prokinetic agents in gastrointestinal tract.

Figure 2  Chemical structures of 5-HT₄ agonists.
2.1.4. **TD-8954**

TD-8954 (4, also developed by Theravance) is highly selective for the 5-HT₄c receptor, with the binding affinity 2000-fold stronger than for the other 5-HT receptors and non-serotonin receptors. TD-8954 showed no hERG channel inhibitory activity and no significant off-target effect. Preclinical trials showed that doses as low as 0.1 mg of TD-8954 produced prokinetic effects and 0.5 mg attained a maximal response. Increased colonic transit was observed in TD-8954 treated animals (0.03 mg/kg). Compared with tegaserod, cisapride and mosapride, TD-8954 more potently inhibited spontaneous and electrically-evoked contractions in the healthy human colon. TD-8954 was also able to increase bowel movement frequency and reduce the time to first stool.

2.2. **Motilin agonists**

Motilin, an endogenous 22-amino acid peptide hormone secreted from the enterochromaffin cells of the small intestine, is cyclically released during the interdigestive state to initiate well-coordinated gastrointestinal contraction. By acting on the G-protein coupled motilin receptor (expressed on the smooth muscle cells of gastrointestinal tract and the enteric nervous system), motilin can improve the delay in gastric emptying associated with many types of illness.

Erythromycin (5, Fig. 3) is a typical macrolide-type antibiotic widely used for decades. In clinical use of erythromycin as an antibiotic drug, it was found that erythromycin could accelerate the gastric emptying in patients with gastroparesis and stimulated the

![Figure 3](https://example.com/figure3.png)  
**Figure 3** Chemical structures of motilin agonists.

| Table 2 | Prosecretory agents⁶. |
|---------|-----------------------|
| **Agent** | **Class** | **Company** | **Clinical consideration** | **Status** |
| Lubiprostone | CIC-2 activator, EP4 agonist | Takeda | Accelerate of small bowel frequency and colonic transit, and improve abdominal bloating, discomfort and constipation severity ratings (24 mg twice-daily capsule) | Marketed for CIC, IBS-C and OIC |
| Misoprostol | Synthetic PGE₂ analogue | Pfizer | Increase fluid and bicarbonate secretion, improve colonic transit time, stool weight and bowel movement frequency | No development reported |
| Linaclotide | GC-C agonist | Ironwood, Forest | Accelerate colonic transit and bowel movement frequency, and act locally in the intestine (once-daily capsule) | Marketed for CIC and IBS-C in USA |
| Plecanatide | GC-C agonist | Synergy | 8-fold more potent than uroguanylin, non-systemic distribution, once-daily oral tablet | Phase III (CIC) |
| Sodium chenodeoxycholate | Bile acid analogue | Mayo Clinic | Enhance colonic motility and mucosal permeability, and increase mucus secretion | Phase II (IBS-C) |
| Elobixibat | IBAT inhibitor | Albireo, Ferring | Act locally in the gut with minimal systemic exposure, modulate enterohepatic circulation of bile acids, and increase colonic fluid secretion and motility | Phase III (CIC) |

⁶CIC: chronic idiopathic constipation; OIC: opioid-induced constipation; IBAT: the ileal bile acid transporter (also known as the apical sodium-dependent bile acid transporter); IBS-C: irritable bowel syndrome with constipation; GC-C: guanylate cyclase C.
myoelectric complex to migrate in the fasting small intestine\textsuperscript{20}. Preliminary studies showed that oral administration of erythromycin could increase the stool frequency and decrease the colonic transit time in healthy volunteers or patients with idiopathic constipation\textsuperscript{21}. These findings motivated people to discover non-antibiotic macrolide as promotility agents. Mitemcinal fumarate (6, GM-611), an acid-stable erythromycin derivative with very weak antibiotic activity, was identified as a potent motilin agonist\textsuperscript{22}. It is being developed in clinical phase II for the treatment of irritable bowel syndrome, non-ulcer dyspepsia and diabetic gastroparesis. It was also suggested that mitemcinal fumarate should be considered for the treatment of chronic constipation. Studies demonstrated that GM-611 could stimulate and promote the peristalsis of gastrointestinal tract. Oral administration of GM-611 (2.5–10 mg/kg) in normal rabbits produced sustained depolarization of the duodenal smooth muscle and increased stool weight in a dose-dependent manner without causing loose stools\textsuperscript{23}. In conscious dogs, GM-611 (0.3–3 mg/kg) reduced the time to first bowel movement without inducing diarrhea.

