Review on Various Approaches to Treat Irritable Bowel Syndrome and Superiority of Combinations Over the Existing Therapy

Dharati Rami1*, Nehal Shah1, Pinak Patel1, Vivek Rami2

Abstracts: Current paper describes potential therapies available to treat Irritable bowel syndrome is a brain gut disorder characterized most commonly by cramping, abdominal pain, bloating, constipation, and diarrhea which is the most common and fatal disease. The pathophysiology provides the rationale for pharmacotherapy: abnormal gastrointestinal motor functions, visceral hypersensitivity, psychosocial factors, autonomic dysfunction, and mucosal immune activation. Understanding the mechanisms, and their mediators or modulators including neurotransmitters and receptors have led to several therapeutic approaches including agents acting on the serotonin receptor or serotonin transporter system, antidepressants, novel selective anticholinergics, α-adrenergic agonists, opioid agents, cholecystokinin-antagonists, somatostatin-antagonists, corticotropin releasing factor antagonists, chloride channel activators, guanylate cyclase-c agonists, melaton, atypical benzodiazepines, antibiotics, immune modulators and probiotics. The mechanisms and current evidence regarding efficacy of these agents are reviewed.

INTRODUCTION

Irritable bowel syndrome is a brain gut disorder characterized most commonly by cramping, abdominal pain, bloating, constipation, and diarrhea. IBS causes a great deal of discomfort and distress, but it does not permanently harm the intestines and does not lead to a serious disease, such as cancer. The pathophysiology of IBS is still not well understood, but is most likely multifactorial. Several factors such as motor and sensory dysfunction, neuroimmune mechanisms, psychological factors, and changes in the intraluminal milieu appear to play a role. The increased release of serotonin in the circulation especially in the IBS-D group and increased serine proteases (derived from mast cells) in stool of patients with IBS provide evidence for the potential role of neurotransmitters or chemical mediators such as proteases in the disorder. [1,2]

There are Three Types of IBS

- IBS with Constipation: This comes with stomach pain and discomfort, bloating, abnormally delayed or infrequent bowel movements, or lumpy/hard stool.
- IBS with Diarrhea: This comes with stomach pain and discomfort, an urgent need to move your bowels, abnormally frequent bowel movements, or loose/watery stool.
- IBS with alternating constipation and diarrhea [3,6]

Background of IBS

Irritable bowel syndrome is a functional gastrointestinal disorder affecting up to 3–15% of the general population in western countries. Most people can control their symptoms with diet, stress management, and prescribed medications. For some people, however, IBS can be disabling. They may be unable to work, attend social events, or even travel short distances. It occurs more often in women than in men, and it begins before the age of 35 in about 50 percent of people. [4,5]

Approaches to Treat IBS

This article reviews recent and novel approaches in IBS therapy (Table 1, Figure 2) that have preclinical efficacy, Phase Ila studies of pharmacodynamics or proof of concept, and Phase IIb or phase III studies that show evidence of efficacy.

SEROTONERGIC SYSTEM

Serotonin (5-hydroxytryptamine) is an important neurotransmitter of the enteric nervous system (ENS), the peristaltic reflex (chiefly 5-HT4-receptor), the brain–gut axis and vagal and visceral afferent cell bodies or pathways, chiefly 5-HT3-receptors [16,17]. 5-HT plays a pivotal role in the modulation of multiple gut functions such as motility, sensation, blood flow and secretion [18,19]. In humans, the highest level of specific binding has been found in the amygdalae, which are integral to the emotional responses to visceral stimulation.

Activity at 5-HT-receptors is regulated by the 5-HT reuptake transporter protein (SERT [20]). It is controversial whether there is reduced expression of SERT (mRNA or immunohistochemistry) in IBS [21,22] 5-HT2 antagonists and 5-HT4 agonists have demonstrated efficacy and effectiveness in the treatment of multiple or global symptoms of IBS. The prototype medications were alosetron and tegaserod.

5-HT3-receptor Antagonists

5-HT3-receptor antagonists retard colonic transit, reduce secretion, and increase colonic compliance in response to distension [23] and have central effects that contribute to their beneficial effects on sensation in IBS [24].

