Drugs Acting on the Gut: Prokinetics, Antispasmodics, Laxatives

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Introduction

Disorders of gastrointestinal motility result from abnormal contractions of the smooth muscles of the gastrointestinal tract. This may result in diarrhea and bloating or constipation with or without accompanying abdominal pain. Drugs that act on the gastrointestinal tract may be categorized into three groups: (1) agents that enhance smooth muscle contractions, referred to as prokinetic agents; (2) agents that inhibit contractions, which may be agents that retard normal peristalsis referred to as antimotility agents (opiates and opiate receptor agonists) or agents that reduce abnormally elevated gastrointestinal smooth muscle tone, referred to as antispasmodics (anticholinergics, direct smooth muscle relaxers, and calcium channel blockers); (3) agents that act to promote evacuation of stool, referred to as laxatives. This chapter discusses prokinetics, antimotility agents, and antispasmodics, as well as laxatives commonly used in clinical practice.

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Prokinetic Agents

Available prokinetic medications generally fall under three groups of drugs: dopamine receptor antagonists, motilin receptor agonists, and 5-hydroxytryptamine-4 ($5HT_4$) receptor agonists.

Dopamine-2 (D2) Receptor Antagonists

Domperidone

Domperidone is a peripheral dopamine-2 (D2) receptor antagonist that is used to treat gastroesophageal reflux, gastroparesis, functional dyspepsia, nausea, and vomiting. While it is available in over 50 countries worldwide, it is only available in the USA as an investigational drug. D2 receptors are located both within the brain and in the peripheral nervous system, however since domperidone has poor penetration of the blood–brain barrier, most of its effects are derived from peripheral receptors. Domperidone has the ability to cross the placenta and small amounts are excreted in breast milk (2 ng/mL when dosed at 10 mg PO TID) [1]. It is rapidly metabolized in the liver and has a half-life of 7.5 h [2, 3]. In the gastrointestinal tract, D2 receptor stimulation leads to inhibition of gastric motility, therefore D2 receptor antagonists decrease the symptoms of bloating, premature satiety, nausea, and vomiting by accelerating gastric emptying, increasing antroduodenal contractions, and promoting

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esophageal motility [4]. Domperidone also exerts an antiemetic effect on the chemoreceptor trigger zone, which is not protected by the blood–brain barrier. One of the side effects of domperidone is hyperprolactinemia and it has been used off-label to increase milk production for mothers of preterm infants.

Safety and efficacy has not been adequately established for the pediatric population. In children admitted to the hospital for vomiting, compared to placebo and metaclopramide (10 mg) the symptoms of nausea and vomiting were significantly lower using domperidone (30 mg), however this study was conducted for a 24 h period only [5]. Using domperidone to treat gastroesophageal reflux in children, a double-blind placebo-controlled trial was done on 17 patients [6]; after 4 weeks of therapy there was a significant decrease in the number of measured postprandial reflux episodes but no decrease in reported symptoms. The most commonly reported adverse event was diarrhea. Two systematic reviews of pediatric GERD treatments did not recommend the use of domperidone in this patient population due to lack of data showing its efficacy [7, 8]. Oral domperidone in neonates is associated with prolonged QTc interval in patients ≥32 weeks of gestation [9]. Mean QTc prolongation was 14 ms with increasing gestational age and serum potassium at the upper limit of normal being independent risk factors.

A systematic review of qualified studies in adults found that approximately 64% of studies showed that domperidone was effective in improving symptoms of diabetic gastroparesis and 60% showed efficacy in improving gastric emptying [10]. In cases of GERD without evidence of gastric dysmotility, domperidone does not provide increased benefit to adult patients in comparison to acid suppression alone [11]. For adult treatment of functional dyspepsia, a meta-analysis revealed that there was significant improvement in the patient's global assessment with an OR of 7 (95% CI 3.6–16), however there was not enough data to support measured improvement in gastric emptying [12]. Patients with postoperative nausea as well as nausea from cytotoxic medications have improvement of their symptoms compared to placebo; however domperidone was given in the IV form which is no longer available [13–16].

Due to poor CNS penetration, domperidone does not have the neurologic side effects seen with metoclopramide, which is also a D2 receptor antagonist. Domperidone is a CYP3A4 inhibitor and should be avoided in combination with other CYP3A4 inhibitors. There is the potential for prolongation of the QT interval leading to arrhythmias as it acts similar to class III antiarrhythmic agents. Arrhythmia and sudden cardiac death have been associated with patients given intravenous domperidone in the setting of hypokalemia and as a result the IV formulation is no longer available [17, 18]. Risk of cardiac events associated with oral domperidone use compared to PPI use and nonuse of either medication was evaluated in a large-scale nested case–control study [19]. 83,212 patients were exposed to oral domperidone, PPI, or both and within this group there were 49 confirmed cases of serious ventricular arrhythmia and 1,559 confirmed cases of sudden cardiac death. Up to four controls were matched to each case and the adjusted odds ratio for serious ventricular arrhythmia and sudden cardiac death with current use of domperidone was 1.59 (95% CI: 1.28–1.98) compared to nonuse of PPI and 1.44 (95% CI: 1.12–1.86) compared to current use of PPI. Past use of domperidone was not associated with increased risk of cardiac events. Risk may also be increased in patients older than 60 years, males, and those without diabetes.

Domperidone is available in oral tablet, oral suspension, and rectal formulations. The recommended dosing is 10–20 mg two to four times daily 15–30 min before meals. Pediatric dosing is 0.3 mg/kg/dose two to four times daily, not exceeding adult dose. Tablets may be crushed and given through gastrostomy, nasogastric, or jejunostomy tubes.

Metoclopramide

Metoclopramide is a dopamine (D2) receptor antagonist that stimulates the stomach and duodenum by causing efferent myenteric cholinergic neurons to release acetylcholine. There is also an increase in the lower esophageal sphincter tone [20, 21]. Metoclopramide's antiemetic properties are due to its effects on the central nervous system D2 receptors in the chemoreceptor trigger zone.

However, due to its ability to cross the blood–brain barrier it also has the potential to cause acute extrapyramidal reactions [22, 23] and tardive dyskinesia with long-term or high-dose use [24, 25]. Metoclopramide is used to treat gastroesophageal reflux, chemotherapy-induced nausea, postoperative nausea and vomiting, and gastroparesis. Evidence for use in pediatric gastroesophageal reflux is conflicting as some studies show that there is no significant improvement in symptoms and esophageal pH measurements compared to placebo, while others show significant improvement [26, 27]. Metoclopramide is used frequently to treat postoperative nausea and vomiting, and in the setting of strabismus surgery where, a review determined that there was significant improvement in symptoms for the early postoperative period compared to that of placebo [28].

