New therapeutic approaches in irritable bowel syndrome

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Objective
To review advances in peripheral approaches to treatment of irritable bowel syndrome, with special focus on serotonergic agents, antibacterial agents, probiotics, secretion, opioid agents and others, specifically steroids and clonidine.

Serotonergic Agents for IBS
Pharmacodynamic studies show that 5-HT₃ antagonists (e.g., alosetron) retard transit in the colon, increase colonic compliance, and may reduce sensitivity, e.g. to distension. Alosetron is indicated for patients with severe diarrhea-predominant IBS. The 5-HT₄ agonists (e.g. tegaserod, ATI-7505) accelerate small bowel or colonic transit, and tegaserod may reduce colonic sensitivity. Tegaserod used to be approved for C-IBS and chronic constipation, but was recently withdrawn because of possible cardiovascular toxicity.

Novel observations include:

- A combined 5-HT₄ agonist/5-HT₃ antagonist (renzapride) also accelerates transit and loosens stool consistency.
- Alosetron is also efficacious in men.
- Cilansetron results in adequate relief of IBS symptoms in 3- or 6-month randomized controlled trials.
- Alosetron was initially withdrawn from the market and is now available under restricted conditions only in the U.S. Its side effects are constipation in 20-30% of patients and ischemic colitis in 0.1 to 0.15% of patients. The causal relationship with ischemic colitis is unclear, since there is an increased incidence of ischemic colitis in IBS. Nevertheless, the timing of events (26% of ischemic colitis within 7 days of alosetron treatment and 58% within 30 days) suggests a causative relationship. Ischemic colitis is not a class effect of 5-HT₃ antagonists and there is no clear experimental basis for its occurrence in IBS patients exposed to alosetron. Even with perfusion pressures of 60 mmHg, autoregulation in mucosal blood flow increases oxygen extraction and maintains normal colonic mucosal oxygen uptake. There is no experimental basis for linking severe constipation with the development of ischemic colitis.

- The 5-HT₄ agonist, tegaserod, was recently suspended. While no coronary ischemic events were observed in 7,031 placebo patients, there were event rates (5.5 per 1000 patient years) with tegaserod (compared to general population rates of 4-5.1 for women and 10.6-12.5 for men, per 1000 PY). There was no pattern to time to event (range 2-63 days/median 35) and no dose relationship, and events occurred primarily in patients with evidence of established and/or symptomatic CV disease at baseline.

- The novel 5-HT₄ agonist, ATI-7505, is a derivative of cisapride. It accelerates gastric emptying and colon transit. Chemically, it is not metabolized by CYP 3A4 (potentially reducing risk of drug interactions), and early studies suggest it is safer from a cardiac arrhythmia perspective.

- SSRIs or tricyclic antidepressants potentially act peripherally via SERT-inhibition in the ENS (not demonstrated with paroxetine except for accelerated SB transit); venlafaxine reduces colonic tone and sensation, possibly via a noradrenergic effect.

Antibacterial/Probiotics
A large randomized controlled trial of rifaximin suggests it provides greater benefit over placebo in a 10-week follow-up period. Probiotics are promising, especially for flatulence, bloating and borborygmi. Mechanisms of action...
include improved immune function (e.g. IL-10/IL-12 ratios are low at baseline in IBS; following therapy with *L. salivarius* UCC4331 and *B. infantis* 35624, they increase to almost normal). The combination probiotic VSL#3 is effective for relief of flatulence in IBS with significant bloating. Other potential mechanisms of action of probiotics are effects on motility, secretion, mucus secretion, sensation, and fermentation.

**Secretion**

A chloride channel (ClC-2) activator (lubiprostone) and a guanylate cyclase C agonist (linaclotide) induce enterocyte secretion by activating surface mechanisms, accelerate colonic transit, and alter stool consistency. Lubiprostone has been approved for chronic constipation, and both drugs show efficacy in phase IIB studies of C-IBS. Lubiprostone is derived from prostones. Linaclotide is a 14 AA peptide (similar to guanylin, 15 AAs, and uroguanylin, 16 AAs).

**Opoid Agents**

Three major opiate receptors (µ, δ, κ) have potential for use in IBS. The receptors are widely distributed in the central and peripheral nervous system; µ-agonists (codeine, morphine) reduce nociception (central effect) and slow down GI transit (peripheral effect). The peripheral κ-agonist, fedotozine, was shown to increase pain thresholds and improve abdominal pain in IBS. Asimadoline, a new peripheral κ-agonist, had some pharmacodynamic efficacy, and it was tested in an on-demand randomized controlled trial versus placebo for pain episodes of moderate severity in 100 females with IBS. The average pain reduction 2 hours post-treatment was not significantly different between the groups. However, post-hoc analyses suggest it was effective in IBS-Alt. Further studies are needed. Alvimopan, a new peripheral µ-antagonist, has impressive effects on colonic transit, but recent imbalance in the numbers of patients developing cardiac adverse effects in trials of opiate bowel dysfunction has led to its suspension.

**Others: Steroids and Clonidine**

Corticosteroids are no better than placebo in the treatment of post-infectious IBS. Clonidine was efficacious in a small randomized controlled trial versus placebo, with a 0.1 mg bid (but not 0.05 mg bid) dose being superior to placebo.

**Conclusion**

Peripheral targets to therapy in IBS may be effective, and further studies are needed to more fully understand their benefit: risk ratio.