



Review Article

Demarcating Therapeutic Interventions in IBS

Sunil Chaudhry^{1,*}¹Bioclinitech Technologies Pvt Ltd, Mumbai & GPATutor.com, India

ARTICLE INFO

Article history:

Received 27-11-2020

Accepted 22-12-2020

Available online 13-02-2021

Keywords:

Irritable bowel syndrome (IBS)

Bloating

Rome Criteria

FODMAP

5HTagonists and antagonists

ABSTRACT

Irritable bowel syndrome (IBS), also referred to as mucus colitis, nervous colon, and spastic colitis is a long-term chronic gastrointestinal disorder that can cause continuous discomfort. IBS has a significant impact on patients' quality of life due to physical suffering, psychological co-morbidity, social disability and economic non-productivity. It is more common in females and in lower socioeconomic groups. The diagnosis declines with age (with most affected individuals younger than age 50) The diagnosis of IBS relies on a symptom-based classification system known as Rome criteria. The low FODMAP diet is recommended for patients with digestive disorders like Irritable Bowel Syndrome. Current therapy of IBS focuses on the major symptoms experienced by patients. The novel approach in the treatment of IBS is based either on targeting specific receptors in the gastrointestinal tract that are known to be involved in the pathogenesis of the disease.

© This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>) which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

1. Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder in which abdominal pain or discomfort is associated with defecation and/or a change in bowel habit. Sensations of discomfort (bloating), distension, and disordered defecation are commonly associated features. It is known that only approximately 30% of patients with IBS will consult a or gastroenterologist.

Additional features of IBS are :

1. It is not known to be associated with an increased risk for the development of cancer or inflammatory bowel disease, or with increased mortality.
2. A transition of IBS to, and overlap with, other symptomatic gastrointestinal disorders (e.g., gastroesophageal reflux disease, dyspepsia, and functional constipation) may occur.
3. No universal pathophysiological substrate has been demonstrated in IBS.

4. Symptoms may be episodic associated with food intake and, characteristically, with defecation.
5. Symptoms may develop following abdominal and/or pelvic surgery
6. It generates significant direct and indirect health-care costs.¹

1.1. Types of IBD

IBS is more common in monozygotic twins than in dizygotic twins. Other gene polymorphisms involved in IBS include mitochondrial DNA polymorphism, alpha 2 receptor gene C polymorphism, cytokine gene polymorphisms and tumor necrosis factor super family (TNFSF) polymorphism.²

The reported prevalence of IBS in India varies from 4.2%-7.5%. It has been reported that the prevalence of IBS in Asian countries is rising. An urban lifestyle is reported to be associated with greater psychological stress, and thus may be associated with a higher prevalence of IBS compared to rural living. The highest rates of IBS are seen in persons who are in middle aged, younger than 45, common

* Corresponding author.

E-mail address: sunil.r.chaudhry@gmail.com (S. Chaudhry).

Table 1:

IBS-C (Constipation)	IBS-D (Diarrhoea)	IBS M (Mixed)	IBS U (unsubtyped)
Constipation Hard or lumpy stools >25% .	Diarrhoea Hard or lumpy stools <25%	Constipation and Diarrhoea Hard or lumpy stools < 25 %	Constipation and Diarrhoea Hard or lumpy stools > 25 %
Loose or watery stools < 25 %	Loose or watery stools >25 %	Loose or watery stools <25%	Loose or watery stools >25%

more in females. Research shows that many people with IBS have a first-degree relative (parent, child or sibling) with the disorder. Some studies indicate that psychological distress, especially anxiety, depression and childhood adversity, may be a risk factor. Vitamin D deficiency is also common in individuals affected by irritable bowel syndrome³

1.2. Pathophysiology of IBS

Altered gastrointestinal motility, visceral hypersensitivity, post infectious reactivity, brain-gut interactions, alteration in fecal micro flora, bacterial overgrowth, food sensitivity, carbohydrate malabsorption, and intestinal inflammation all have been implicated in the pathogenesis of IBS. Patients sometimes complain about IBS symptoms after an infection. This is generally known as post-infectious IBS and usually occurs after an acute bacterial, viral or protozoal gastroenteritis, when around 20% of patients will develop symptoms of IBS. Ninety percent of 5-hydroxy-tryptamine (5-HT) and 50% of dopamine production is in the gastrointestinal tract, mainly by (EC) enterochromaffin cells. GABA-b receptors involved in the gastrointestinal tract, affecting visceral sensation, pain and intestinal motility. Up to 75% of patients with IBS symptoms usually have existing anxiety or depression. 2% of IBS patients had IBS-C. Idiopathic bile acid diarrhea is estimated to affect up to 20% of IBS-D patients, while IBS-C patients have altered bile acid metabolism.⁴

1.3. Diagnosis of IBS (Rome Criteria)

Evaluation for suspected IBS includes a complete history and physical examination, although examination findings often are normal. These criteria include improvement in pain with defecation, onset associated with a change in frequency of stools, and onset associated with a change in the form (appearance) of stools; criteria must have been met for the previous three months, with symptom onset at least six months before diagnosis. Complete blood count, serum chemistries, thyroid function studies, stool testing for ova and parasites, and abdominal imaging are low-yield tests that are not recommended in the routine diagnostic evaluation of IBS.⁵

1.4. Nutritional support in IBS

FODMAP stands for Fermentable Oligo-Di-Monosaccharides and Polyols. The low FODMAP diet is recommended for patients with digestive disorders like Irritable Bowel Syndrome or functional abdominal pain to decrease symptoms such as excessive gas, bloating, abdominal pain, nausea, vomiting, diarrhea and/or constipation. The goal of the low FODMAP diet is to remove high FODMAP foods and then slowly reintroduce them back into the diet. The low-FODMAP diet restricts the intake of some food, such as certain fruits, dairy products, grain legumes, and wheat. Adherence to this diet provides re-markable improvement of symptoms in irritable bowel syndrome

1.5. The low FODMAP diet produces

1. Fewer digestive symptoms, like gas, bloating, diarrhea, and constipation.
2. Manage IBS symptoms without taking medicine
3. Improve your quality of life

Whenever possible, implementation of a low-FODMAP diet should be done with the help of an experienced dietician.⁶

1.6. Optimizing management of IBS

1.6.1. Lifestyle changes

The following lifestyle changes may help to prevent or ease IBS symptoms.

