Irritable Bowel Syndrome: A Multifaceted World Still to Discover

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INTRODUCTION

- IBS is a functional disorder of the gastrointestinal tract characterized by chronic abdominal pain and altered bowel habits.

- Approximately 40 percent of individuals who meet diagnostic criteria for IBS do not have a formal diagnosis .

- In the United States, IBS accounts for 25 to 50 percent of all referrals to gastroenterologists.

EPIDEMIOLOGY

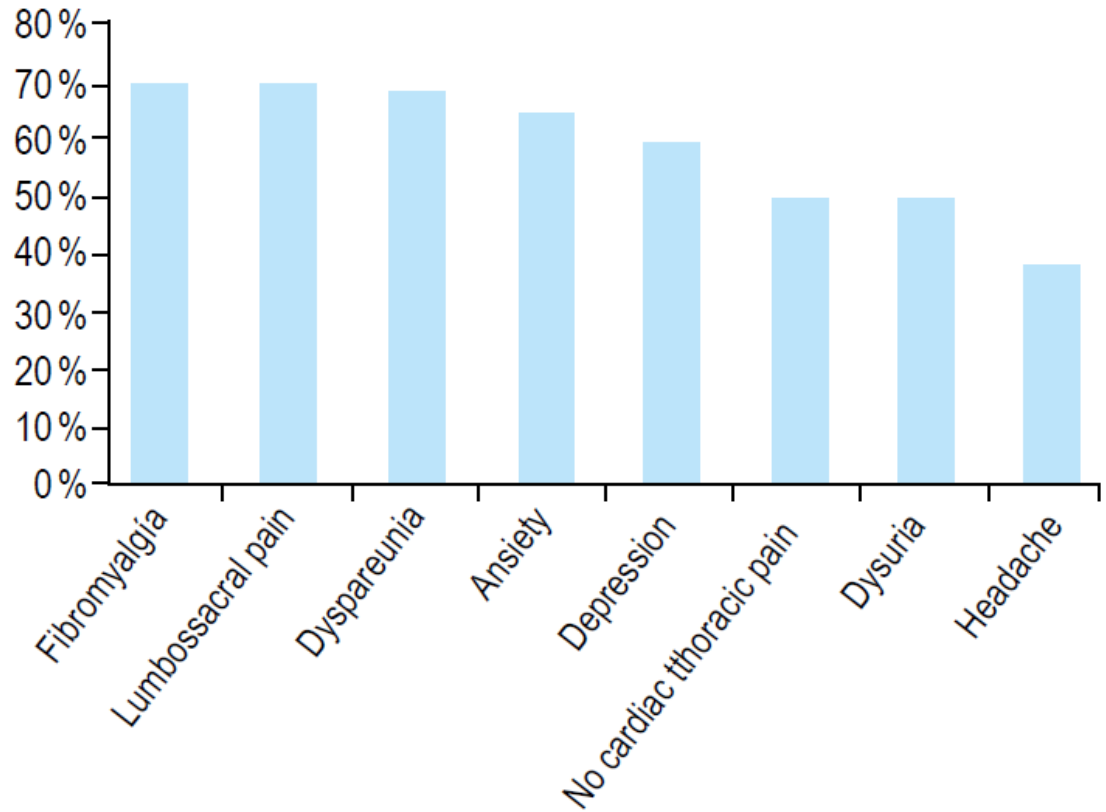
- In a meta-analysis that included eight international studies, the pooled prevalence of IBS was estimated to be 11 percent, with wide variation by geographic region.

- The overall prevalence of IBS in females was higher as compared with males.

- Females may be more likely to have constipation-predominant IBS as compared with males.

Associated conditions

- fibromyalgia
- chronic fatigue syndrome
- gastroesophageal reflux disease
- functional dyspepsia
- non-cardiac chest pain
- psychiatric disorders including major depression, anxiety, and somatization


80 %
70 %
60 %
50 %
40 %
30 %
20 %
10 %
0 %
Fibromyalgia
Lumbossacral pain
Dyspareunia
Ansiety
Depression
No cardiac tthoracic pain
Dysuria
Headache

CLINICAL MANIFESTATIONS

- **Chronic abdominal pain**:
  - usually described as a cramping sensation with variable intensity and periodic exacerbations
  - The location and character of the pain can vary widely.
  - The severity of the pain may range from mild to severe.
  - The pain is frequently related to defecation.
  - While in some patients abdominal pain is relieved with defecation, some patients report worsening of pain with defecation.
  - Emotional stress and meals may exacerbate the pain.
  - Patients with IBS also frequently report abdominal bloating and increased gas production in the form of flatulence or belching.
- **Altered bowel habits:**
  - Diarrhea
  - Constipation

DIAGNOSIS

- A clinical diagnosis of IBS requires the fulfillment of symptom-based diagnostic criteria and a limited evaluation to exclude underlying organic disease.

- Diagnostic criteria: In the absence of a biologic disease marker, several symptom-based criteria have been proposed to standardize the diagnosis of IBS.

- The most widely used among them are the Rome IV criteria.

Rome IV criteria for IBS

- According to the Rome IV criteria, IBS is defined as recurrent abdominal pain, on average, at least one day per week in the last three months, associated with two or more of the following criteria :

- Related to defecation

- Associated with a change in stool frequency

- Associated with a change in stool form (appearance)

Table 1. Diagnosis criteria for IBS (Roma IV).

Recurrent abdominal pain, at least once a week in the last 3 months, associated with 2 or more of the following criteria.

- Associated with defecation;
- Associated with changing stool frequency;
- Associated with changes in the appearance of stools;
- symptoms mentioned should begin at least 6 months before diagnosis

IBS subtypes

- IBS with predominant constipation
- IBS with predominant diarrhea
- IBS with mixed bowel habits

- Other criteria : The Manning criteria include relief of pain with bowel movements, looser and more frequent stools with onset of pain, passage of mucus, and a sense of incomplete emptying .