3. Prosecretory agents

Main investigational prosecretory agents for the treatment of chronic constipation are listed in Table 2. Their mechanisms of action are summarized in Fig. 4. Activation of the GC-C receptor can promote intracellular synthesis of cGMP and subsequently stimulates the cGMP-dependent protein kinase II (PKGII) to phosphorylate CFTR, thereby increasing chloride secretion and paracellular movement of sodium and water into the intestinal lumen. cGMP is also able to inhibit the sodium–hydrogen exchanger NHE3, thereby decreasing sodium absorption. Lubiprostone can induce chloride secretion into intestinal lumen by opening of the CLC-2 chloride channel. Misoprostol and lubricating gut pills (LGP) can activate EP2/4 receptors to stimulate cAMP production with a resultant increase in chloride secretion. Elobixibat inhibits ileal bile acid reabsorption to increase bile acid load into the colon. The increasing bile acid enhances colonic electrolyte secretion by acting with TGR5 on enterocytes, thus stimulating cAMP generation and electrogenic chloride secretion. EPX-16006 activates the colonic P2Y\textsubscript{2} receptor to open the calcium-activated chloride channel (CaCC), increase the production and release of PGE\textsubscript{2}, and subsequently trigger chloride secretion. The P2Y\textsubscript{2} receptor also plays a role in the inhibition of amiloride-sensitive sodium transport via the epithelial sodium channel (ENaC). The end results of both mechanisms are the preservation of intestinal water and prokinesis of the luminal contents.

3.1. Chloride channel activators

Chloride channels are involved in a wide range of biological functions including epithelial fluid secretion and smooth-muscle contraction\textsuperscript{24}. Chloride secretion (Fig. 4) is the major determinant of mucosal hydration throughout the gastrointestinal tract, and chloride transport is also pivotal in the regulation of fluid secretion into the intestinal lumen\textsuperscript{25}. Two specific chloride channels CIC-2 (chloride channel protein 2) and CFTR (cystic fibrosis transmembrane conductance regulator) have been validated as targets for the treatment of constipation\textsuperscript{26}. CIC-2 has been localized on gastrointestinal parietal cells and small and large intestinal epithelial cells\textsuperscript{27}. Activity of the CIC-2 channel enables pass of chloride ions across the cellular membrane and subsequent release of sodium and water through paracellular

\begin{figure}[h]
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\caption{Mechanism of prosecretory agents in the gastrointestinal tract.}
\end{figure}
pathways into the intestinal lumen. The luminal distension caused by increased intestinal fluid promotes the gastrointestinal tract motility, thereby increasing intestinal and colonic transit. Once this isotonic solution reaches the colon, the colon reabsorbs the excess fluid, resulting in more frequent bowel movements. However, ClC-2 was also found on the basolateral membrane of distal colonic epithelial cells in guinea-pigs. There is another opinion that ClC-2 channels may serve as an exit pathway for Cl⁻ in the basolateral membranes of the distal colon.

Lubiprostone (7, Fig. 5), a first-in-class drug for the treatment of chronic idiopathic constipation and irritable bowel syndrome in adult constipation women, is believed to be a highly selective locally-acting activator of ClC-2 channels. Lubiprostone can tautomerize between the inactive form I and the active form II. However, controversy still remains on the mechanism of action of lubiprostone. There is now considerable evidence that lubiprostone primarily activates CFTR by binding to the basolateral prostaglandin receptor EP4. Lubiprostone has low systemic bioavailability due to its high lipophilicity. The plasma concentration of lubiprostone is too low to be quantified. The absorbed lubiprostone is rapidly and extensively metabolized by microsomal carbonyl reductase in the stomach and jejunum to form the metabolite M3, which is the only measurable metabolite in blood. Several large trials proved that lubiprostone could increase the number of spontaneous bowel movements (SBMs), improve the stool consistency and reduce straining, bloating and the overall constipation symptoms in chronic constipation patients and irritable bowel syndrome patients complicated with constipation. Lubiprostone (24 μg twice daily) has been approved by the US. FDA for women and men with chronic constipation. A lower dose (8 μg) has been approved for irritable bowel syndrome with constipation in women. Lubiprostone is also beneficial for patients with opioid-induced constipation. The common and dose-dependent side-effects of lubiprostone include nausea, headache and diarrhea.