1.6.2. Fruits in Diet

Dried plums (prunes) not only contain fiber but also sorbitol and fructans, non-absorbable carbohydrates that, when fermented by colonic bacteria, create an osmotic load that can dramatically alter stool frequency and consistency. The IBS-C kiwifruit group also reported increases in defecation frequency and improvements in bowel function. Exercise regularly to promote movement of the colon and reduce stress. Exercise can take many forms, but 20 to 30 minutes of activity at least three times per week can be helpful.

1.6.3. Get enough rest

A Lack of sleep and fatigue can worsen the symptoms of IBS

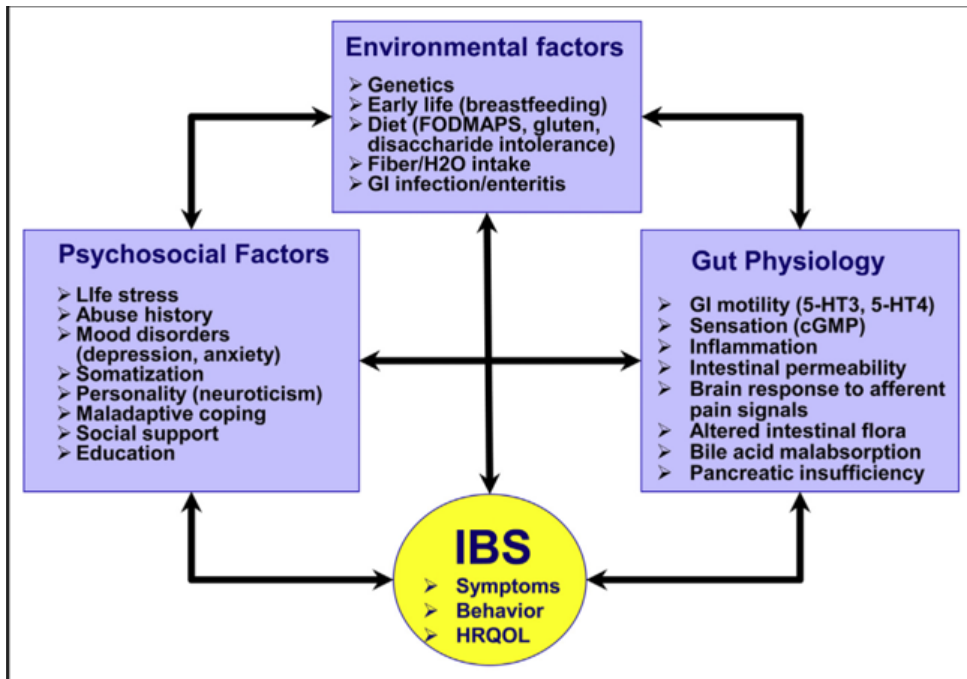


Fig. 1:

Table 2:

ROME III	ROME IV
<p>Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two or more of the following criteria:</p> <ol style="list-style-type: none"> 1. Improvement with defecation 2. Onset associated with a change infrequency of stool 3. Onset associated with a change in form (appearance) of stool 	<p>Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following criteria:</p> <ol style="list-style-type: none"> 1. Related to defecation 2. Associated with a change in frequency of stool 3. Associated with a change in form (appearance) of stool

Note: Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

1.6.4. Psychological Therapies

Many IBS patients who seek medical care suffer from anxiety or depression and benefit from psychological therapies, including hypnotherapy (a method to focus on the perception of intestinal symptoms), Cognitive behavioral therapy (CBT) to become aware of inaccurate or negative thinking and dynamic psychotherapy. It was shown that psychotherapeutic interventions decreased the symptoms immediately after the treatment, while 1–6 months (short-term) and 6–12 months (long-term) after start of the treatment the reduction remained significant compared to the control group(s).

1.7. Pharmacological Classification of Drugs used in IBS based on Symptoms:

1.8. Symptomatic treatment of IBS

1. Antispasmodics for pain.
2. Laxatives, fiber, and bulking agents for constipation. The chloride-channel agonist lubiprostone (2 × 8

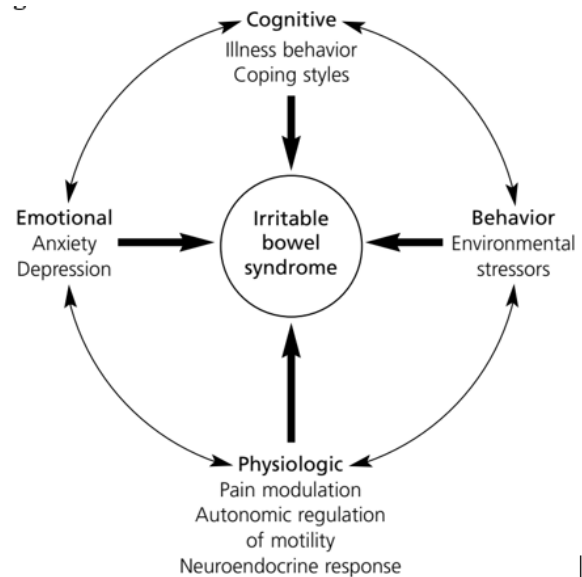


Fig. 2:

Table 3:

Symptom	First Line	Second Line	Future
Constipation	Fiber Osmotic laxative including polyethylene glycol Lactulose/Lactitol Stool softner eg. docusate	Bisacodyl Sodium Picosulfate Tegaserod (withdrawn) Lubiprostone Linaclotide Prucalopride (5-HT ₄ agonist)	Elobixibat (ileal bile acid transporter inhibitor)
Diarrhea	Loperamide Diphenoxylate	Alosetron Ramosetron Ondasetron Bile acid sequestrant (cholestyramine, cholestipol) Clonidine	
Bloating Pain	Treat Constipation	Probiotic Antibiotic (rifaximin) Antispasmodics Anticholinergics Mebeverine Pinnaverium Otilonium bromide Antidepressant • Tricyclic anti-depressants • SSRI SNRI	

µg/day) for chronic constipation and constipation-predominant IBS, and the guanylate cyclase agonist linaclotide for chronic constipation and constipation-predominant IBS

- Fiber, bulking agents, and anti-diarrheals for diarrhea. Very recently, the poorly absorbable antibiotic rifaximin (at a dosage of 550 mg t.i.d. for 14 days) and eluxadoline, a mu opioid receptor agonist and delta opioid receptor antagonist, were approved in the United States for diarrhea-predominant IBS.
- Charcoal resins, antiflatulents, and other agents are widely used, although without supporting evidence, for bloating, distension, and flatulence.⁷

1.9. Pharmacological Strategies in treating IBS

1.9.1. 5HT Agonists

Pumosestrag, a 5-HT₃ receptor partial agonist, is a novel enteroprogenetic compound which stimulates small bowel transit dose dependently. A single-blind study showed that pumosestrag 0.5 mg improved bowel motility.