Metoclopramide is available in the PO, SC, IM, IV forms. The adult dose is 10 mg three to four times daily. The pediatric dose is 0.4–0.8 mg/kg/day divided 4 times a day not to exceed adult dosage. A black box warning issued by the United States Food and Drug Administration cautions that cumulative use greater than 12 weeks in duration, increases risk of tardive dyskinesia, which may be irreversible. Extrapyramidal symptoms occur more commonly within 24–48 h of initiation of therapy and children are at increased risk especially with higher dosing. Pseudoparkinsonism has also been reported and is usually reversible. Other side effects include sedation and hyperprolactinemia. The half life in children is around 4 h with 85% being eliminated in the urine; therefore, dosing should be adjusted in cases of renal dysfunction. Metoclopramide does cross the placenta and is excreted in breast milk. Onset of action is 15–30 min after oral dosing and 1–3 min after intravenous administration [29].

Motilin Agonists

Erythromycin

Erythromycin is a macrolide antibiotic, and it also acts as a motilin agonist and its primary prokinetic use is for the treatment of gastroparesis. Motilin is a peptide hormone secreted by the small intestine from the enterochromaffin cells [30]. The receptors for motilin are found mainly in the smooth muscle and cholinergic neurons of the stomach antrum and proximal duodenum [31]. The effect of motilin pertains to stimulation of phase 3 MMCs in the interdigestive state [31]. Janssens et al. first studied the effect of erythromycin on gastric motility in 10 adult diabetic patients with gastroparesis in 1990 [32]. Compared with placebo, an IV dose of 200 mg significantly improved gastric emptying from a 120 min mean retention of 63 ± 9–$4 \pm 1\%$. This preliminary study also showed an improvement in gastric emptying in the same 10 patients after 4 weeks of 250 mg, PO, TID, but to a lesser degree.

Erythromycin may be given through both oral and intravenous routes. Adult dosing ranges from 50 to 250 mg, three or four times a day and pediatric dosing is typically 5 mg/kg/dose. Different motor patterns are elicited from varying erythromycin dosages [33]. Low dose erythromycin (1–3 mg/kg IV) stimulates the neural motilin receptors leading to augmentation of phase 3 MMCs [33, 34]. A higher dose of the drug stimulates the smooth muscle motilin receptors leading to sustained contractions in the antrum and antroduodenal coordination [33–35]. Long-term therapy appears to be safe; however, decreased efficacy is seen after prolonged treatment due to downregulation of motilin receptors. There has been no evidence that erythromycin has any prokinetic effect on the colon as shown by administration of the drug during colonic manometry studies [36, 37].

Commonly reported side effects include nausea, vomiting, and abdominal pain. There have been reports of erythromycin being associated with serious cardiac arrhythmias and prolonged QTc [38–40]. Erythromycin should not be used concurrently with medications metabolized by cytochrome P450 3A4 (CYP3A4) such as cisapride, terfenadine, pimozide, or astemizole as it is a CYP3A4 inhibitor. Caution must be used in young infants as there is an eight- to tenfold increased risk of developing hypertrophic pyloric stenosis in term or near-term infants when used within the first 2 weeks of life and when the treatment course

is >14 days [41]. There is insufficient data in the preterm infant population as to whether there is increased risk of pyloric stenosis and a recent review did not show increased incidence for this particular population for treatment of dysmotility due to immaturity of the gastrointestinal tract [42]. Erythromycin is excreted in breast milk at levels ranging from 50 to 100% of maternal serum levels [43] and should be taken into consideration when treating nursing mothers.

Cholinergics

Bethanechol

Bethanechol is a cholinergic medication, which acts as a muscarinic receptor agonist leading to stimulation of esophageal peristalsis and increased antral contractility. It is also used to treat urinary retention secondary to neurogenic bladder. It causes decreased episodes of esophageal reflux by increasing lower esophageal sphincter (LES) pressure and increasing esophageal clearance [44–47]. Bethanechol's effect on the amplitude and duration of esophageal contractions are more pronounced in the distal esophagus and there is less effect on upper esophageal motility [48]. In patients with normal lower esophageal sphincter tone and normal esophageal motility, it is questionable if bethanechol is useful in the treatment of uncomplicated gastroesophageal reflux and acid suppression may better serve this population [49, 50]. Patients with known esophageal dysmotility and abnormal LES tone, such as those post-tracheoesophageal fistula or esophageal atresia repair, may benefit from bethanechol [51]. It improves smooth muscle function in patients with ineffective esophageal motility documented by esophageal manometry [52].

Bethanechol is available by oral and subcutaneous administration only and the onset of action is 30–90 min. It should not be used in combination with anticholinesterase inhibitors. The mechanism of metabolism and excretion is unclear. Pediatric dosing is 0.1–0.2 mg/kg/dose before meals up to four times a day and the adult dose is 10–50 mg two to four times a day. Side effects to note include bronchial constriction and it should be used with caution in asthmatics. Bethanechol does produce other cholinergic effects including urinary frequency, miosis, lacrimation, and flushing.

Neostigmine

Neostigmine is a synthetic, reversible acetylcholinesterase inhibitor. It is used in the treatment of myasthenia gravis and for reversing nondepolarizing muscle relaxants. Neostigmine has also been used to treat patients with acute colonic pseudo-obstruction (ACPO), known as Ogilvie's Syndrome. Its use as a promotility agent has not been well studied in pediatric patients. The first reported case of successful treatment of a pediatric patient with ACPO was in a 4-year-old male with spastic quadriplegia who was 10 days postoperative for bilateral femoral varus derotational osteotomies and botulinum toxin injections of the gastrocnemius muscles [53]. Neostigmine was administered intravenously at a total dose of 0.05 mg/kg over 5 h [53]. In a group of 10 pediatric patients with hematologic malignancies who experienced ACPO, 8 responded to doses of neostigmine at 0.01 mg/kg/dose administered subcutaneously, given twice a day for no more than 5 doses [54]. One patient reported diplopia and one reported abdominal pain [54]. In another case report, a 9-year-old boy with cerebellar medulloblastoma, on chemotherapy, was successfully treated for ACPO with the same subcutaneous dosage after 3 injections [55]. In a third case report, a 3-year-old girl with sickle cell disease with acute colonic pseudo-obstruction had resolution after 2 doses of neostigmine at 10 mcg/kg [56]. The patient was in vaso-occlusive crisis and had a colon measuring 6.5 cm in diameter and no mechanical obstruction found on gastrograffin enema. She started passing stool within 6 h of neostigmine injection.