Alosetron and subsequently cilansetron were efficacious in several large, multicentre, randomised controlled clinical trials, reviewed in an updated meta-analysis [25]. 5-HT3
antagonists more effective than the comparators in achieving global improvement in IBS symptoms (pooled relative risk, 1.60; 95% confidence interval [CI], 1.49–1.72; heterogeneity index, $I^2 = 0\%$) and relief of abdominal pain and discomfort (pooled relative risk, 1.30; 95% CI, 1.22–1.39; $I^2 = 22\%$). Benefit was apparent for both agents, in both genders. These agents were more likely to cause constipation (pooled relative risk, 4.28; 95% CI, 3.28–5.60, $I^2 = 65\%$); 0.2% using 5-HT3 antagonists had possible ischaemic colitis versus none in control groups. Cilansetron was never approved; alosetron is associated with clear benefits on quality of life [26], but warnings about potential lack of safety has resulted in only a minority of patients being prescribed the medication.

5HT3-receptor Agonists

The 5-HT3 agonist, MKC-733, also named DDP733 and pumosetrag in the literature, stimulated fasting antroduodenal migrating motor complex activity and accelerated small intestinal transit [27]. A preliminary report of a phase 2a study in IBS-C showed a significant overall benefit in overall clinical response rate (54%) in patients receiving 1.4 mg t.i.d. versus a 15% for placebo [28].

5HT4-receptor Agonists

5HT4-receptor agonists generally accelerate small bowel and colonic transit.

Tegaserod: Tegaserod is a selective partial agonist of the 5-HT4-receptor. Several trials in IBS and chronic constipation were summarized in a Cochrane meta-analysis [29]. In IBS-C, tegaserod did not significantly improve the patients’ individual symptoms of abdominal pain and discomfort although bowel habit showed a statistically significant improvement with tegaserod 4 mg and there was a non-significant trend in this outcome in favour of tegaserod, 12 mg. In patients with chronic constipation, the
Inventi Rapid: Molecular Pharmacology Vol. 2013, Issue 1
ISSN 0976-3856

2013 pmp 188, CCC: $10 © Inventi Journals (P) Ltd
Published on Web 17/10/2012, www.inventi.in

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RR of being a responder in terms of complete spontaneous bowel movements per week with tegaserod 12 mg was 1.54 (95% CI, 1.35–1.75). The drug was essentially withdrawn because of possible, rare cardiovascular adverse effects.

**Newer 5-HT4-receptor Agonists**

*ATI-7505* is a novel, potent agonist of the 5-HT4-receptor and is chemically related to the 5-HT4-receptor agonist, cisapride. However, it has been chemically designed to eliminate cardiac liabilities (e.g., QT prolongation, tachycardia) and CYP450-dependent metabolism at therapeutically relevant concentrations. Pharmacodynamic data in healthy human volunteers \(^{30}\) indicate prokinetic effects with acceleration of gastric emptying (20 mg t.i.d.) and colonic transit (10 mg t.i.d.; overall and ascending colon emptying), as well as inducing looser stool consistency. Thus, it appears to be promising for IBS-C. Extensive human safety data are not available. To date, there are no reports of adverse cardiac side effects.