3.2. PGE₂ receptor agonist

Postaglandins E₂ and E₁ (PGE₂ and PGE₁) can activate the prostaglandin receptors EP2/4 and subsequently stimulate cAMP production. These actions increase fluid and bicarbonate secretion in the small intestine, which are clinically beneficial for patients with chronic constipation. It was demonstrated that PGE₁ caused a net fluid secretion in the canine small intestine and PGE₂ decreased sodium absorption and increased chloride secretion in human jejunum.
Misoprostol (Fig. 5) was approved by the U.S. FDA for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers. In clinical use, it was found that misoprostol could cause diarrhea. Further studies showed that misoprostol could activate EP2, EP3 and EP4 receptors. In a small trial involving nine patients with severe chronic constipation, misoprostol (1.2 mg per day) was able to stimulate mucosal water and ion secretion, increase the weight and frequency of stools, and shorten colonic transit time. However, high doses of misoprostol caused abdominal cramping, bloating and nausea. In addition, administration of misoprostol to women of child-bearing age could lead to spontaneous abortion, premature birth or birth defects. For these reasons, the U.S. FDA did not approve misoprostol for any constipation.

3.3. Uroguanylin and GC-C receptor agonists

Uroguanylin (16 amino acids) and guanylin (15 amino acids) are small cysteine-rich peptide hormones predominantly secreted and locally acting in the intestinal tract. These agents bind to a unique receptor found on the intestine epithelial cells, called guanylate cyclase C (GC-C, also known as STA receptor). GC-C plays key roles in the regulation of intestinal fluid and electrolyte homeostasis. Activation of the GC-C receptor promotes intracellular synthesis of cGMP and subsequent activation of CFTR, resulting in chloride and bicarbonate secretion as well as paracellular movement of sodium and water into the intestinal lumen. These changes in the intraluminal milieu facilitate the fluid movement into the gut lumen, leading to improved transit of fecal material through the lower gastrointestinal tract to facilitate defeation.

3.3.1. Linaclotide acetate

Linaclotide acetate (MD-1100) is an orally administered available first-in-class 14-amino acid peptide with three disulfide bonds, which is being developed by Microbi Inc. for the treatment of constipation, predominant irritable bowel syndrome, and chronic idiopathic constipation. Linaclotide acts as an agonist of GC-C and also inhibits the sodium absorption from lumen via a sodium proton exchanger. The U.S. FDA has approved 290 μg of linaclotide daily for irritable bowel syndrome with constipation and 145 μg daily for chronic idiopathic constipation. The company may, according to the recent preclinical studies, expand the therapeutic range to post-operative ileus and opioid-induced constipation. Linaclotide-potently and pH-independently binds to GC-C receptors in human colon carcinoma T84 cells (Ki = 1.23–1.64 nmol/L), resulting in a significant, concentration-dependent accumulation of intracellular cGMP (EC50 = 99 nmol/L). Linaclotide was observed to function locally in the lumen. Pharmacokinetic analysis showed that linaclotide had very low oral bioavailability (0.1%), and was undetectable in the systemic circulation at therapeutic doses. In a rat model, oral linaclotide dose-dependently increased intestinal secretion and improved symptoms in patients with chronic constipation. The adverse effects were primarily diarrhea and other gastrointestinal symptoms. Linaclotide is acid-stable and resistant to aminopeptidase and chymotrypsin under non-reducing conditions, but is degraded rapidly in the duodenum by the carboxypeptidase. This result in loss of the C-terminal tyrosine, and formation of the active 13-amino acid metabolite, MM-419447. MM-419447 also stimulates the accumulation of cGMP in T84 cells and accelerates gastrointestinal transit in rats. The binding affinity of MM-419447 for GC-C on T84 cells and rat small intestine brush-border membranes was comparable to that of linaclotide.