5-Hydroxytryptamine-4 Receptor Agonists

Cisapride

Cisapride is a $5HT_4$ receptor agonist which acts on the myenteric plexus of the bowel wall to stimulate smooth muscle contraction by release

of acetylcholine. $5HT_4$ receptors are found throughout the gastrointestinal tract and stimulation causes increased peristalsis as well as intralumenal fluid secretion. Stimulation of the stomach smooth muscle leads to accelerated gastric emptying. Amplitude of esophageal peristalsis as well as resting lower esophageal sphincter tone is increased [57]. Cisapride also decreases mouth to cecum time and colonic transit time [58].

While cisapride has never been approved for children under the age of 12, it has historically been used extensively in this population. The consensus statements issued by NASPGHAN and ESPGHAN in 2000 states that cisapride is recommended for pediatric GERD when non-pharmacologic treatment fails, but that the medication does require close monitoring, and specific precautions should be taken [59, 60]. However, more recently the 2010 Cochrane Review did not show any difference in symptom improvement or weight gain when cisapride is compared to placebo [61]. Nine studies comparing cisapride with placebo or no treatment, that met inclusion criteria, were included in the meta-analysis [62–69]. The authors reviewed five studies comparing results of esophageal pH probe in patients being treated with cisapride vs. placebo and while there was improvement in the reflux index, there was no significant improvement in the number of reflux episodes and episodes lasting longer than 5 min. Histologic examination of the esophagus was performed in three studies and in 2 ($n-6$, $n=20$) studies there was no statistical difference between cisapride and placebo [63, 67], however 1 study ($n=17$) did have histologic improvement from baseline. Further large-scale studies are needed to assess the utility of cisapride for GERD, though due to limited access, it is unlikely this information will be obtained. Although cisapride may be efficacious in treating constipation, it is not recommended for treatment of standard constipation as the risks do not outweigh the benefits [70].

Availability of cisapride is restricted due to risk of prolonged QTc interval and serious cardiac arrhythmias and it is only available in most countries through limited-access programs. Multiple studies have shown increase in QTc interval in neonates, infants and children, however in many of these cases the medication was dosed above the recommended dosing and some were taking a macrolide antibiotic concurrently [71–75]. Arrhythmias have also been reported ranging from notched t waves to torsades de points [71, 74, 76]. In a multicenter, double-blind placebo-controlled trial of 49 children (age 6 months–4 years), however, a dose of 0.2 mg/kg given three times a day in patients without cardiac risk factors, for a treatment duration of at least 6 weeks, did not show a statistically significant increase in QTc interval and no subjects experienced cardiac events [62].

Cisapride is metabolized in the liver by cytochrome P450 into norcisapride. It is eliminated in urine and feces and its half-life is 7–10 h. Adult dosing should start at 10 mg PO two to four times a day 15 min before meals; dose may be increased to 20 mg for efficacy. Pediatric dosing is 0.8 mg/kg/day divided into 3–4 doses and not exceeding adult dose. 50% of the recommended dose should be started in the case of renal or hepatic failure. It is contraindicated in combination with macrolide antibiotics, azole antifungals, and any drug that prolongs the QT interval. It should be avoided while CYP3A4 inhibitors are being used. Also grapefruit juice should be avoided as it can increase cisapride serum concentrations. Caution must be taken in infants who are breastfed as mothers may excrete medications in their breast milk that are contraindicated while using cisapride. Patients with known history of prolonged QTc should not be prescribed cisapride and patients with other known arrhythmias need careful monitoring. Electrolyte imbalance, especially hypokalemia, increases the risk of serious cardiac side effects.

Tegaserod

Tegaserod is a $5HT_4$ receptor partial agonist. It was previously approved for treatment of females ≤55 years of age with constipation-predominant IBS or for chronic idiopathic constipation; however, it has subsequently been withdrawn from the US market due to an increased risk of cardiovascular events. In an open label study, 22 adult patients with symptoms of upper intestinal dysmotility underwent a 24 h antrodoudenal motility study comparing the effects of tegaserod (12 mg

PO) and erythromycin (125 mg IV) [77]. Both medications showed significantly increased motility in the antrum, duodenum, and jejunum. There were differences in the timing and where the two medications exerted their prokinetic effects—tegaserod had higher motor responses in the duodenum and jejunum, which occurred 2–3 h after administration, whereas erythromycin had stronger motor effects on the antrum that occurred within 30 min. Both tegaserod and erythromycin induced phase III migrating motor complexes (MMCs) in 55 and 36% of patients, respectively.

While tegaserod was never approved for pediatric use, it was widely used off label in many practices. A report on a single center's experience in pediatric patients reviewed 72 patients with a median age of 10 (1.1–18.3) [78]; most of these children were treated for functional constipation and the mean follow-up time was 11.3 months (2.3–45.2). Patients reported a statistically significant improvement in bowel frequency and fecal continence. The most common adverse events were diarrhea (20%), abdominal pain (8%), and headache (4%). No cardiovascular events were reported.

Adult dosing is 6 mg, PO, BID before meals and the tablets come in 2 and 6 mg forms. Bioavailability is 11% and decreased by up to 65% when taken with food [79, 80]. It is metabolized in the liver and 66% is excreted unchanged in stool and 33% as metabolites in urine. Use is contraindicated in severe hepatic or renal impairment. Adverse reactions include diarrhea, abdominal pain, nausea, flatulence, headache, and back pain.

Prucalopride

Prucalopride is a highly selective, high affinity 5-HT_4 receptor agonist, which increases colonic motility by stimulating serotonin release leading to giant migrating contractions [81]. Gastropyloro-duodenal motility as well as gastric emptying is also enhanced in the canine model [82]. Prucalopride is structurally different from previously available 5-HT_4 receptor agonist and due to its selectivity; the cardiac side effects seen with cisapride and tegaserod have not been reported. Use of prucalopride has mostly been in adult patients with chronic constipation. No pediatric studies have been published. Evaluation of prucalopride in healthy volunteers showed accelerated orocecal transit, colonic transit, and total gastrointestinal transit time [83–85]. Treatment of patients with chronic constipation showed similar improvements in transit times [86–89] and significant increases in spontaneous complete bowel movements, stool consistency, urge to defecate, and quality of life compared to placebo [86, 88–92]. No significant increase in QTc interval has been reported and the most common complaints have been abdominal pain, abdominal distension, diarrhea, nausea, flatulence, back pain, headache, and dizziness [89–91, 93].