1.9.2. Mosapride

The 5-HT₄ receptor agonist has documented stimulatory effects on gastric and colonic motility. Unlike cisapride, mosapride does not bind to K⁺ channels or D₂ dopaminergic receptors. Mosapride was primarily developed for upper GI tract conditions, such as functional dyspepsia, gastro esophageal reflux disease, and nausea and vomiting⁸

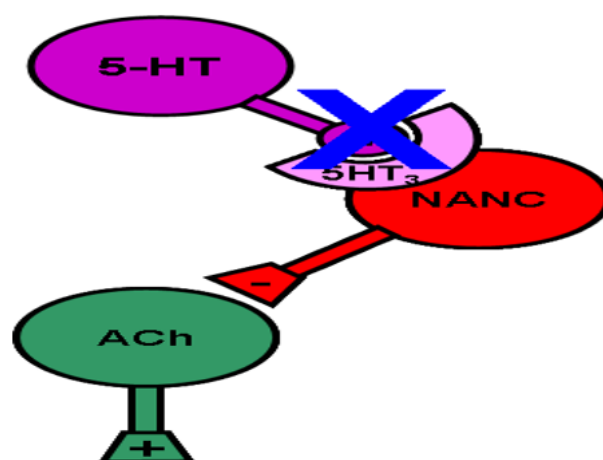
1.9.3. 5HT₃ antagonist

The 5-HT₃ receptor antagonists (alosetron and cilansetron) prevent the activation of 5-HT₃ receptors on extrinsic afferent neurons and decrease visceral pain in IBS. They also decrease small intestinal and colonic motility

1.9.4. Alosetron

Is a powerful and particular 5-HT₃ receptor antagonist. 5-HT₃ receptors are cationic channels actuated by the ligand that are broadly appropriated in enteric neurons in the

human gastrointestinal tract.

**Fig. 3:**

Indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have: chronic IBS symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy. Plasma concentrations are 30% to 50% lower and less variable in men compared to women given the same oral dose. Starting dose is 0.5 mg twice a day. Unlike other 5HT₃ antagonists, Alosetron is associated with rare but serious GI toxicities constipation occurs in up to 30% of patients, with 10% requiring discontinuation of the drug. Evidence from two studies that enrolled women with more severe IBS-D suggests that alosetron improves global IBS symptoms

Ramosetron is a novel potent and selective 5-HT₃ receptor antagonist, which is reportedly useful in patients with IBS-D. Ramosetron was as effective as mebeverine in male patients with IBS-D⁹

5HT₄ agonist 5-HT₄ receptor agonists potentiate peristalsis initiated by 5-HT₁ receptor stimulation in the gut.

1.9.5. Prucalopride

Is a dihydro-benzofurancarboxamide derivative. Prucalopride is a highly selective agonist and has high affinity for 5-HT₄ receptors promoting cholinergic and nonadrenergic, noncholinergic neurotransmission by enteric neurons. 5-HT₄ agonists facilitate gastrointestinal motility by promoting longitudinal smooth muscle contractility while suppressing the resistance to propulsion due to circular smooth muscle contraction.

Prucalopride has a low potential for drug-drug interactions, due to lack of extensive binding to plasma protein. Prucalopride also ameliorated frequency of straining during bowel movements, stool consistency, subjective sense of constipation. In opioid-induced constipation, patients with spinal cord injury, In patients with multiple sclerosis and constipation, the drug is effective. Prucalopride 1–2 mg once daily may be given to patients suffering from chronic constipation for whom laxatives do not provide adequate relief of their symptoms. (Tablets of 0.5, 1, 2mg, are available). The most common adverse events (which occur in 10% or more of treated subjects) are headache, nausea, abdominal pain, and diarrhea. Prucalopride also appears to be a safe drug and there is no evidence at the present time that it affects the electrocardiogram or prolongs QTc interval.¹⁰

1.9.6. Opioid receptor agonist

k-opioid agonist, appeared to be effective and safe for the treatment of abdominal pain and bloating associated with IBS

1.9.7. Eluxadoline

Is a gut-targeting μ and κ opioid receptor agonist and a δ opioid receptor antagonist. The dual mechanism of eluxadoline may explain the antidiarrheal and abdominal pain-modulating properties and lack of profound constipation.

In phase III clinical trials eluxadoline was administered orally twice daily at 75mg or 100mg, improved HR QOL (Health Related Quality of Life). It also improved IBS severity and other abdominal symptoms such as bloating, discomfort, and risk of urgency and fecal incontinence. Its main side effects included constipation, vomiting, abdominal pain and nausea. The overall quality of trials was satisfactory with the meta-analyses providing largely homogeneous outcomes.¹¹

1.9.8. Antibiotics

There is growing evidence of the pathogenetic role of disturbed gut flora in the development of IBS symptoms. Besides significantly altered fecal microbiota in IBS, small intestinal bacterial overgrowth is relatively frequent in the IBS patient. Treatment with neomycin improves constipation in IBS-C. In contrast to systemic absorption

and side effects of neomycin, rifaximin is a gut selective, nonabsorbable antibiotic with a broad-spectrum activity.

1.9.9. Rifaximin

Minimally absorbed, broad-spectrum antibacterial that inhibits bacterial RNA synthesis. The specific mechanism of action of rifaximin in irritable bowel syndrome (IBS) has not been determined. The most likely mechanism of rifaximin is reduction in overall bacterial load, particularly in the large bowel 1; however, rifaximin also seems to modulate gut microenvironment and produce cytoprotective effects. It possesses anti-inflammatory and antibacterial properties and additionally, it is a nonabsorbable antibiotic that acts locally in the gut.