3.3.2. Plecanatide

Plecanatide (SP-304) is an orally available synthetic analogue of uroguanylin under development by Synergy Pharmaceuticals Inc. for the treatment of chronic constipation and irritable bowel syndrome with constipation. Plecanatide mimics the endogenous agonist of GC-C receptor in the intestinal tract. Like that of uroguanylin, plecanatide's actions are pH-dependent, with most favorable efficacy in the acidic environment of the duodenum. Similar to linaclotide, plecanatide luminaly activates the GC-C receptor on gastrointestinal mucosal epithelial cells, leading to intracellular secretory and extracellular anti-nociceptive effects via a cGMP mediated second messenger pathway. Plecanatide potentially has low risk of cardiovasular adverse effects as its systemic absorption is very low. According to the phase I study for evaluation of the safety and tolerability of plecanatide in humans, no measurable systemic absorption was observed at any doses of oral plecanatide. Plecanatide was safe and well tolerated up to the highest dose. Diarrhea was the most prevalent side effect, but its frequency did not statistically significantly differ between placebo and plecanatide, and appeared not to be dose-related in the plecanatide-treated subjects. Other gastrointestinal events were nausea, abdominal discomfort and pain, and vomiting. In a Phase IIa dose escalation trial involving a total of 84 chronic constipation patients recruited with modified Rome III criteria, 14 days of plecanatide therapy improved stool frequency, stool consistency, straining and overall relief of chronic constipation symptoms. To confirm the safety and efficacy of plecanatide, two Phase III trials (NCT01982240 and SP034203-00) have been planned. In the US and Canada, the Phase III trial NCT01982240 was initiated in November 2013 with adult chronic constipation patients and was expected to complete in February 2015.

3.4. Increasing colonic bile acids

Bile acids including chenodeoxycholic acid (CDCA) and cholic acid are synthesized in the liver through hydroxylation and conjugation of cholesterol to hydrophobic primary bile acids. Normally, up to 95% of intestinal bile acids are reabsorbed by ileal bile acid transporters located in the terminal ileum and returned to the liver via the portal vein (enterohepatic circulation). Therefore, under normal circumstances, only small quantities of bile acids spill over to the colon, where bile acids are deconjugated and dehydroxylated by colonic microbiota to produce secondary bile acids such as deoxycholic acid. However, if ileal function is compromised by either resection or disease, reabsorption of bile acids would be inadequate and therefore delivery of bile acids into the colon increases to induce mucus production, colonic motility and stimulate defeation. Bile acids can induce colonic electrolyte secretion by acting on the membrane-bound bile acid GPBA receptor (TGR5) on enteroctyes (Fig. 4) and subsequently leading to stimulation of cAMP generation and electrolytic chloride secretion. Thus, supplementation of specific bile acid
analgesics or use of drugs that inhibit ileal bile acid reabsorption may benefit constipation patients.

3.4.1. Sodium chenodeoxycholate
Bile acids such as chenodeoxycholic acid (CDCA), previously used for dissolution of gallstones, are known to elicit diarrhea at high doses in healthy controls and constipation patients. The effects of CDCA on gastrointestinal and colonic function have been evaluated in healthy volunteers and patients with irritable bowel syndrome with constipation. In a randomized controlled trial, CDCA 500 mg and 1000 mg given to 60 healthy volunteers for 4 days led to dose-dependent acceleration of colonic transit. In addition, significant increases in stool frequency, decreases in stool consistency, and improvements in ease of stool passage were reported with CDCA. Rao et al. showed in a double-blind placebo-controlled study that sodium chenodeoxycholate (11) accelerated colonic transit and improved bowel function in 36 female patients with irritable bowel syndrome with constipation. Increased stool frequency, greater ease of stool passage and looser stool consistency were observed in patients treated with sodium chenodeoxycholate 500 mg or 1000 mg for 4 days as compared with controls. Unfortunately, over 40% of sodium chenodeoxycholate treated patients had light abdominal cramping or pain. Whether these side effects could be mitigated at a lower dose remains to be determined.

3.4.2. Elobixibat
Elobixibat (12) is an orally administrated available potent inhibitor of ileal bile acid transporter with minimal systemic exposure. It is under development by Albireo AB and Ferring Pharmaceuticals Inc. for the treatment of chronic constipation. Elobixibat dose-dependently inhibited the reabsorption of bile acids and thus increased the delivery of bile acids to the proximal colon, which in turn increased fluid secretion, colonic motility and stool frequency, and also improved stool consistency and relieved constipation-related symptoms in chronic idiopathic constipation patients. According to the results of Phase II trials in chronic idiopathic constipation patients, elobixibat was safe and generally well-tolerated, even at the dose up to 20 mg per day. Elobixibat was found to decrease the time to complete spontaneous bowel movement in dose-dependent manner. Elobixibat also significantly relieved constipation-related symptoms such as stool consistency, straining on evacuation and abdominal bloating, according to the claims of several patients. Chronic constipation patients with dyslipidemia might specially benefit from elobixibat because it has the potential to lower plasma lipid levels by the shunting of cholesterol. To support this point, further validation studies should be conducted. The side effects of elobixibat are mainly gastrointestinal tract–related. Although higher dosages of elobixibat caused abdominal pain and diarrhea more frequently, no severe adverse effects occurred in the Phase I and Phase II clinical trials. The Phase III clinical trials are ongoing to determine the best tolerated dose and to examine the effects of long-term administration. As illustrated by elobixibat, the advantages of IBAT inhibitors may be especially attractive, which may boost the research of other IBAT inhibitors, for example, SC-435, S-8921 and S-09607-254.