Prucalopride is approved in Europe for use in women with chronic constipation that is not relieved by laxatives. Recommended adult dose is 2 mg, PO, daily. The half life is 24–30 h, it is minimally metabolized, and excreted mainly by the kidneys [94]. Dosing for geriatrics and patients with severe renal or hepatic dysfunction should start at 50% of the recommended dose.

Velusetrag (TD-5108)

Velusetrag is a highly selective $5HT_4$ receptor agonist. A phase 2 study has investigated the effect of velusetrag on colonic transit, colonic filling and emptying, and gastric emptying in healthy volunteers and patients with chronic constipation [95]. In this double-blind placebo-controlled study, healthy subjects were given 5, 15, 30, and 50 mg of Velusetrag or placebo. Gastric emptying was not affected after a single dose, however there was a significant increase in emptying after 6 days of consecutive treatment for the 15, 30, and 50 mg dosing. Small bowel transit as measured by colonic filling at 6 h was significantly increased after a single dose at 30 and 50 mg, but there was no statistical significance after multiple day dosing. Colonic transit as measured by $t_{1/2}$ of ascending colon emptying, and colonic geometric center at 24 h was increased for the 30 and 50 mg doses after a single dose; however, there was no significant increase in colonic transit compared to placebo after multiple doses. Patients with chronic

constipation were age- and sex-matched to the control group and given a single oral dose of 15 mg. There was no significant difference in pharmacokinetics between the control and constipation groups. The two study groups reported similar stool consistency, time to first bowel movement, and number of bowel movements in the 24 h after administration. There was an increase in heart rate by 10 bpm at 4 h after ingestion, but no change in blood pressure or EKG tracings. Subjects reported nausea, diarrhea, and headache as the most common adverse events, which was dose related. A single subject on 30 mg experienced palpitations and one patient on 50 mg developed asymptomatic junctional escape rhythm.

Other Prokinetic Agents

Octreotide

Octreotide is a synthetic cyclic tetradecapeptide that is a long acting somatostatin analogue used to treat many disease processes including gastrointestinal bleeding, pancreatitis, secretory diarrhea, chylous leakage, hypoglycemia, and gastrointestinal dysmotility. For the purposes of this section, only the use of octreotide in gastrointestinal dysmotility will be discussed. Somatostatin, studied in patients with normal gastrointestinal motility as well as the canine model, causes inhibition of gastric activity and stimulation of small intestinal phase 3 migrating motor complexes (MMCs) beginning in the duodenum [96, 97]. It is commercially available for SC, IV, and IM use. Subcutaneous absorption is rapid and IM is released slowly in a depot formulation. Metabolism is through the liver with 32% unmetabolized excretion through the urine [98]. Half-life is 1.7–1.9 h, but it is 3.7 h in patients with cirrhosis and 3.1 h in patients with renal impairment [79].

Octreotide has been studied in adult patients with scleroderma and pseudo obstruction; subcutaneous octreotide increased the frequency of intestinal migrating complexes in this group of patients [99]. After 3 weeks of treatment patients had a reduction in bacterial overgrowth as measured by hydrogen breath testing and had reported decrease in bloating, nausea, vomiting, and abdominal pain [99]. A single case report described a 12-year-old girl with chronic idiopathic pseudo obstruction who was successfully treated using 50 mcg of subcutaneous octreotide daily [100].

Methylnaltrexone

Methylnaltrexone is a peripheral μ-opiate antagonist that has been used to treat patients in the setting of opiate-induced constipation [101]. It is a quaternary ammonium derivative of naltrexone which, due to its low polarity, has reduced penetration of the blood–brain barrier [102, 103]. μ-Receptors are found throughout the gastrointestinal tract [106] and their stimulation leads to delayed transit and non-propulsive activity [107]. Decreased intestinal secretion as well as increased absorption in the small bowel and colon also contributes to the constipating effect of opioid medications [108]. Opioid-induced constipation is reversed, without inducing withdrawal symptoms or decreasing analgesic effect, by methylnaltrexone [101, 104, 105].

In the treatment of adult patients receiving chronic opioids for nonmalignant pain doses of 12 mg every day and every other day have been used; both regimens significantly decreased the time to rescue-free bowel movement as well as increased the number of weekly bowel movements compared to placebo [109]. In the treatment of adults with advanced illness and opioid-induced constipation using doses of 0.15 and 0.3 mg/kg, subjects had significantly increased rates of rescue-free bowel movements within 4 h of administration compared to placebo [104, 105].

A single case report of the use of methylnaltrexone to treat postoperative ileus in a neonate demonstrated success in restoring bowel motility 15 min after a 0.15 mg/kg IV infusion [110]. The infant had undergone two separate exploratory laparoscopies for necrotizing enterocolitis and was on a fentanyl drip for pain control. Five doses were given in total on POD 8–12.

Methylnaltrexone is available in subcutaneous form with onset of action between 30 min

to 4 h and a half life of 8–9 h [109, 111, 112]. It is administered every other day with dosing based on body weight. Excretion is through both urine and feces, primarily as unchanged drug [112]. Side effects include flatulence, abdominal pain, nausea, dizziness, excessive sweating, and diarrhea. Intestinal perforation has been reported with use and it should be used with caution in patients with diminished gastrointestinal wall integrity. Patients with severe renal impairment (creatinine clearance <30 mL/min) should be dosed at 50% of recommended dosing Table 41.1.

Antimotility Agents

The commonly used agents are the opioid receptor agonists loperamide and diphenoxylate.

Loperamide

Loperamide is a synthetic opioid receptor agonist acting on the μ opioid receptors in the myenteric plexus of the large intestine [113]. It is a peripherally acting agent and does not cross the blood–brain barrier. It has been shown in meta-analysis of randomized controlled trials to be safe and effective in treating acute diarrhea in adults and children [114, 115]. In children serious side effects were reported more often in those younger than 3 years old [115]. Loperamide has also been shown in clinical trials to be effective in reducing stool frequency and urgency in patients with diarrhea-predominant irritable bowel syndrome [116]. It is available in tablet and liquid suspension. The side effects include abdominal pain and bloating, constipation, sedation, dry mouth and, rarely, paralytic ileus. This medication should not be used in the setting of acute diarrhea caused by enteric bacterial pathogens such as salmonella and Shigella and in acute ulcerative colitis as it can precipitate toxic megacolon. It should also not be used in children less than 2 years old; indeed deaths have been reported in young children given loperamide to treat acute diarrhea [117].