These properties make it efficacious in relieving chronic functional symptoms of non-constipation type irritable bowel syndrome. Rifaximin was safe and well-tolerated in this study, it is unknown whether long-term use could lead to antibiotic resistance or antibiotic-induced diarrhea or Clostridium difficile colitis. Initial studies of rifaximin for the treatment of IBS-D patients were based on the hypothesis that a large proportion of IBS-D patients had small intestinal bacterial overgrowth (SIBO), a disorder characterized by the presence of abnormally high numbers of bacteria in the small intestine. The recommended dose of Rifaximin is one 550 mg tablet taken orally three times a day for 14 days. Patients who experience a recurrence of symptoms can be retreated up to two times with the same dosage regimen.¹²

1.9.10. Chloride channel activators

Activation of type 2 Cl⁻ channel in the gastrointestinal tract increases Cl⁻ transport into the lumen, thus enhancing intestinal fluid secretion

1.9.11. Lubiprostone

is a bicyclic fatty acid derivative of prostaglandin E₁ used for the treatment of chronic idiopathic constipation and constipation predominant irritable bowel syndrome. The underlying mechanism of lubiprostone is stimulation of electrogenic chloride secretion by activating chloride channel type-2 (ClC-2) and cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels in the apical membrane of the intestinal epithelial cells. Activation of ClC-2 channels or CFTR chloride channels in intestinal epithelial cells produces an active secretion of chloride ions from cells into the intestinal lumen followed by a passive secretion of electrolytes and water which increases the liquidity of the luminal contents. The luminal distension by increased intestinal fluid promotes the gastrointestinal (GI) tract motility which in turn increases the intestinal and colonic transit.

8 mcg taken twice daily orally with food and water is usual dose. (IBS -C). For Chronic idiopathic constipation

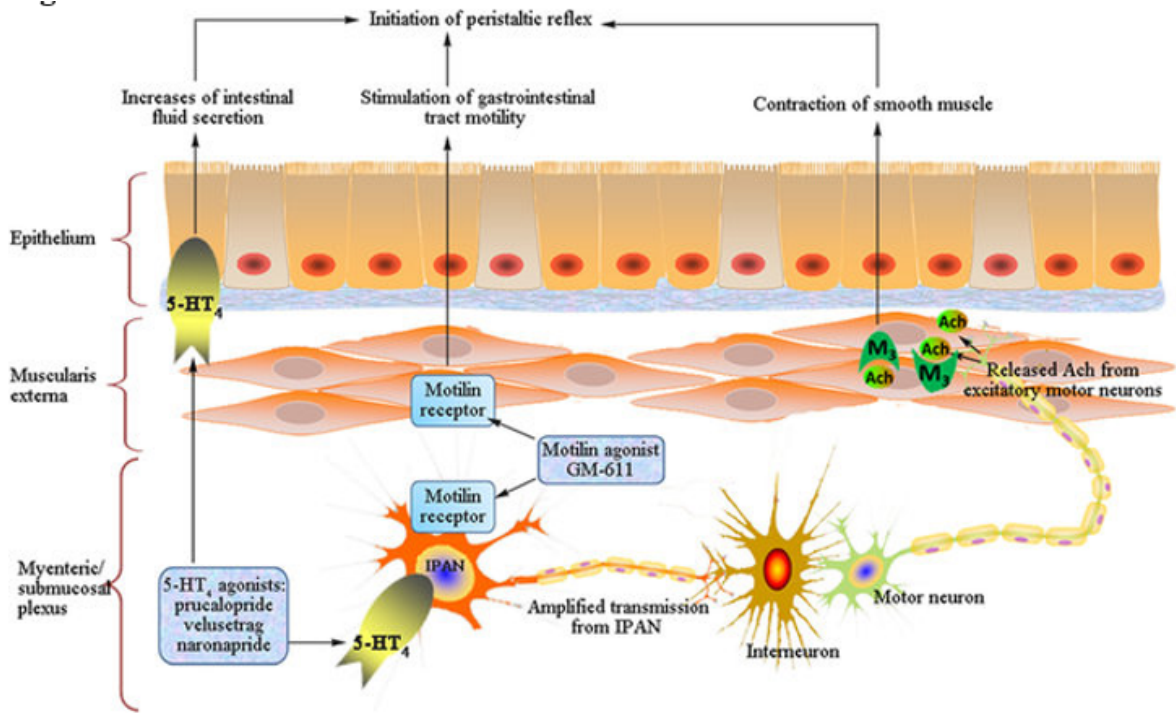


Fig. 4:

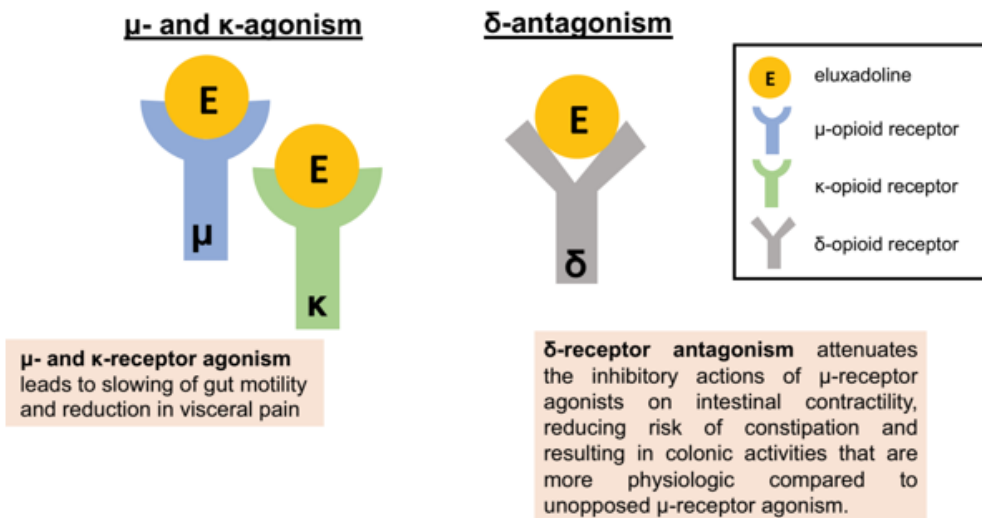


Fig. 5:

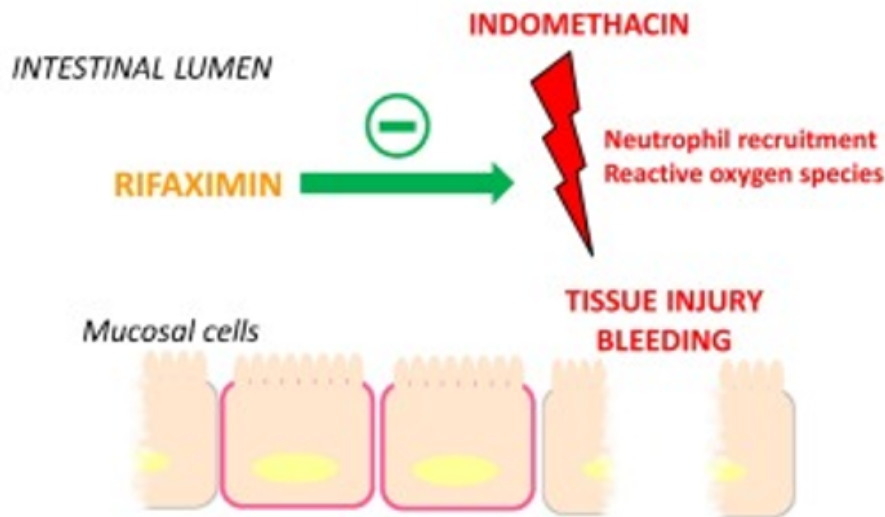


Fig. 6:

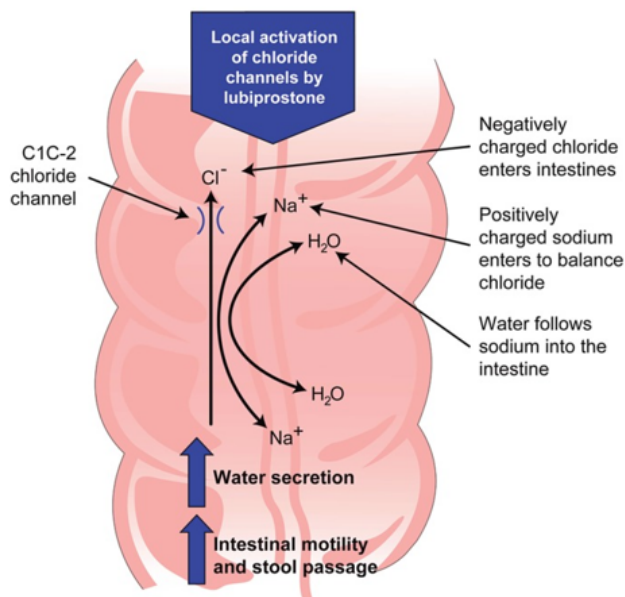


Fig. 7:

it is 24 mcg twice daily. Symptoms of constipation such as pain and bloating are usually improved within one week.¹³

1.9.12. Guanylate cyclase C agonists

Activation of the guanylate cyclase-C receptors increases anion efflux into the intestinal lumen and concomitant fluid secretion

1.9.13. Linaclotide

Is an orally administered, peptide agonist of guanylate cyclase 2C for the treatment of irritable bowel syndrome. Linaclotide is an agonist of guanylate cyclase-C (GC-C). Once linaclotide and its active metabolite binds to GC-C, it has local effect on the luminal surface of the intestinal epithelium. Activation of GC-C by linaclotide results in the intra- and extracellular increase of cyclic guanosine monophosphate concentrations (cGMP). This elevation of cGMP levels stimulates the secretion of chloride and bicarbonate into the intestinal lumen. Indicated for irritable bowel syndrome with constipation (IBS-C)

290 mcg PO Day, for chronic idiopathic constipation (CIC) it is 145 mcg PO Day. The most frequent adverse events with a greater incidence with linaclotide compared with placebo in the Phase 3 studies were diarrhoea, abdominal pain, flatulence, headache, viral gastroenteritis and abdominal distension.

Plecanatide is a lumenally acting secretagogue that is efficacious and safe for the treatment of Chronic idiopathic constipation and IBS -C in doses of 3mg and 6mg. Plecanatide works as a laxative by drawing water in to the gastrointestinal tract thereby softening stool and encouraging its natural passage. Plecanatide activates guanylate cyclase-C on endothelial cells within the gastrointestinal tract. The activation of guanylate cyclase-C catalyses the production of the second messenger guanosine 3',5'-cyclic monophosphate (cGMP) which leads to the protein kinase A. The most notable difference between the clinical trials was that patients taking linaclotide reported incidence of diarrhea three times higher than patients taking plecanatide (16% vs 6%, respectively)[14 a, b]

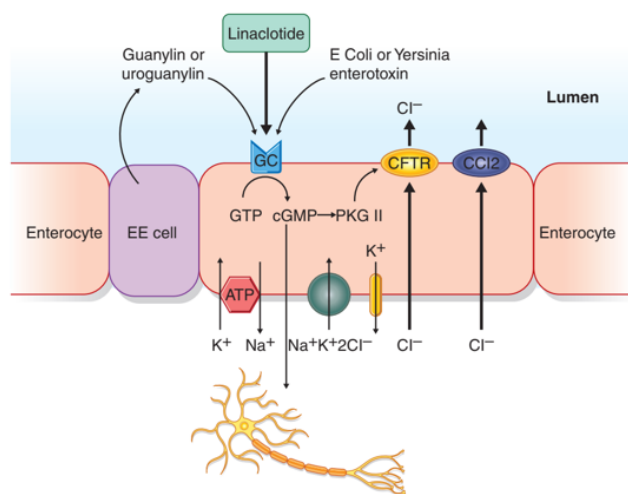


Fig. 8:

1.9.14. Monoamine uptake inhibitors and Tricyclic antidepressants

Treatment of IBS-C is individualized for the patient. Symptoms can vary between patients, but they usually include infrequent bowel movements, cramping, nausea, abdominal pain, weight loss, and bloating. Serotonergic psychoactive agents have been widely used in the treatment of irritable syndrome when psychiatric comorbidities are present. The selective serotonin reuptake inhibitors (SSRIs) fluoxetine and citalopram significantly improve IBS symptoms. Treatment of IBS with antidepressants seems to effect global improvements, although the evidence comes from a small number of trials. . Combination therapy of MAOIs and SSRIs or SNRIs is dangerous due to the increased risk for serotonin syndrome. SSRIs accelerate small bowel transit; others have effects on colorectal sensation, compliance or tone e.g., citalopram, venlafaxine. Antidepressants are effective in managing IBS symptoms.