**Table 1: Drugs in Use or in Clinical Development for IBS.**

<table>
<thead>
<tr>
<th>Target System</th>
<th>Receptor Activity</th>
<th>Compounds</th>
<th>Human Physiological Effects</th>
<th>Potential or Approved Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonergic receptor system</td>
<td>5-HT4-agonists</td>
<td>Prucalopride, ATI-7505 TD-5108</td>
<td>Prokinetic,secretagogue</td>
<td>IBS-C FC</td>
</tr>
<tr>
<td></td>
<td>5-HT3-antagonist</td>
<td>Alosetron, cilansetron</td>
<td>Decrease motility and secretion, increase compliance, decrease pain</td>
<td>IBS-M FD</td>
</tr>
<tr>
<td></td>
<td>5-HT3-agonist</td>
<td>DDP-733, e.g. Venlafaxine,</td>
<td>Accelerates small bowel transit</td>
<td>IBS-C FC</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>SSRI SNRI</td>
<td></td>
<td>Increase compliance, decrease tone, and sensation</td>
<td>IBS FAP</td>
</tr>
<tr>
<td>Cholinergic system</td>
<td>Selective M3-antagonists</td>
<td>Zamifenacn, darifenacn, Clidinium bromide</td>
<td>Reduce colonic motility</td>
<td>IBS-D FD</td>
</tr>
<tr>
<td></td>
<td>Î±2-agonist</td>
<td>Clonidine</td>
<td>Decrease compliance, decreases tone and sensation</td>
<td>IBS-D FAP</td>
</tr>
<tr>
<td>Opioid system</td>
<td>Peripheral Î¼-opioid antagonists</td>
<td>Alvimopan, methylaltrexone</td>
<td>Prokinetic Increase laxation</td>
<td>IBS-C FC, OIC</td>
</tr>
<tr>
<td></td>
<td>Î³-Opoid-agonist</td>
<td>Asimadoline</td>
<td>Decrease sensation</td>
<td>IBS-FAP</td>
</tr>
<tr>
<td>Corticoids</td>
<td>CRH antagonist</td>
<td>Î³shCRH, pexacerfont</td>
<td>Reduce stimulation induced motility and sensitivity</td>
<td>IBS-D FAP</td>
</tr>
<tr>
<td></td>
<td>CRF1 antagonist 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Benzodiazepine receptor</td>
<td>Dexofisopam, Chlordiazepoxide</td>
<td>Reduces stool frequency, increases stool consistency</td>
<td>IBS-D</td>
</tr>
<tr>
<td>Melatonin</td>
<td></td>
<td>Melatonin</td>
<td>Decreases Pain</td>
<td>IBS, FAP</td>
</tr>
<tr>
<td></td>
<td>CCK</td>
<td>Loxiglumide, dexloxiglumide</td>
<td>Accelerates gastric emptying, delay prox. colonic transit</td>
<td>IBS</td>
</tr>
<tr>
<td></td>
<td>Somatostatin</td>
<td>Octreotide</td>
<td>Slows down transit, decreases secretion</td>
<td>IBS-D FD</td>
</tr>
<tr>
<td></td>
<td>Neurokinin (NK)</td>
<td>Ezlopitant, napudant</td>
<td>Reduce visceral sensation (NK1 and NK2)</td>
<td>IBS FAP</td>
</tr>
<tr>
<td></td>
<td>NK antagonists 1 and 2</td>
<td></td>
<td>Accelerates transit, increases secretion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NK antagonist 3</td>
<td>Talnetant</td>
<td>Decreases stool consistency, increases stool frequency</td>
<td>IBS-C FC</td>
</tr>
<tr>
<td>Chloride channel</td>
<td>Activator</td>
<td>Lubiprostone</td>
<td>Overall symptom relief</td>
<td>IBS-C FC</td>
</tr>
<tr>
<td>Guanylate cyclase-c</td>
<td>Agonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Neomycin, rifaximin</td>
<td>Linaclotide</td>
<td>Decrease bloating and pain, slow colon transit</td>
<td>IBS-C FC</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Bacterial flora</td>
<td>VSL#3, Lactobacilli bifidobacteria</td>
<td>Increase bloating flatulence</td>
<td>IBS-C FL</td>
</tr>
<tr>
<td>Proton Pump inhibitor with Antidepressant &amp; anticholinergic</td>
<td>----</td>
<td>Pantoprazole sodium, Chlordiazepoxide, clidinium bromide</td>
<td>Reduce acid secretion, increases stool frequency, increases stool consistency, increases colonic motility</td>
<td>IBS bloating flatulence</td>
</tr>
</tbody>
</table>

Inventi Rapid: Molecular Pharmacology Vol. 2013, Issue 1
ISSN 0976-3856

2013 pmp 188, CCC: $10 © Inventi Journals (P) Ltd
Published on Web 17/10/2012, www.inventi.in
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large clinical trials in patients with severe chronic constipation [31,32,33,34]. The medication has greater selectivity (≈150-fold) for 5-HT₄-receptors than for hERG channel, and it is anticipated that this will be sufficient to prove safely from a cardiac arrhythmia perspective. Certainly, administration for approximately 1 year in more than 80 people with cardiovascular co-morbidity proved safe [35].

TD-5108 (or velusetrag) is a potent agonist at human 5-HT₄-receptors with high intrinsic activity that displays preferential binding to the 5-HT₄-receptor compared with other 5-HT-receptor subtypes or hERG channel [36]. In vivo studies have shown that TD-5108 increases colonic transit in guinea pigs, relaxes oesophageal body musculature in rats, and increases contractility in multiple regions of the GI tract including the gastric antrum, duodenum, jejunum and proximal colon in conscious dogs with implanted strain gauges [37]. In healthy volunteers, single dose, 30- and 50 mg, TD-5108 accelerated colonic and small bowel transit; with multiple doses, TD-5108 30 mg also accelerated colonic transit [38]. A 400-patient, randomised, controlled trial demonstrated efficacy on bowel frequency and consistency in chronic constipation [39].