Diphenoxylate

Diphenoxylate is a synthetic opioid receptor agonist related to meperidine and fentanyl [113]. Like loperamide it inhibits gastrointestinal propulsion and has been shown to be effective in treating acute diarrhea. Unlike loperamide however, diphenoxylate crosses the blood–brain barrier and therefore can be habit forming. Atropine is reportedly added to the preparation to reduce the abuse potential [118, 119]. Side effects include sedation, euphoria, lethargy, confusion, respiratory depression, restlessness, hyperthermia, tachycardia, nausea, vomiting, paralytic ileus, and toxic megacolon. Like loperamide, diphenoxylate should not be used in the setting of acute diarrhea caused by enteric bacterial pathogens and acute ulcerative colitis because of potential to precipitate toxic megacolon. Diphenoxylate should not be used in children less than 2 years old; opiate and atropine toxicity from diphenoxylate-atropine overdosage leading to death has been reported in children less than 2 years old [120].

Antispasmodics

Antimuscarinics

Antimuscarinics are a class of drugs that work by blocking the action of acetylcholine at postganglionic parasympathetic receptors in the intestinal smooth muscle. They are the most frequently prescribed antispasmodics in the USA. Meta-analysis of placebo-controlled trials of drugs used to treat irritable bowel syndrome confirm the therapeutic benefit of this class of drugs in adults, although many of the trials were reportedly of low quality [121]. Similar studies in children are lacking. The antimuscarinics currently available in clinical practice are derivatives of belladonna, a naturally occurring plant alkaloid, and include drugs such as hyoscyamine, dicyclomine, cimetropium, scopolamine, clidinium, and trimebutine.

Hyoscyamine is the levorotatory Isomer of atropine. It is available as oral tablets, extended

Table 41.1 Prokinetics

Medication	Dosing	Notes
Domperidone	0.3 mg/kg/dose two to four times daily[a] (PO, PR)	Adult dose 10–20 mg two to four times daily
Metoclopramide	0.4–0.8 mg/kg/day divided four times daily[a] (PO, SC, IM, IV)	Adult dose 10 mg three to four times daily
Erythromycin	1–3 mg/kg/dose (IV); 5 mg/kg/dose (PO) up to four times a day	Adult dose 50–250 mg three or four times a day
Bethanechol	0.1–0.2 mg/kg/dose up to four times a day[a] (PO,SC)	Adult dose 10–50 mg 2–4 times a day
Neostigmine	0.01 mg/kg/dose (IV, SC)	Oral formulation is available, but absorption is poor and not studied for treatment of acute colonic pseudo-obstruction
Cisapride	0.8 mg/kg/day divided three to four times daily[a] (PO)	Adult dose 10–20 mg two to four times a day
Tegaserod	Not determined in children	Adult dose 6 mg PO twice a day
Prucalopride	Not determined in children	Adult dose 2 mg, PO, daily
Octreotide	1–10 mcg/kg every 12 h (SC, IV, IM)	Adult dose 50 mcg up to three times a day. IM route is delayed release
Methylnaltrexone	<38 kg—0.15 mg/kg/dose 38 to ≤62 kg—8 mg 62–114 kg—12 mg >114 kg—0.15 mg/kg/dose	Round to nearest 0.1 mL Administered every other day

[a]Not to exceed maximum adult dose

release tablets, sublingual tablets, oral solutions, elixirs, and drops. It has been used to treat symptoms of colic and irritable bowel syndrome [122, 123]. Although commonly used, there are no randomized controlled trials establishing the safety and efficacy of this medication in treating gastrointestinal disorders, particularly in children. Anticholinergic poisoning has been reported in some colicky infants treated with hyoscyamine [122].

Dicyclomine is an m1-specific muscarinic antagonist which has been used to treat symptoms of colic, irritable bowel syndrome and diverticulitis. It has been shown in many double-blind studies to be effective in the treatment of infantile colic [124, 125]; however, 5% of treated infants had side effects [126]. Although commonly used to treat irritable bowel syndrome, there are no randomized controlled trials establishing the safety and efficacy of the drug in treating irritable bowel syndrome in children. It has been shown in only one study to reduce symptoms of irritable bowel syndrome including pain and fecal urgency in adults [127].

Scopolamine (hyoscine) is another m1-specific muscarinic antagonist which has been used to treat various gastrointestinal disorders including irritable bowel syndrome and motion sickness [128]. Methscopolamine and butylscopolamine are derivatives of scopolamine which have also been used to treat irritable bowel syndrome. Scopolamine was found in a meta-analysis study to offer benefit in the treatment of irritable bowel syndrome in adults [129] however, there are no published randomized controlled studies establishing its effectiveness in treating this condition in children.

Cimetropium is a synthetic derivative of scopolamine which has both antimuscarinic and direct myolytic activity [130]. It has been shown to be more effective than placebo in reducing the duration of crying in children with infantile colic [130] and a double-blind placebo-controlled study in adults showed that it is effective in relieving pain in patients with irritable bowel syndrome [131].

Clidinium is a rarely used muscarinic antagonist which is marketed in combination with chlordiazepoxide as a treatment for irritable bowel syndrome, although there are no randomized controlled trials showing its safety or efficacy in treating this condition.

Trimebutine is an antimuscarinic drug which also has some opioid agonistic effects; it accelerates gastric emptying and induces premature phase III of the migrating motor complex in the small bowel, but it inhibits colonic motility through its antimuscarinic activity [132]. This drug has been found to be efficacious in the treatment of recurrent abdominal pain and irritable bowel syndrome in children and adults. It was found in a meta-analysis study to be effective in the treatment of irritable bowel syndrome in adults [129].

Common side effects of antimuscarinic agents include dry mouth, urinary retention, blurred vision, constipation, sedation, and palpitations.

Direct Smooth Muscle Relaxers

Mebeverine and related drugs including alverine, otilonium, and drotaverine [133–135] are not available in the USA but are available in many countries. They are antispasmodics which are believed to be mostly musculotropic. These drugs exert their antispasmodic effect by acting directly at the cellular level of the gastrointestinal smooth muscle. They have been used to treat irritable bowel syndrome. A systematic review of several studies in adults found these agents to be efficacious in improving the symptoms of abdominal pain in adult patients with irritable bowel syndrome [136, 137].