1. TCAs antidepressants may reduce IBS symptoms through different mechanisms.
2. Long term antidepressant treatment may be required to suppress IBS symptoms; vigilance for adverse effects adverse effects is necessary to optimise chronic management.¹⁴

1.9.15. α_2 adrenoreceptor agonists

In a double-blind, randomized, parallel group, placebo-controlled trial, clonidine relieved bowel dysfunction and appeared promising in relieving IBS-D symptoms without significant alterations in gastrointestinal transit. Clonidine had a statistically significant though numerically small effect on sensation thresholds for gas, urgency and pain. Drowsiness, dizziness and dry mouth were the most common adverse events during the 4 weeks of clonidine treatment. **IBS** symptoms could be curtailed at 0.1 mg twice

daily. The onset of efficacy was apparent after 4 weeks of treatment.¹⁵

1.9.16. Benzodiazepines

Dextofisopam has effectively improved pain relief and stool consistency in IBS patients with diarrhea or alternating bowel habits. Patients treated with dex-tofisopam (200 mg b.i.d.) noted adequate relief of global IBS symptoms at the end of month one ($p < 0.002$). 2,3-benzodiazepine receptors where Dextofisopam acts are concentrated in the subcortical ganglia, substantia nigra, and hypothalamus, and do not appear to be present in the gastrointestinal tract. It has been postulated that 2,3-benzodiazepine receptors may be important in the modulation of autonomic function, including gastrointestinal motor and sensory activity, and produce no sedation. . Dextofisopam appeared to have a good safety and tolerability profile, with minimal constipation or diarrhoea.¹⁶

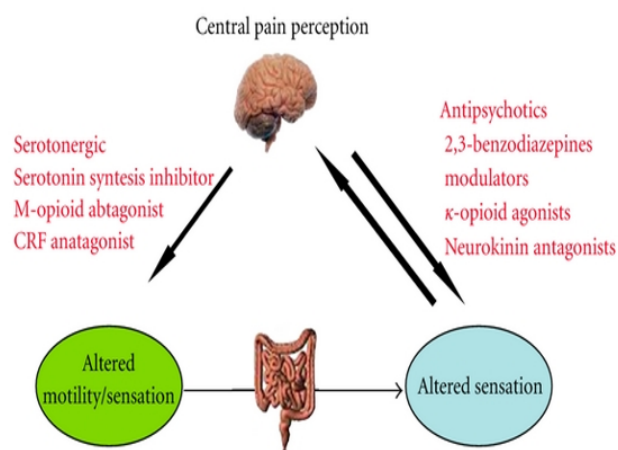


Fig. 9:

1.9.17. Somatostatin analogue

Octreotide, a synthetic somatostatin analog, has a direct effect on visceral pain perception. Acute administration of octreotide reduces rectal hyperalgesia and rectal pressure in IBS patients. Octreotide improved stool consistency compared with placebo. Prolonged treatment of non-constipated IBS patients with octreotide significantly, Octreotide improved stool consistency compared with placebo (loose stools after eight weeks: octreotide: 52%, placebo: 81%, $P < 0.05$).¹⁷

1.9.18. Probiotics

May influence the intestinal immune function, induce qualitative and quantitative changes in the intestinal flora, and modulate colonic bacterial gas production, intestinal intraluminal milieu and colonic transit. *Lactobacillus plantarum* and *Lactobacillus acidophilus*

significantly reduce abdominal pain or discomfort in IBS. *Bifidobacterium lactis* improves gastrointestinal transit and relieves abdominal discomfort and bloating in constipated IBS patients. Multi-species probiotics are effective in IBS patients, and induced the alterations in the composition of intestinal microflora.

Probiotic mechanisms of action include enhancement of the epithelial barrier, increased adhesion to intestinal mucosa, and concomitant inhibition of pathogen adhesion, competitive exclusion of pathogenic microorganisms, production of anti-microorganism substances and modulation of the immune system. A 2015 meta-analysis of 24 human clinical trials concluded that probiotics, overall, were more beneficial than placebo in reducing pain and symptom severity scores. A 2016 systematic review produced by the British Dietetic Association (BDA) analysed the findings of 35 human randomised controlled trials, of which 83% showed improved at least one outcome.¹⁸

1.9.19. Anti-Psychotic Agent

Quetiapine (antagonist at α -2-adrenergic receptor and binds to the D2 dopamine receptor agonist) is an atypical antipsychotic agent that ameliorates anxiety and sleep disturbances, augments the effect of antidepressants, and provides an independent analgesic effect. Quetiapine in low doses appeared beneficial in more than half of the adults with IBS who stayed on treatment.¹⁹

Gabapentin, a 3-alkylated analogue of γ -amino butyric acid (GABA), has been shown to reduce elements of central sensitization in human experimental hyperalgesia. Patients with IBS-D were randomized for 5-day treatment with gabapentin, 300 mg/day and then 600 mg/day, which increased rectal sensory thresholds through attenuating rectal sensitivity to distension and enhancing rectal compliance.²⁰

1.9.20. Pregabalin

Has been tested in IBS patients in pharmacodynamic study. Pregabalin increased distension sensory thresholds to normal levels in IBS patients with rectal hypersensitivity. A concomitant increase in rectal compliance appeared to be unrelated to the reduction in sensitivity²¹.

1.9.21. Neurokinin antagonists

Class of drug used to treat nausea and vomiting associated with chemotherapy. Aprepitant, casopitant, fosaprepitant, and rolapitant are NK1 drugs. Ibodutant, a selective neurokinin-2 receptor antagonist, significantly improved overall symptoms, abdominal pain and stool pattern in women with diarrhea-predominant irritable bowel syndrome. Ibodutant or placebo once daily for 8 weeks showed. Satisfactory (75% of the study weeks) improvements in overall IBS.²²

1.9.22. CRF (corticotropin releasing factor) receptor antagonists

A growing body of experimental evidence has demonstrated that CRF1 receptor antagonists alleviate the development of anxietylike behaviour and stress related alterations of gut function and enterotoxin mediated intestinal inflammation. The positive results associated with the use of CRF receptor antagonists in IBS. The rank order of potency is as follows: *Urotensin I, Astressin, ovine CRF, bovine CRF, alpha helical CRF and arginine vasopressin*.²³

Elobixibat is an inhibitor of the ileal bile acid transporter (IBAT), undergoing development in clinical trials for the treatment of chronic constipation and irritable bowel syndrome with constipation (IBS-C). By inhibiting the uptake of bile acids, elobixibat increases the bile acid concentration in the gut, and this accelerates intestinal passage and softens the stool. Patients with constipation have reduced colonic bile acid concentrations, which are associated with slow colonic transit. Elobixibat, a locally acting ileal bile acid transporter inhibitor, accelerated colonic transit in with functional constipation. Elobixibat should be taken before breakfast. Once-daily administration of elobixibat was found to be safe and tolerated up to 20 mg in female and male patients with chronic constipation.²⁴

1.9.23. Mast cell stabilizer

Mast cell has a role in the pathophysiology of IBS. There are found mast cell hyperplasia in patients with IBS. *Disodium cromoglycate* is an example of a mast cell stabilizer. This drug is being evaluated in the IBS animal model. The results showed that this drug can reduce abdominal pain caused by colorectal distension significantly ($P < 0.05$). Cromolyn sodium at a dose of 150 mg daily divided in 3 times effective reduces abdominal pain on patients with IBS-C and D after the 6th week²⁵