**ANTIDEPRESSANTS**

Many patients with IBS receive psychoactive agents for their co-morbid psychiatric illnesses, including anxiety, mood, and somatoform disorders, and for the potential effects on visceral sensation. Some SSRIs accelerate small bowel transit; others have effects on colorectal sensation, compliance or tone (e.g., citalopram, venlafaxine).

There may also be racial or ethnic differences, as efficacy appears greatest in trials conducted in Iran. In intention-to-treat analysis, complete responses were significantly more common in the amitriptyline group. Efficacy of antidepressants in treatment of IBS has been appraised in a recent meta-analysis. At first evaluation, one might conclude that this class of drugs is extremely effective. The calculated relative risk of IBS symptoms persisting or remaining unimproved after treatment with

### Table 2: Comparative Analysis of Pantoprazole with other PPI's

<table>
<thead>
<tr>
<th>Proton Pump Inhibitor</th>
<th>Bioavailability (%)</th>
<th>Cmax (μmol/L)</th>
<th>Duration of Effect (Hrs)</th>
<th>Protein Binding (%)</th>
<th>Drug Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole</td>
<td>77</td>
<td>5.73 5 (40 mg)</td>
<td>24-72</td>
<td>98</td>
<td>None</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>30-40</td>
<td>0.70 5 (20 mg)</td>
<td>24-72</td>
<td>95</td>
<td>Diazepam, Warfarin, Digoxin, Phenytoin, Ketoconazole, Ketoconazol, Theophylline</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>77-80</td>
<td>2.25 5 (30 mg)</td>
<td>24</td>
<td>97</td>
<td>None</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>52</td>
<td>0.48 6 (20 mg)</td>
<td>24</td>
<td>96</td>
<td>None</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>64</td>
<td>1.86 2 (20 mg)</td>
<td>24-72</td>
<td>97</td>
<td>None</td>
</tr>
</tbody>
</table>

### Table 3: Comparison of Pantoprazole Vs Omeprazole

**Pantoprazole**
- It has least drug interaction
- Bioavailability is 77%
- Pantoprazole is a category-B drug
- Can be used for maintenance therapy in duodenal ulcer

**Omeprazole**
- More drug interaction because has greater interaction with cytochrome system. It has drug interaction with Diazepam, Phenytoin, Warfarin.
- Bioavailability is 30-40%
- Pantoprazole is a category-C drug
- Can not be used for maintenance therapy in duodenal ulcer

### Table 4: Comparison of Pantoprazole Vs Lansoprazole

**Pantoprazole**
- It has least drug interaction
- Duration of action is 24-72 hr.
- It does not have drug food interaction

**Lansoprazole**
- It has drug interaction with Ketoconazole, Theophylline.
- Duration of action 24 hr.
- It has drug food interaction

### Table 5: Comparison Of Pantoprazole Vs Rabeprazole

**Pantoprazole**
- Duration of action is 24-72 hr.
- Bioavailability is 77%
- Protein binding of Pantoprazole is 97%
- Mechanism of action is to bind both Cysteine 813 & 833 Cysteine

**Rabeprazole**
- Duration of action 24 hr.
- Bioavailability is 54%
- Protein binding of Rabeprazole is 95%
- It binds to Cystein 813 and not to Cysteine 822

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ANTIDEPRESSANTS

Many patients with IBS receive psychoactive agents for their co-morbid psychiatric illnesses, including anxiety, mood, and somatoform disorders, and for the potential effects on visceral sensation. Some SSRIs accelerate small bowel transit; others have effects on colorectal sensation, compliance or tone (e.g., citalopram, venlafaxine).
Several compounds (mebeverine, otilinium, pinaverium, antimuscarinic agents such as cimetropium), used in Europe, have never been approved in the U.S. Several meta-analyses suggest global improvement with this class of agents, with a mean odds ratio of 2.13 [95% CI, 1.77–2.58]. The low quality (Jadad Scores) of the individual clinical trials compromises the overall interpretation of efficacy of this drug class. Whether these results are generalizable is unclear.