OnabotulinumtoxinA (Botox®)

Onabotulinumtoxin A is the drug name for botulinum toxin A—it is used commonly in cosmetic procedures, but is also used to treat strabismus, blepharospasm, muscle spasticity, cervical dystonia, and hyperhidrosis. It has been used off-label to treat esophageal achalasia, gastroparesis, anal fissure, and anal achalasia. Botulinum toxin A is one of seven serotypes of botulinum neurotoxins produced by the aneorobic bacteria *Clostridium*

Botulinum [138]. The neurotoxin targets the neuromuscular junction and blocks acetylcholine release causing flaccid paralysis.

In a single center report, postoperative follow-up of adult patients treated for esophageal achalasia revealed recurrent or persistent symptoms in 71.4% ($n=7$) of patients treated with endoscopic botulinum injection [139] compared to recurrent/persistent symptoms in 50% of patients who underwent endoscopic balloon dilation ($n=30$) and recurrent/persistent symptoms in 30% of patients who underwent surgical myotomy ($n=20$). Thus in this report, patients who underwent surgical myotomy had the most reliable outcome. Treatment with Botox injections has an initial success rate of 70%, however the effect usually lasts 6–12 months and repeated injections are required [140]. There have been conflicting reports on whether prior injection with Botox decreases the effectiveness of a later Heller myotomy or whether it impacts the ease of the procedure [141–144]. A single center reviewed their experience with pediatric patients diagnosed with esophageal achalasia; out of their 33 patients, 7 were treated with Botox [145]. They used 100 U of Botox per session with 25 U injected into each quadrant of the lower esophageal sphincter. Six of the seven required 2–3 repeated injections and the longest duration of symptom-free period postinjection was 10 months. Four eventually had a Heller myotomy. One case report also reported response for 8 months postinjection in an 11-year-old boy [146]. A single case report of the use of Botox to treat a diabetic, obese adult with esophageal achalasia was complicated by mediastinitis [147]. The development of a sinus tract between the esophagus and gastric fundus has been reported in a 10-year-old girl following her fifth Botox injection for esophageal achalasia [148].

In two studies, pediatric patients treated with Botox injections for anal outlet obstruction (post-surgical repair of Hirschsprung Disease and primary internal anal sphincter achalasia) had variable outcomes [149, 150]. The dosage used was 3–6 U/kg/session to a maximum of 100 U. 31–53% of patients had good long-term outcome and 62–89% had initial clinical improvement after a single injection. About 75% required more than one session. Complications included pain following the injection and fecal incontinence.

Botox injections have also been used to treat chronic anal fissures. At one center, 13 children (age 1–10 years) were given Botox injections in the external anal sphincter under light sedation to treat chronic anal fissures [151]; patients under age 2 were injected with 1.25 U ×2 doses and patients over age 2 were injected with 2.5 U×2 doses. 11 of the 13 patients had resolution of their symptoms within 1 week of treatment and no adverse events were reported. In a systematic review of nonsurgical therapies for chronic anal fissures, Botox was found to be equivalent to topical nitroglycerin in efficacy; however, nitroglycerin itself was only marginally better than placebo [152].

There is a paucity of data on the usefulness of intrapyloric injections of Botox for treatment of gastroparesis. One randomized controlled crossover study of 23 adult patients with gastroparesis showed no benefit of Botox injection (25 U/quadrant; 100 U total) compared to placebo [153] and no pediatric studies have been published.

Topical Nitrates

Topical nitrates have been used to treat painful anal conditions. There are three formulations available—mono, di, and trinitrates—all act to relax smooth muscle by stimulating production of cGMP, irrespective of autonomic innervations [154]. The only topical formulation available in the USA is nitroglycerin, which is a trinitrate. Its most common use in gastroenterology is for treatment of chronic anal fissures.

In children with anal fissures, 0.2% glyceryl trinitrate (GTN) applied topically to the distal anal canal twice a day resulted in improvement of symptoms by day 10 of treatment and higher rates of complete resolution after 8 weeks compared to placebo and topical lidocaine [155, 156]. However, one study comparing GTN plus oral senna and lactulose with placebo plus oral senna and lactulose, found similar response rates, with 84% healing overall [157]. Concentrations of 0.05 and 0.1% ointments were also found to be

effective for fissure healing after 8 weeks of treatment [158]. Results at 8 weeks of treatment were similar to results using a eutectic mixture of 5% prilocaine and 5% lidocaine (EMLA) [156].

Long-term treatment of chronic anal fissure in 31 children using 0.2% GTN resulted in a 32% relapse 1 year after treatment and no relapses for 4 years following initial treatment in 68% [159].

Glycerine trinitrate has also been used to treat proctalgia fugax, which mainly occurs in patients aged 30–60 years [160, 161].

Calcium Channel Blockers

It has been suggested that calcium channel blockers may be effective in the treatment of some gastrointestinal motility disorders because of their ability to relax smooth muscles. Nifedipine and verapamil have been shown to inhibit sigmoid colon myoelectric response to eating in healthy adult volunteers [162] and reduce internal anal sphincter pressures in patients and controls with high resting anal sphincter pressures [163].

Nifedipine has been used to treat disorders of esophageal hyper motility such as nutcracker esophagus and achalasia in children and adults [164–167]. Diltiazem has been used anecdotally to treat diffuse esophageal spasm in adolescents [168]. Verapamil has anecdotally been used to treat antral spasms in children [169]. Pinaverium is a calcium channel blocker which acts selectively on the gastrointestinal tract; it has been found to reduce the duration of abdominal pain in randomized, placebo-controlled studies of adult patients with irritable bowel syndrome [170, 171]. Peppermint oil is believed to be a calcium channel blocker which has been found to relax the lower esophageal sphincter, and reduce colonic spasms in patients undergoing colonoscopy [172, 173]. It has been found in double-blind randomized controlled studies to be effective in treating children and adults with irritable bowel syndrome [174, 175] and in meta-analysis studies of published trials, it was found to be effective in the treatment of both adults and children with irritable bowel syndrome [176, 177]. Side effects of calcium channel blockers include headaches, lightheadedness, and constipation.

Meta-analysis studies of controlled trials of antispasmodics in the treatment of irritable bowel syndrome have found them to be superior to placebo, at least for the short term, in the management of irritable bowel syndrome in both adults and children [121, 129, 178, 179].