4. Traditional Chinese medicines
Hemp seed extract as a popular Chinese herbal medicine is often used for the treatment of constipation. In a 8-week trial with 120 constipation patients, 43.3% of patients treated with 7.5 g of hemp seed pill twice daily had a mean increase in the number of completely spontaneous bowel movements (≥1/week). Moreover, 30% of hemp seed pill treated patients had a sustained increase in the frequency of completely spontaneous bowel movements. The constipation symptoms and severity was obviously relieved in hemp seed treated patients, and no serious adverse effects took place. In addition, Wu et al. recently demonstrated that a traditional Chinese formula, LGP, could generate laxative effect in loperamide-induced constipation rats. LGP increased the production of endogenous PGE2 in colonic mucosa via activation of EP4 receptor.

5. Other agents
KWA-0711, developed by Kissei Pharmaceutical Co., Ltd., can inhibit water absorption in the gastrointestinal tract. Several phase II clinical trials have been conducted in Japan to evaluate the efficacy and safety of KWA-0711 in constipation patients. However, the clear action mechanism of KWA-0711 is unknown. And, to date, there is no clinical trial result of KWA-0711 published.

A luminaly active dinucleotide mimic MDT-006 (formerly EPX-16006) is under investigation by the MicroDose Therapeutics as a first-in-class oral drug for the treatment of chronic constipation. It was reported that MDT-006 is a non-absorbable highly selective P2Y1 agonist, which stimulated chloride secretion in gut lumen. Preclinical trials demonstrated that MDT-006 dose-dependently reduced the total gastrointestinal transit time, improved the gastrointestinal motility and increased the production of feces and its water content with no effect on the gastric emptying. In January 2013, this drug candidate was ready for phase I development. Because MDT-006 is not absorbed and its action site is restricted to the colon, it was estimated that MDT-006 might have a good profile of safety and tolerability, with the incidence of nausea and systemic liabilities reduced.

Colchicine, usually used as an anti-inflammatory drug, has also been investigated in the management of chronic constipation. In clinical use of colchicine as an anti-inflammatory drug, patients were found to often suffer from diarrhea. Further study demonstrated that colchicine could stimulate the intestinal motility and the myoelectric activity in rats. Colchicine was also able to reduce intestinal absorption and increase intestinal secretion in a cAMP-mediated manner, resulting in a net increase of intestinal secretion. In a randomized, double-blind and placebo-controlled crossover trial, oral administration of colchicine 0.6 mg three times daily increased the frequency of bowel movement and accelerated the colonic transit in refractory constipation patients. In another randomized, double-blind and placebo-controlled study, colchicine was demonstrated to be effective for the treatment of slow transit constipation. It was found that 1 mg of colchicine per day caused a significant increase in the number of spontaneous bowel movements and an obvious improvement in the patient's symptoms. Unfortunately, increased occurrence of abdominal pain was observed in the colchicine group. In addition, long-term use of colchicine may cause granulocytopenia, renal dysfunction, reversible myopathy or neuropathy and hepatitis. Thus, further long-term study is necessary before it could be recommended for long-term use.

6. Conclusions
Traditional laxatives are widely used and commonly recommended for the initial treatment of chronic constipation. Unfortunately, most of them showed poor effects in clinical evaluation trials. Thus, new pharmacological therapeutics are needed to achieve substantial relief of
constipation symptoms and normalization of gastrointestinal motility. Tegaserod and cisapride as prokinetic drugs have never been approved, but withdrawn from the market because of their cardiotoxic adverse effects. New prokinetic drugs with potent intrinsic activity, high selectivity and low cardiotoxic effects may be clinically available in the coming years. Luminally acting agents, e.g., lubiprostone, are also promising because they could improve not only intestinal motility but also secretion in small bowel or colon with low risk of causing non-gastrointestinal adverse effects. In the meantime, current drugs need to be further studied. For example, the active ingredients of lubiprostone are yet unknown.

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