**ANTIMUSCARINICS/ANTICHOLINERGICS/SMOOTH MUSCLE RELAXANTS**

Gastrointestinal effects of acetylcholine are mediated by nicotinic receptors in the myenteric plexus, and by muscarinic receptor subtypes M1–3, in the myenteric plexus, as well as the neuromuscular junction. Acetylcholine is the main excitatory neurotransmitter in the gastrointestinal (GI) tract. Nonselective anticholinergics or specific antimuscarinic agents reduce bowel motility and associated pain. Relaxant drugs act directly on the smooth muscle e.g. by blocking smooth muscle Ca2+ channels. Several compounds (mebeverine, otilinium, pinaverium, and cimetropium), used in Europe, have never been approved in the U.S. Several meta-analyses suggest global improvement with this class of agents, with a mean odds ratio of 2.13 [95% CI, 1.77–2.58]. The low quality (Jadad Scores) of the individual clinical trials compromises the overall interpretation of efficacy of this drug class.

Newer anticholinergics specifically targeting the muscarinic type-3 receptor (M3) on smooth muscle decrease non-specific anticholinergic side effects (dry mouth or increased heart rate) and have promising gastrointestinal effects in animal models. Amongst M3-selective antagonists, darifenacin (used to treat overactive bladder) is associated with constipation, and zamifenacin significantly reduced colonic motility without other anticholinergic effects in 36 IBS patients. [43,44]

**α-ADRENERGIC AGENTS**

The adrenergic nervous system provides extrinsic tonic inhibitory control of non-sphincteric gut motility. The α2-adrenergic agents such as clonidine affect human colonic and rectal motor and sensory functions, increasing colonic compliance, reducing fasting tone without altering the colonic response to a meal or colonic transit, and significantly reducing sensation within a dose range of 0.1–0.3 mg b.i.d. In a study of 44 patients with IBS-D, 67% of the patients treated with clonidine 0.1 mg twice daily compared to 46% in the placebo group achieved satisfactory relief, the primary endpoint. Clonidine also significantly improved bowel functions without altering gastrointestinal transit. Drowsiness, dizziness and dry mouth were observed at doses >0.1 mg b.i.d. This suggests benefits of α2-adrenergic agents in IBS. [45,46,47]

**GABA-ERGIC AGENTS AND α2δ LIGAND**

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

Preclinical studies suggest that the α2δ ligand, pregabalin, reduces both visceral allodynia and hyperalgesia, but is inactive on basal sensitivity. The perception of rectal distension was tested in 26 hypersensitive IBS patients randomised to increasing doses of oral pregabalin for 3 weeks or placebo control. Pregabalin significantly increased the sensory thresholds from baseline for first sensation desire to defecate and pain compared with placebo; it also increased rectal compliance, an effect unrelated to the changes in sensitivity. Studies of GABA-ergic agents and α2δ ligands on clinical outcomes in IBS are not available. [48]

**OPIOID AGENTS**

Three major opioid receptors, μ, δ, and κ, are distributed in the peripheral and central nervous systems. μ-Agonists modulate visceral nociception and to slow down gastrointestinal transit resulting in constipation or central side effects. κ-Opioid receptors are involved in visceral perception. [49]

**κ-Opioid Agonist**

Asimadoline: The κ-opioid agonist, asimadoline, was shown to reduce sensation in response to distensions in the non-noxious range applied to the colon and to relax colonic and gastric tone during fasting. There were no significant effects on gastrointestinal or colonic transit or postprandial tone response to meal ingestion. Delvaux et al. showed that this drug increased sensory thresholds in patients with IBS. On demand treatment of IBS pain with asimadoline was not significantly better than placebo; however, a recent trial using daily administration of asimadoline demonstrated efficacy in patients with IBS-D and IBS with mixed bowel habits (IBS-M). [50]
Dexofisopam: Dexofisopam is the R-enantiomer of the non-sedating homophthalazine anxiolytic, tofisopam. It binds to 2,3-benzodiazepine receptors located in subcortical and hypothalamic regions. In animal models, dexofisopam reduced stimulation-induced colonic motility and visceral sensitivity. A 12-week, placebo-controlled, phase II study in patients with diarrhoea-predominant or alternating-IBS showed more months with adequate relief in the dextofisopam compared to the placebo group. The effects were most prominent within the first 4 weeks of treatment, and also included an improvement of stool consistency and a reduction of stool frequency. The drug was well tolerated, with only 3% reporting constipation; however, 12% of the patients experienced a worsening of abdominal pain (versus 4% in the placebo group). [55,56]