Other Antispamodic Agents

Oral Nitrates have been used in adults to treat spastic disorders of the esophagus, although there are no randomized controlled studies supporting their effectiveness [167]. Sildenafil, a Phosphodiesterase inhibitor, has been found in a double-blind placebo-controlled study to reduce lower esophageal sphincter pressure [167]. No studies of nitrates or sildenafil for these purposes have been reported in children Table 41.2.

Laxatives

Laxatives can be divided into osmotic/lubricant laxatives and stimulant laxatives (see Table 41.3). First-line treatment for constipation starts with osmotic/lubricant laxatives followed by stimulants for cases that are poorly responsive.

Osmotic and Lubricant Laxatives

Lactulose

Lactulose (1-4-beta-galactosidofructose) is a semi-synthetic disaccharide created through the isomerization of lactose [180]. Lactulose increases osmotic load as well as decreases the stool pH thereby increasing colonic propulsion [181]. It passes through the small intestine intact without degradation by dissacharidases and is broken down by bacteria in the colon to produce lactic and acetic acid [182]. Systemic absorption is minimal with majority of excretion through the stool and <3% excretion in urine. Formulations contain both lactose and galactose so use is contraindicated in patients with galactosemia. Onset

Table 41.2 Antimotility and antispasmodic agents

Medication	Dosing	Notes
Loperamide	Acute Diarrhea (first 24 h) – 2–5 years (13–20 kg): 1 mg three times a day – 6–8 years (21–30 kg): 2 mg twice a day – 9–12 years (>30 kg): 2 mg three times a day—After first 24 h–0.1 mg/kg doses after each loose stool not exceeding initial dose Chronic diarrhea—0.08–0.24 mg/kg/day divided 2–3 times a day, maximum: 2 mg/dose(PO)	Adult dose acute and chronic diarrhea—first dose 4 mg, then 2 mg after each loose stool, maximum 16 mg daily
Diphenoxylate	– 2–5 years—2 mg three times a day – 5–8 years—2 mg four times a day – 8–12 years—2 mg five times a day (PO)	Adult dose 5 mg four times a day
Hyoscyamine	2–12 years—0.0625–0.125 mg every 4 h as needed—maximum daily dose 0.75 mg (PO, SL)	Adult dose—0.125–0.25 mg every 4 h as needed—maximum daily dose 1.5 mg (PO, SL) Adult dose—0.25–0.5 mg every 4 h for 1–4 doses only (IV, IM)
Dicyclomine	>6 months old—5 mg, three to four times a day Children—10 mg, three to four times a day (PO)	Adult dose 20 mg, four times a day—may increase to 40 mg, four times a day (PO) Adult IM dose 20 mg, four times a day
Scopolamine	Antiemetic – 6 mcg/kg/dose (maximum 0.3 mg per dose) every 6–8 h (PO, IV, SC)	Adult dose for antiemetic 0.3–0.65 mg/dose every 6–8 h (PO, IV, SC) Adult dose and children >12 years—for motion sickness 10–20 mg every 8 h as needed (PO) Adult dose for transdermal patch—1 patch behind the ear every 72 h as needed
Trimebutine	Children >12 years—100–200 mg three times a day (PO)	Adult dose 100–200 mg three times a day (PO)
Mebeverine	Children >10 years—100 mg three times a day (PO)	Adult dose 100–135 mg three times a day (PO) OR 200 mg twice a day (PO modified release)
Onabotulinumtoxin A	Esophageal achalasia – 20–25 U into each quadrant (80–100 U total per treatment) Anal outlet obstruction – 3–6 U/kg/session to a maximum of 100 U divided into 4 quadrants Chronic anal fissure 1.25–2.5units ×2 per session	Adult gastroparesis – 25 U into each quadrant (100 U total per treatment)
Glyceryl trinitrate (0.2%)	Apply ointment to the distal anal canal twice a day	
Nifedipine		Adult dose 10–20 mg before meals (PO, SL)

Table 41.3 Laxatives

Therapy	Dosage
Osmotic agents	
Lactulose	– 1–3 mL/kg/day in divided doses
Magnesium citrate	– May use divided doses – <6 years—1–3 mL/kg/day – 6–12 years—100–150 mL/day – >12 years—150–300 mL/day
Magnesium hydroxide	– May use divided doses – 1–3 mL/kg/day of 400 mg/5 mL solution
Polyethylene glycol	– 1 g/kg/day
Sorbitol	– 1–3 mL/kg/day in divided doses
Lubricants	
Mineral oil	– 1–3 mL/kg/day
Stimulants	
Bisacodyl	– 3–12 years—5 mg/day – >12 years—5–15 mg/day
Senna	– 2–5 years—2.5–7.5 mL at bedtime – 6–12 years—5–15 mL at bedtime
Lubiprostone (adult dosing only)	– Chronic idiopathic constipation—24 mcg BID – Female IBS with constipation—8 mcg BID

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of action is 24–48 h and side effects include cramping, abdominal distension, flatulence, diarrhea, nausea, vomiting, and electrolyte imbalances. Long-term use is safe with few reported adverse events [70].

Magnesium Salts

Magnesium salts are available commercially as magnesium citrate and magnesium hydroxide. All magnesium salts promote bowel evacuation by osmotic fluid retention. Absorption is 15–30% and excretion is in the urine. Use is contraindicated in patients with renal failure and renal insufficiency as hypermagnesemia is a significant risk. Caution should be used even in patients who do not have renal dysfunction as excessive ingestion can lead to severe hypermagnesemia in otherwise healthy children [183, 184]. Other side effects include diarrhea, abdominal cramps, flatulence, hypotension, and respiratory depression. There are few studies evaluating the efficacy of magnesium salts in treatment of constipation, however compared to a bulk laxative, it may produce more frequent bowel movements [185]. Palatability of magnesium may decrease compliance. When compared to PEG solution over a 12-month period, 95% of children using PEG were compliant vs. 65% using magnesium hydroxide [186].

Polyethylene Glycol

Polyethylene glycol (PEG) is a high molecular weight, non-soluble polymer that acts as an osmotic laxative. Hydrogen bonds are formed between PEG and water, which prevents reabsorption of water in the colon. With increased water retention, stool is thereby softened and its bulk is increased. The onset of action is 24–96 h; excretion is 93% through feces with minimal systemic absorption and a bioavailability of 0.2% [187]. Contraindications to PEG include hypersensitivity, ileus, bowel perforation or obstruction, and toxic megacolon.