2. Endocannabinoid system

The Endocannabinoid system (ECS) plays a key role in maintaining normal physiology of the gastrointestinal tract as well as involves abnormalities including functional diseases like IBS. The gastrointestinal tract also has this endocannabinoid system with CB ligands, anandamide, and 2-arachidonoylglycerol (2-AG) and different cannabinoid receptors like cannabinoid 1 receptor (CB1), cannabinoid 2 receptor (CB2) causing a variety of function in the human body in both physiological and pathophysiological conditions. Activation of CB1 and CB2 receptors decreases gastrointestinal motility, secretions, and hyper-sensitivity. The alteration of this endocannabinoid system might play a major role in IBS.²⁶

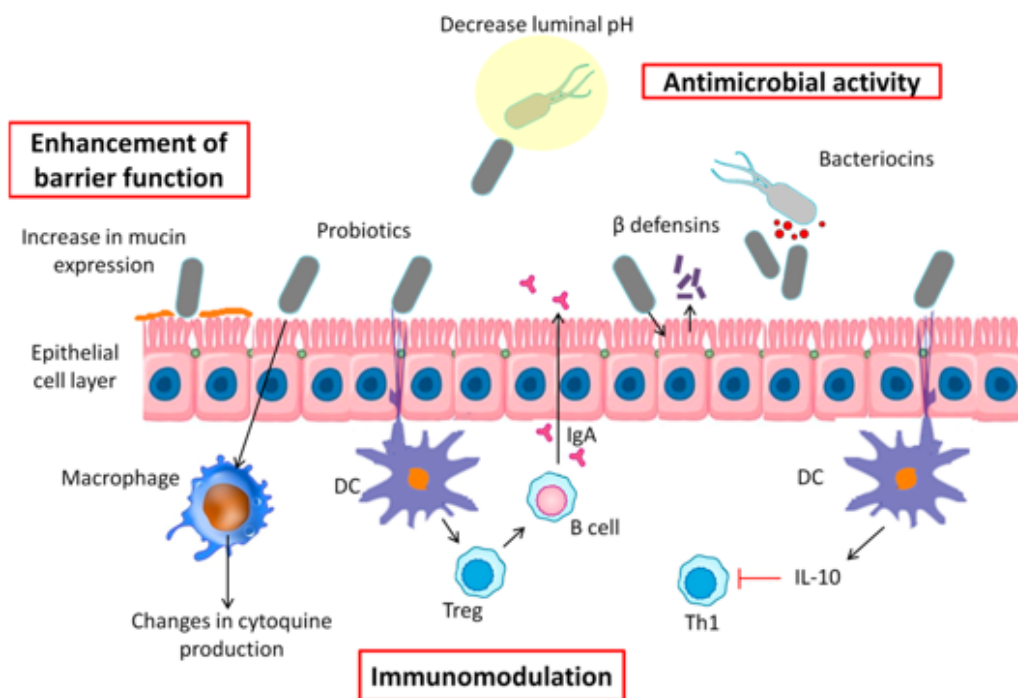


Fig. 10:

2.1. Traditional Medicine for IBS

Mentha piperita (peppermint oil) may have several mechanisms of action including: smooth muscle relaxation (via calcium channel blockade or direct enteric nervous system effects); visceral sensitivity modulation (via transient receptor potential cation channels); anti-microbial effects; anti-inflammatory activity; modulation of psychosocial distress. *Aloe vera*, *curcuma*, *fumaria officinalis*, and *hypericum perforatum* showed different mechanisms such as prosecretory activity, anti-inflammatory activity and inducing gastrointestinal motility, in the management of IBS. Antidepressant activity and modulating psychological stress are the *Hypericum perforatum* mechanisms in relieving IBS. The use of turmeric (*Curcuma longa*) in gastrointestinal disorders such as IBS, the data suggested that the inhibitory effects of extract of turmeric (curcumin) are mediated primarily through a calcium channel blockade in hyperactive states of the gut and airways. The efficacy of curcuma in IBS may be due to antibacterial, anti-inflammatory, and spasmolytic activities. *Bulking agents* are fiber supplements, such as *psyllium* (ispaghula husks), *calcium polycarbophil*, *methylcellulose*, and *bran*. Soluble fiber can provide overall symptom relief in IBS patients, but possibly only in patients with constipation-dominant IBS (IBS-C)²⁷

3. Conclusion

Irritable bowel syndrome is not a disease, but rather a condition that affects the function and behavior of the

intestines. QOL in patients with IBS is affected by age, sex, BMI, and presence of symptoms such as dyspepsia, flatulence, and abdominal pain. Multi-disciplinary approach is required for optimal treatment. Besides the treating physician opinion from dietician and psychologist may also be required. It is often best to focus on the predominant symptom: diarrhea constipation, or pain/gas/bloat and then treat accordingly. There are many class therapies for IBS among others: Antibiotic, Antidepressant, serotoninreceptor antagonist, agonis reseptor 5-HT4, guanylate cyclase C agonis, mast cell stabilizer, Luminal Adsorbent, and opioid agonis and antagonis to relieve symptoms of IBS Relief of IBS Symptoms is often a slow process. It may take six months or more for definite improvement to be appreciated. Patience is extremely important in dealing with chronic problem.

4. Conflict of Interest

None.

5. Source of Funding

None.

References

1. Eamonn MM, Quigley. 2015.
2. Rahman MM, Mahadeva S, Ghoshal UC. Epidemiological and clinical perspectives on irritable bowel syndrome in India, Bangladesh