MELATONIN
Melatonin is a pineal gland neurohormone involved in the regulation of the sleep–wake cycle; it is also synthesized in the gastrointestinal tract, and may participate in the regulation of gastrointestinal motility and sensitivity, possibly by blocking nicotinic channels or Ca2+ activated K+ channels. Two small studies of the effects of melatonin in IBS patients reported improvement of abdominal pain and IBS symptom score or a reduction of rectal pain sensitivity. This appears to be a peripheral effect, since there was no alteration of sleep or anxiety or depression. The role of melatonin modulation in IBS requires further study. [57,58]

3-BENZODIAZEPINE RECEPTOR MODULATOR
Dexofisopam is the R-enantiomer of the non-sedating homophthalazine anxiolytic, tofisopam. It binds to 2,3-benzodiazepine receptors located in subcortical and hypothalamic regions. In animal models, dexofisopam reduced stimulation-induced colonic motility and visceral sensitivity. A 12-week, placebo-controlled, phase II study in patients with diarrhoea-predominant or alternating-IBS showed more months with adequate relief in the dextofisopam compared to the placebo group. The effects were most prominent within the first 4 weeks of treatment, and also included an improvement of stool consistency and a reduction of stool frequency. The drug was well tolerated, with only 3% reporting constipation; however, 12% of the patients experienced a worsening of abdominal pain (versus 4% in the placebo group). [55,56]

NEUROKININ-ANTAGONISTS
NK₁-receptors play a role in nociception, whereas NK₂ receptors have a greater influence on smooth muscle contractility and of NK₂-antagonists on gut motility. In a small pharmacodynamic study of IBS patients, the NK₁-receptor antagonist, ezlozipant, reduced the emotional response to rectosigmoid distension but did not significantly decrease rectal sensitivity. In healthy controls, the NK₂-receptor antagonist, nepudant, reduced contractile force and amplitude on migrating motor complexes in the small intestine and effectively antagonized the motility-stimulating effects of infused NK₄a.
The NK3 antagonist, talnetant, was tested in pharmacodynamics and clinical trials, and proved ineffective. [62,63]

**CHLORIDE CHANNEL MODULATORS**

### Cl− Channel (ClC2) Opener

Intestinal Cl− secretion is critical for intestinal fluid and electrolyte transport. In the gastrointestinal tract, chloride channels type 2, ClC2, has been found in gastric parietal cells, small intestinal and colonic epithelia. Lubiprostone is a prostane that acts as a selective ClC2 activator and increases intestinal water secretion. In a pharmacodynamic study, lubiprostone was shown to accelerate small bowel and colonic transit time in healthy volunteers. In several clinical trials, lubiprostone, 24 µg b.i.d., had positive effects on stool consistency, frequency and straining, and was safe and effective for treating constipation. Interestingly, lubiprostone accelerated colonic transit without accelerating ascending colon emptying, suggesting it affects distal colonic function. Lubiprostone also reduced abdominal pain and improved bowel dysfunction in IBS-C. Side effects of lubiprostone include diarrhea and nausea that is usually mild and transient. In January 2006, the FDA approved lubiprostone. [64]

### Guanylate Cyclase-c Agonist

Linaclotide is a novel agonist of the human guanylate cyclase-c (GC-C), a transmembrane protein located in the gut epithelium. Activation of the GC-C induces secretion of fluid, sodium and bicarbonate in the intestinal lumen. In animal and early human safety studies, linaclotide has been observed to increase stool frequency, decrease stool consistency and decrease visceral pain. A phase IIA pilot, randomised, controlled study shows efficacy of this drug in treatment of chronic constipation. Therefore, the drug seems to be promising for the treatment of IBS-C and chronic constipation. [65]

### Crofelemer

Crofelemer reduces excess chloride ion secretion via the CFTR channel. Crofelemer does not affect gut motility and is not absorbed systemically to any significant level. It has been used in the past to treat diarrhoea associated with intestinal secretion. In a dose-ranging study of crofelemer versus placebo b.i.d. for 12 weeks in 242 IBS-D patients, crofelemer did not produce improvement in the primary endpoint related to bowel function, urgency or adequate relief. On the other hand, female IBS-D patients exposed to the highest dose of 500 mg b.i.d. crofelemer had a higher proportion of pain and discomfort free days. These post hoc observations suggest that further studies are indicated to assess the visceral analgesic potential of crofelemer. [66]