PEG is available with or without electrolytes added. In general PEG with electrolytes is used for colonoscopy preparation or disimpaction. PEG without electrolytes is more commonly used for daily management of chronic constipation, but has been used in children for colonoscopy preparation as well [188, 189]. High-dose PEG

without electrolytes can be as successful as rectal enemas for disimpaction in the pediatric population [190] with highest success for doses of 1–1.5 g/kg/day [191]. PEG is safe and well tolerated for long-term treatment of chronic constipation with few noted side effects [186, 192–195].

Sorbitol

Sorbitol is a polyalcoholic sugar and acts as a hyperosmotic laxative. Absorption is minimal and it is metabolized in the liver mainly into fructose. There is a paucity of studies evaluating the efficacy of sorbitol for treatment of constipation. Compared to lactulose it has similar safety and efficacy in the geriatric population [196]. Excessive ingestion of sorbitol in non-constipated pediatric patients is known to cause loose stool and diarrhea [197, 198]. Side effects include diarrhea, nausea, vomiting, lactic acidosis, and electrolyte imbalances.

Mineral Oil

Mineral oil is a lubricant laxative with minimal systemic absorption and primary elimination in the feces. It is a mixture of hydrocarbons derived from petroleum. The oil lubricates the colon, but it also decreases water reabsorption and softens the stool. It should not be used in infants and patients with swallowing dysfunction since there is a risk for lipid pneumonitis with aspiration [199–201]. Other adverse effects include diarrhea, nausea, vomiting, anal itching, and anal seepage. Chronic use could theoretically decrease absorption of fat soluble vitamins; however, there is no published evidence to support this [202, 203]. One study showed a reduction in beta-carotene levels after just 1 month of treatment [203].

Stimulant Laxatives

Bisacodyl

Bisacodyl is a diphenolic laxative that stimulates intestinal fluid secretion and motor activity. It induces intestinal fluid secretion by direct action on the enterocyte, activating adenylate cyclase and causing an increase in production of cyclic-AMP [204, 205]. Chloride and bicarbonate ions are actively secreted, while sodium and potassium are passively effluxed into the bowel. Sodium and chloride are then inhibited from reabsorption back into the enterocyte. Contraction of the colonic smooth muscle is caused by increasing the myoelectrical activity through direct irritation of the bowel wall [206, 207]. Systemic absorption is <5% with onset of action between 4 and 6 h for oral administration and 0.25–1 h for rectal administration [207, 208]. The small fraction that is absorbed is conjugated by the liver and excreted in urine. Most formulations are enteric coated and should not be administered within 1 h of antacids. Side effects include nausea, vomiting, diarrhea, abdominal cramping, proctitis, and electrolyte imbalance.

Bisacodyl and other stimulant laxatives should be used as second-line agents for patients who are refractory to osmotic/lubricant laxatives [70]. There is no data on safety and efficacy of bisacodyl for treatment of constipation, particularly in the pediatric population [209]; however, there is clear evidence that it does increase colonic transit and stimulates colonic motor activity [210–212]. Chronic and prolonged use of stimulant laxatives may lead to loss of haustra and anatomic changes in the colon, possibly due to muscular or neuronal injury [213, 214]; it is unclear, however, if this is a true risk of long-term usage of bisacodyl [215].

Senna

The mechanism of action of senna as a stimulant laxative is unclear; however, it may increase production of cyclic-AMP in the colon leading to increased ion secretion and increased peristalsis, by direct irritation of the colon [216]. Senna is derived from the plant *Senna alexandrina* and has been used for centuries. Absorption is minimal and onset is 6–12 h after ingestion. Senna is metabolized in the liver and excreted through feces and urine. Reported adverse events include hepatitis, hypertrophic osteoarthropathy, analgesic nephropathy, and melanosis coli, which is reversible. There is poor evidence for development of cathartic colon with long-term use of senna [217]. As with other stimulant laxatives, it is a second-line agent and is used in constipated patients failing first-line

treatment. Although it is commonly used, there is a paucity of studies evaluating its efficacy in treatment of constipation [209].

Lubiprostone

Lubiprostone is a prostone that acts locally on the gastrointestinal tract by activation of type-2 chloride channels (CIC-2) [218]. It is approved for use in adults with chronic idiopathic constipation and females older than 18 years of age with constipation-predominant irritable bowel syndrome. Prostones are bicyclic fatty acids derived from prostaglandin E_1 that do not significantly act on prostaglandin E or F receptors or cause smooth muscle contractions [219]. Activation of the chloride channels increases intestinal fluid chloride concentration and fluid secretion, leading to increased stool passage without causing significant change in serum electrolyte levels [218]. Lubiprostone decreases gastric emptying while increasing small bowel and colonic transit time in normal adult volunteers [220]. There are currently no published studies of its use in the pediatric population. Adult dosing is 24 mcg PO BID for chronic idiopathic constipation and 8 mcg PO BID for constipation-predominant IBS.

Lubiprostone is distributed mainly in the gastrointestinal tract with minimal systemic absorption; it is rapidly metabolized in the stomach and jejunum by carbonyl reductase into the active metabolite M3. 60% is excreted in the urine and 30% through the feces. Most common reported side effects include nausea, diarrhea, and headache [221]. There have been no studies on patients with hepatic or renal insufficiency and caution is recommended in these populations. No teratogenic effects have been reported; however, there has been increased fetal loss in the guinea pig model and therefore female patients should have a negative pregnancy test prior to initiation of therapy and be advised on contraception [219].

Linaclotide (MD-1100)

Linaclotide is a new guanylate cyclase-C (GC-C) agonist [222] that is currently undergoing phase III trials for the treatment of IBS-C and chronic constipation. Activation of GC-C leads to activation of the cystic fibrosis transmembrane conductance regulator causing secretion of chloride and bicarbonate into the small intestinal lumen [223]. Visceral hypersensitivity is suppressed by cGMP acting on submucosal afferent pain fibers to decrease nerve reactivity [224] and a decrease in abdominal pain compared to baseline and to placebo has been reported [225]. Doses ranging from 75 to 600 mcg improved bowel habits in men and women >18 years of age with IBS-C [225]. In adult women with IBS-C, colonic transit was improved over a 5-day treatment period with 1,000 mcg of linaclotide [226]. For adult patients with chronic constipation, bowel movement frequency, stool consistency, and straining as well as overall quality of life were improved on trials of linaclotide [227, 228] (Table 41.3).

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