- and Malaysia: A review. *World Journal of Gastroenterology*. 2017;23(37):6788–6801. Available from: <https://dx.doi.org/10.3748/wjg.v23.i37.6788>. doi:10.3748/wjg.v23.i37.6788.
3. Róka R, Gece K, Wittmann T. Novel strategies and future landmarks in the treatment of irritable bowel syndrome. *Therapy*. 2009;6(4):603–613. Available from: <https://dx.doi.org/10.2217/thy.09.22>. doi:10.2217/thy.09.22.
 4. Gregory S, Sayuk MD, Gyawati MD. John Cochrane veterans affairs. 2015.
 5. Rubin G, Wit ND, Meineche-Schmidt V, Seifert B, Hall N, Hungin P. The diagnosis of IBS in primary care: consensus development using nominal group technique. *Family Practice*. 2006;23(6):687–692. Available from: <https://dx.doi.org/10.1093/fampra/cml050>. doi:10.1093/fampra/cml050.
 6. Diets I. 2019.
 7. Camilleri M, Andresen V. Current and novel therapeutic options for irritable bowel syndrome management. *Digestive and Liver Disease*. 2009;41(12):854–862. Available from: <https://dx.doi.org/10.1016/j.dld.2009.07.009>. doi:10.1016/j.dld.2009.07.009.
 8. Eswaran S, Guentner A, Chey WD. Emerging Pharmacologic Therapies for Constipation-predominant Irritable Bowel Syndrome and Chronic Constipation. *Journal of Neurogastroenterology and Motility*. 2014;20(2):141–151. Available from: <https://dx.doi.org/10.5056/jnm.2014.20.2.141>. doi:10.5056/jnm.2014.20.2.141.
 9. Lacy BE, Nicandro JP, Chuang E, Earnest DL. Alosetron use in clinical practice: significant improvement in irritable bowel syndrome symptoms evaluated using the US Food and Drug Administration composite endpoint. *Therapeutic Advances in Gastroenterology*. 2018;11:175628481877167–175628481877167. Available from: <https://dx.doi.org/10.1177/1756284818771674>. doi:10.1177/1756284818771674.
 10. Banny S, Wong N, Manabe M, Camilleri. Role of prucalopride, a serotonin (5-HT4) receptor agonist, for the treatment of chronic constipation. *Clin Exp Gastroenterol*. 2010;3:49–56.
 11. Konstantinos C, Fragkos. Update on Eluxadoline for the Treatment of Irritable Bowel Syndrome with Diarrhea. *Clinical and Experimental Gastroenterology*;2017:10–229.
 12. Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, et al. for the TARGET Study Group. Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation. *n engl j med*. 2011;364.
 13. Wilson N, Schey R. Lubiprostone in constipation: clinical evidence and place in therapy. SAGE Publications; 2015. Available from: <https://dx.doi.org/10.1177/2040622314567678>. doi:10.1177/2040622314567678.
 14. Tack J, Broekaert B, Fischler, Oudenhove V, Gevers J, Janssens. A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. *Gut*. 2006;55:1065–1067.
 15. Camilleri M, Kim DY, Mckinzie S, Kim HJ, Thomforde GM, Burton DD, et al. A randomized, controlled exploratory study of clonidine in diarrhea-predominant irritable bowel syndrome. *Clinical Gastroenterology and Hepatology*. 2003;1(2):111–121. Available from: <https://dx.doi.org/10.1053/cgh.2003.50019>. doi:10.1053/cgh.2003.50019.
 16. LEVENTER SM, RAUDIBAUGH K, FRISSORA CL, KASSEM N, KEOGH JC, PHILLIPS J, et al. Clinical trial: dextofisopam in the treatment of patients with diarrhoea-predominant or alternating irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics*. 2007;27(2):197–206. Available from: <https://dx.doi.org/10.1111/j.1365-2036.2007.03566.x>. doi:10.1111/j.1365-2036.2007.03566.x.
 17. KLOOKER TK, KUIKEN SD, LEI A, BOECKXSTAENS GE. Effect of long-term treatment with octreotide on rectal sensitivity in patients with non-constipated irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics*. 2007;26(4):605–615. Available from: <https://dx.doi.org/10.1111/j.1365-2036.2007.03398.x>. doi:10.1111/j.1365-2036.2007.03398.x.
 18. Plaza-Díaz J, Ruiz-Ojeda F, Gil-Campos M, Gil A. Immune-Mediated Mechanisms of Action of Probiotics and Synbiotics in Treating Pediatric Intestinal Diseases. *Nutrients*. 2018;10(1):42–42. Available from: <https://dx.doi.org/10.3390/nu10010042>. doi:10.3390/nu10010042.
 19. Camilleri M. *New Receptor Targets for Medical Therapy in Irritable Bowel Syndrome*. 2010;31:35–46.
 20. Lee KJ. Gabapentin reduces rectal mechanosensitivity and increases rectal compliance in patients with diarrhoea-predominant irritable bowel syndrome. *Alim Pharmacol & Therapeutic*. 2005;p. 981–988.
 21. Houghton LA, Fell C, Whorwell PJ, Jones I, Sudworth DP, Gale JD. Effect of a second-generation 2 ligand (pregabalin) on visceral sensation in hypersensitive patients with irritable bowel syndrome. *Gut*. 2007;56(9):1218–1225. Available from: <https://dx.doi.org/10.1136/gut.2006.110858>. doi:10.1136/gut.2006.110858.
 22. Tack J, Schumacher K, Tonini G, Scaroni S, Capriati A, Maggi CA. The neurokinin-2 receptor antagonist ibodutant improves overall symptoms, abdominal pain and stool pattern in female patients in a phase II study of diarrhoea-predominant IBS. *Gut*. 2017;66(8):1403–1413. Available from: <https://dx.doi.org/10.1136/gutjnl-2015-310683>. doi:10.1136/gutjnl-2015-310683.
 23. Grigoriadis DE. Corticotropin-Releasing Factor Receptor Antagonists: Potential Novel Therapies for Human Disease; 2019.
 24. Kumagai Y, Amano H, Sasaki Y, Nakagawa C, Maeda M, Oikawa I, et al. Effect of single and multiple doses of elobixibat, an ileal bile acid transporter inhibitor, on chronic constipation: A randomized controlled trial. *British Journal of Clinical Pharmacology*. 2018;84(10):2393–2404. Available from: <https://dx.doi.org/10.1111/bcp.13698>. doi:10.1111/bcp.13698.
 25. Daryani E, Hashemian MF, Afkham. Mast cell stabilizers as a potential treatment for Irritable bowel syndrome: A randomized placebo-controlled clinical trial. *Daru -Journal of faculty of pharmacy*. 2009;17(2):72–78.
 26. Pandey S, Kashif S, Youssef M, Sarwal S, Zraik H, Singh R, et al. Endocannabinoid system in irritable bowel syndrome and cannabis as a therapy. *Complementary Therapies in Medicine*. 2020;48:102242–102242. Available from: <https://dx.doi.org/10.1016/j.ctim.2019.102242>. doi:10.1016/j.ctim.2019.102242.
 27. Bahrami HR, Hamed S, Salari R, Noras M. Herbal Medicines for the Management of Irritable Bowel Syndrome: A Systematic Review. Mehr Publishing Group; 2016. Available from: <https://dx.doi.org/10.19082/2719>. doi:10.19082/2719.

Author biography

Sunil Chaudhry, Honorary Medical Director

Cite this article: Chaudhry S. Demarcating Therapeutic Interventions in IBS. *J Pharm Biol Sci* 2020;8(2):65-75.