### PROBIOTICS

Probiotics may have beneficial effects on altered colonic inflammation or barrier function that may be found in some IBS patients. The precise mechanism of action of probiotics is unclear and change of intraluminal milieu and modification of fermentation processes and gas production, inactivation of bile acids with decreased effect of endogenous bile acids on colonic fluid secretion and motility, and alteration of gastrointestinal motility may also contribute to the symptom improvement. A recent meta-analysis identified 19 randomised, controlled trials (18 papers) in 1650 IBS patients. Trial quality was generally good. Amongst 10 randomised, controlled trials involving 918 patients providing outcomes as a dichotomous variable, probiotics were significantly better than placebo with an NNT = 4 (95% CI, 3−12.5); however, there was significant heterogeneity (P = 68%, p = 0.001) and possible funnel plot asymmetry. Amongst 15 trials assessing 1351 patients that reported an improvement in IBS score as a continuous outcome, the standard mean difference was −0.34 (95% CI, −0.60 to −0.07); however, there was statistically significant heterogeneity (P = 79%, p = 0.001). These data suggest overall benefit for probiotics, but the precision of the NNT is uncertain. The safety profile of probiotics suggests they may be considered for the treatment of bloating and flatulence. [67]

### IMMUNE MODULATORS

#### Sodium Cromoglycate

Sodium cromoglycate is a mast cell stabilizer; there is experimental evidence of increased mast cell infiltration and greater proximity of mast cells to intramural nerve endings. Proteases that may arise from mast cells have been associated with activation of visceral algesia in experimental studies. Sodium cromoglycate alone or in association with dietary exclusion of suspected allergens has been tested in trials conducted in IBS-D and childhood IBS. [69]

#### ASA Compounds or Budesonide

Given the efficacy of budesonide in microscopic or collagenous colitis and the increasing evidence of immune activation in IBS, we anticipate more formal trials of these agents, especially in post-infectious IBS. In a recent meta-analysis, Chande et al. report that, amongst 3 trials with budesonide for collagenous colitis, the odds ratio for inducing a response was 12.32 (95% CI, 5.53−27.46), maintaining response was OR 8.82, and NNT of 2. Similar efficacy was observed for trials that included both collagenous and lymphocytic colitis (NNT of 3). Mesalazine and bismuth compounds were less effective for microscopic

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**Note:** The text continues with further discussions on specific treatments and therapies for IBS, including antibiotic treatments, probiotics, and immune modulators. The text also highlights the role of bacterial overgrowth in IBS and the potential benefits of probiotics in treating this condition. Experimental evidence suggests a role for probiotics in improving IBS symptoms, particularly for microscopic or collagenous colitis. The safety profile of probiotics suggests they may be considered for the treatment of bloating and flatulence, providing overall benefit for patients with IBS.

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**References:**

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69. [Link to reference]
colitis. However, a small, pilot clinical trial in IBS suggests that mesalazine reduced total number of immune cells and mast cells and pain severity score, and increased global relief relative to placebo treatment. These interesting and provocative data suggest that 5-ASA compounds deserve further study. [70]

NEW COMBINATION THERAPIES AVAILABLE TO TREAT IBS

Pantoprazole Sodium, Clidinium bromide and Chlordiazepoxidem in their combined Capsule dosage form

Literature survey revealed that the newer approaches to treat IBS is the combination of Pantoprazole sodium, clidinium bromide and chlordiazepoxide. The study was done to assess the IBS efficacy and safety of a combination of 20 mg of Pantoprazole sodium, 2.5mg of clidinium bromide and 5mg of chlordiazepoxide in comparison to Librax® (Clidinium bromide and chlordiazepoxide) in patients with acute uncomplicated IBS bloating flatulence. Results of completed the trial in Pantoprazole Sod. Clidinium Bromide, Chlordiazepoxide group while in Librax® completed the trial. Less side effects was noted in combination of Pantoprazole Sod. Chlordiazepoxide, clidinium bromide group while its Librax® appear side effects as upset stomach, drowsiness, weakness or tiredness, excitement, sleeplessness, dry mouth, heartburn, bloated feeling, eyes more sensitive to sunlight than usual, taste changes, changes in appetite. The available data support the evaluation of drug combination in a larger population as fixed dose combination.

