10.2. The modest therapeutic gain was similar to that yielded by other current available therapies for IBS. However, currently there are still insufficient data to recommend routine use of this antibiotic in the treatment of IBS.

Because altered colonic flora may contribute to the pathogenesis of IBS, this has led to great interest in using probiotics to naturally alter the flora. A meta-analysis of 10 probiotic studies in IBS patients found significant relief of pain and bloating with the use of *Bifidobacterium breve, B. longum*, and *Lactobacillus acidophilus* species compared to placebo. However, there was no change in stool frequency or consistency. Large-scale studies of well-phenotyped IBS patients are needed to establish the efficacy of these probiotics.

Serotonin Receptor Agonist and Antagonists Serotonin receptor antagonists have been evaluated as therapies for IBS-D. Serotonin acting on 5-HT_3 receptors enhances the sensitivity of afferent neurons projecting from the gut. In humans, a 5-HT_3 receptor antagonist such as alosetron reduces perception of painful visceral stimulation in IBS. It also induces rectal relaxation, increases rectal compliance, and delays colonic transit. Meta-analysis of 14 randomized controlled trials of alosetron or cilansetron showed that these antagonists are more effective than placebo in achieving global improvement in IBS symptoms and relief of abdominal pain and discomfort. These agents are more likely to cause constipation in IBS patients with diarrhea alternating with constipation. Also, 0.2% of patients using 5-HT_3 antagonists developed ischemic colitis versus none in the control group. In postrelease surveillance, 84 cases of ischemic colitis were observed, including 44 cases that required surgery and 4 deaths. As a consequence, the medication was voluntarily withdrawn by the manufacturer in 2000. Alosetron has been reintroduced under a new risk-management program where patients have to sign a patient-physician agreement. This has significantly limited its usage.

Novel 5-HT_4 receptor agonists such as tegaserod exhibit prokinetic activity by stimulating peristalsis. In IBS patients with constipation, tegaserod accelerated intestinal and ascending colon transit. Clinical trials involving >4000 IBS-C patients reported reductions in discomfort and improvements in constipation and bloating, compared to placebo. Diarrhea is the major side effect. However, tegaserod has been withdrawn from the market; a meta-analysis revealed an increase in serious cardiovascular events.

Chloride Channel Activators Lubiprostone is a bicyclic fatty acid that stimulates chloride channels in the apical membrane of intestinal epithelial cells. Chloride secretion induces passive movement of sodium and water into the bowel lumen and improves bowel function. Oral lubiprostone was effective in the treatment of patients with constipation-predominant IBS in large phase II and phase III randomized, double-blinded, placebo-controlled multicenter trials. Responses were significantly greater in patients receiving lubiprostone 8 μg twice daily for 3 months than in those receiving placebo. In general, the drug was quite well tolerated. The major side effects are nausea and diarrhea. Lubiprostone is a new class of compounds for treatment of chronic constipation with or without IBS.

Guanylate Cyclase-C Agonist Linaclotide is a minimally absorbed 14-amino-acid peptide guanylate cyclase-C (GC-C) agonist that binds to and activates GC-C on the luminal surface of intestinal epithelium. Activation of GC-C results in generation of cyclic guanosine monophosphate (cGMP), which triggers secretion of fluid, sodium, and bicarbonate. In animal models, linaclotide accelerates GI transit and reduces visceral nociception. The analgesic action of linaclotide appears to be mediated by cGMP acting on afferent pain fibers innervating the GI tract. A phase III, double-blind, controlled trial showed that linaclotide, 290 μg given once daily, significantly improved abdominal pain, bloating, and spontaneous bowel movement. The only significant side effect was diarrhea, which occurred in 4.5% of the patients. The drug has been approved for treatment of constipation in IBS-C patients.

TABLE 352-5 SPECTRUM OF SEVERITY IN IBS

	Mild	Moderate	Severe
Clinical Features			
Prevalence	70%	25%	5%
Correlations with gut physiology	+++	++	+
Symptoms constant	0	+	+++
Psychosocial difficulties	0	+	+++
Health care issues	+	++	+++
Practice type	Primary	Specialty	Referral

SUMMARY

The treatment strategy of IBS depends on the severity of the disorder (Table 352-5). Most IBS patients have mild symptoms. They are usually cared for in primary care practices, have little or no psychosocial difficulties, and do not seek health care often. Treatment usually involves education, reassurance, and dietary/lifestyle changes. A smaller portion have moderate symptoms that are usually intermittent and correlate with altered gut physiology, e.g., worsened with eating or stress and relieved by defecation. For IBS-D patients, treatments include gut-acting pharmacologic agents such as antispasmodics, antidiarrheals, bile acid binders, and the newer gut serotonin modulators (Table 352-6). In IBS-C patients, increased fiber intake and the use of osmotic agents such as polyethylene glycol may achieve satisfactory results. For patients with more severe constipation, a chloride channel opener (lubiprostone) or GC-C agonist (linaclotide) may be considered. For IBS patients with predominant gas and bloating, a low-FODMAP diet may provide significant relief. Some patients may benefit from probiotics and rifaximin treatment. A small proportion of IBS patients have severe and refractory symptoms, are usually seen in referral centers, and frequently have constant pain and psychosocial difficulties (Fig. 352-1). This group of patients is best managed with antidepressants and other psychological treatments (Table 352-6).

TABLE 352-6 POSSIBLE DRUGS FOR A DOMINANT SYMPTOM IN IBS

Symptom	Drug	Dose
Diarrhea	Loperamide	2–4 mg when necessary/ maximum 12 g/d
	Cholestyramine resin	4 g with meals
	Alosetron[a]	0.5–1 mg bid (for severe IBS, women)
Constipation	Psyllium husk	3–4 g bid with meals, then adjust
	Methylcellulose	2 g bid with meals, then adjust
	Calcium polycarbophil	1 g qd to qid
	Lactulose syrup	10–20 g bid
	70% sorbitol	15 mL bid
	Polyethylene glycol 3350	17 g in 250 mL water qd
	Lubiprostone (Amitiza)	24 mg bid
	Magnesium hydroxide	30–60 mL qd
	Linaclotide	290 μg qd
Abdominal pain	Smooth-muscle relaxant	qd to qid ac
	Tricyclic antidepressants	Start 25–50 mg hs, then adjust
	Selective serotonin reuptake inhibitors	Begin small dose, increase as needed
Gas and bloating	Low FODMAP diet	
	Probiotics	qd
	Rifaximin	550 mg bid

[a]Available only in the United States.

Abbreviation: FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

Source: Adapted from GF Longstreth et al: Gastroenterology 130:1480, 2006.