ULRAX [Brand Name]

Composition

Pantoprazole -20mg
Chlordiazepoxide- 5 mg
Clidinium Bromide-2.5 mg

Pantoprazole

Benzimidazole derivative blocks the proton pump by reacting with (H+/K+)-ATPase enzyme by causing it's inhibition of action resulting long lasting inhibition of gastric acid secretion.

Proton Pump Inhibitor

Proton Pump Inhibitors binds Proton Pump (H+K+(-ATPase enzyme) that results in irreversible inhibition of acid secretion by the proton pump. Their duration of action is much longer because of their unique mechanism of action

- PPI only effective when proton pump is actively making acid.
- Proton pump is lost after PPI interaction.
- Proton pumps are reactivated after pumps are renewed.
- Peak serum level post dose 1.5 hrs.
- PPI must be closed before a meal for maximal efficacy.

Indications

- Gastric Ulcers
- Duodenal Ulcers
- NSAID Induced gastritis
- Helicobacter Pylori
- Reflux Esophagitis
- Zollinger Ellison’s Syndrome

Different Proton Pump Inhibitors Available in the Market

- Omeprazole
- Lansoprazole
- Pantoprazole
- Rabeprazole
- Esomeprazole

Dose

- 40 mg once daily for 6-8 week.
- 20 mg once daily for maintenance therapy for healed esophagitis low grade reflux esophagitis.
- Do not break, crush or chewtablets.

Advantages

- Less or no drug interaction.
- For H Pylori eradication.
- FDA approved ( Feb 2, 2000)
- No interaction with antacids

Drug Interactions

Not significant, Advise patient to avoid alcohol, products containing NSAIDs and foods that may cause an increase in Gl irritation.

Precautions

- Hepatic impairment
- Pregnancy

Chlordiazepoxide

Thus chlordiazepoxide is an anxiolytic & act as an agonist at specific benzodiazepine receptor, located on the membrane of GABA neuron which are inhibitory in nervous system, Chlordiazepoxide and GABA forms complex with chloride ion leads to stimulation of benzodiazepine receptors and potentiate the action of GABA which in turn controls the flow of chloride ions across neuron membrane, thereby relieves the patient from anxiety.

Pharmacokinetics

Peak Plasma Level -0.5 – 4 hrs.
Protein Binding -96%
Elimination -5 – 30 hrs.

Advantage over other similar drugs

- Produces a smooth long lasting effect.
- Preferred in chronic anxiety state.

Dose

15 – 100 (mg/day)
Uses
Treatment of moderate to severe depression associated with moderate to severe anxiety. Symptoms which respond in the first week of treatment are:
- Insomnia
- Feeling of guilt
- Agitation
- Psychic and somatic anxiety.
- Anorexia
- Muscle pain
- Alcohol withdrawal syndrome

Side effects
Drowsiness
CNS depression with concomitant alcohol intake

Contraindications
Hypersensitivity to either benzodiazepine or tricyclic antidepressants.
- During acute recovery phase following myocardial infarction.

Precautions
- Use cautions while driving or performing other tasks requiring alertness.
- Avoid alcohol and other CNS depressants

Clidinium Bromide
It is an antispasmodic agent, Antispasmodic agents relax smooth muscle in the gut and reduce propulsive contractions, decreasing postprandial abdominal pain, gas, bloating, and fecal urgency. It works through anticholinergic or antimuscarinic properties and may be used in an as-needed or in an anticipatory fashion.

CONCLUSION
The field of IBS therapeutics is vibrant, with greater understanding of neuroenteric mechanisms, effectors and transmitters in the brain–gut axis. These should provide opportunities for the development of new therapeutic agents for IBS treatment. For almost all of the drug classes described here, rigorous phase III trials and assessment of drug safety are eagerly awaited. Combination therapy more effective and safety rather than single drug therapy.

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Abbreviations
- IBS, irritable bowel syndrome;
- IBS-C, irritable bowel syndrome with predominant constipation;
- IBS-D, irritable bowel syndrome with predominant diarrhoea;
- FC, functional constipation;
- FD, functional diarrhoea;
- FAP, functional abdominal pain;
- OR, odds ratio;
- CI, confidence interval;
- SNRI, serotonin and norepinephrine reuptake inhibitor