Pathophysiology

- The pathophysiology of IBS remains uncertain .
- It is viewed as a disorder resulting from an interaction among a number of factors.
- Despite multiple investigations, data have been conflicting and no abnormality has been found to be specific for this disorder.

- IBS, has often been considered rather inappropriately as psychogenic in the past.

- Though psychological issues are important comorbidities in a proportion of IBS patients, the evidences are far from enough to label this condition as psychogenic only.

- In the recent past, evidences are emerging that underscores the concept supporting pure psychogenic theory of IBS and suggest this disorder to be rather micro organic.

- Accordingly, a move of Rome IV Committee attempting to delete the term “functional” and designating these to be disorders of “gut-brain interaction” rather than that of “brain-gut interaction,” it emphasizes the importance of the gut over the brain in the pathogenesis.

- The treatment of the condition largely depends on the subtyping of the condition such as constipation– or diarrhea–predominant syndrome and the underlying pathophysiology that has undergone substantial paradigm shift during the recent years.

- The recognition of the biological factors in the pathogenesis of IBS is a significant paradigm shift in the recent time.

- This is somewhat similar to the progress in the pathogenesis of peptic ulcer disease from psychological factor to acid to Helicobacter pylori infection.

- The traditional focus has been on alterations in gastrointestinal motility and on visceral hypersensitivity.

- More contemporary studies have considered the role of :
  - inflammation
  - alterations in fecal flora
  - bacterial overgrowth
  - food sensitivity
  - genetic predisposition

GASTROINTESTINAL MOTILITY

- Abnormalities observed include:
  - increased frequency and irregularity of luminal contractions
  - prolonged transit time in constipation-predominant IBS
  - an exaggerated motor response to cholecystokinin and meal ingestion in diarrhea-predominant IBS

VISCERAL HYPERSENSITIVITY

- increased sensation in response to stimuli is a frequent finding in IBS patients.

- Perception in the GI tract results from stimulation of various receptors in the gut wall.

- These receptors transmit signals via afferent neural pathways to the dorsal horn of the spinal cord and ultimately to the brain.

- It is unclear whether heightened sensitivity of the intestines to normal sensations is mediated by the local GI nervous system, by central modulation from the brain, or by some combination of the two .

- Other factors may contribute to visceral hyperalgesia:
  - serotonin
  - kinins
  - activation of an NMDAreceptor

INTESTINAL INFLAMMATION

- Mucosal immune system activation characterized by alterations in particular immune cells and markers in diarrhea-predominant IBS and post infectious IBS.

- Elevated levels of plasma pro inflammatory interleukins have been observed in patients with IBS.

- Mast cells: An increased number of mast cells in the terminal ileum, jejunum, and colon of IBS patients

- Studies: a correlation between abdominal pain in IBS and the presence of activated mast cells in proximity to colonic nerves

- Lymphocytes: Increased numbers of lymphocytes in the colon and small intestine in patients with IBS

ALTERATION IN FECAL MICROFLORA

- Emerging data suggest that the fecal microbiota in individuals with IBS differ from healthy controls and vary with the predominant symptom.

- Additional studies are needed to validate these observations.

- In view of potential microflora alterations in IBS, it is possible that patients with diarrhea-predominant IBS would benefit from probiotics, which influence the composition and metabolism of the microflora.

BACTERIAL OVERGROWTH

- Small intestinal bacterial overgrowth (SIBO) is associated with an increased number and/or type of bacteria in the upper gastrointestinal (GI) tract.

- However, data reporting an association between irritable bowel syndrome (IBS) and SIBO have been conflicting.

FOOD SENSITIVITY

- The role of food in the pathophysiology of IBS is not clear.
- Some patients with IBS report worsening of symptoms after eating and perceive food intolerance to certain foods.
- Multiple factors have been considered to contribute to food sensitivity in patients with IBS.
- Investigations have centered on food specific antibodies, carbohydrate malabsorption, and gluten sensitivity.

GENETICS

- Familial studies : genetic susceptibility in some patients with IBS.

- Familial studies: modest contribution of genetics to the development of IBS .
- Studies of twins: contradictory; some studies show a higher concordance rate for IBS in monozygotic twins compared with dizygotic twins

- One study found that having a parent with IBS was a greater independent predictor of IBS than having an affected twin, suggesting that the familial nature of IBS could be due to social learning, as well as genetics .

- Associations between specific genes and IBS are under investigation.
- Some genotyping studies: an association between IBS and polymorphisms in the serotonin transporter gene, resulting in altered serotonin reuptake efficacy that affects intestinal peristalsis.
- Other studies have not confirmed this association.
- Another study: some patients with IBS may be genetically predisposed to an altered pattern of anti-inflammatory cytokine interleukin production.

PSYCHOSOCIAL DYSFUNCTION

- Psychosocial factors may influence the expression of IBS.
- In a study of patients with symptoms of IBS patients reported more lifetime and daily stressful events than control groups .
- Some studies report a positive association between IBS and abuse, although one paper did not confirm this relationship.
- Another study found that, compared with controls, patients with IBS exhibit increased anxiety, depression, phobias, and somatization.

- One unifying hypothesis concerning the role of stress and psycho neuroticism in IBS is based upon corticotropin releasing factor (CRF), a peptide released from the paraventricular nucleus and considered to be a major mediator of the stress response.

- Data suggest that overactivity in the brain CRF and CRF-receptor signaling system contributes to anxiety disorders and depression.

- Intravenous administration of CRF increases abdominal pain and colonic motility in IBS patients to a higher degree than normal controls.

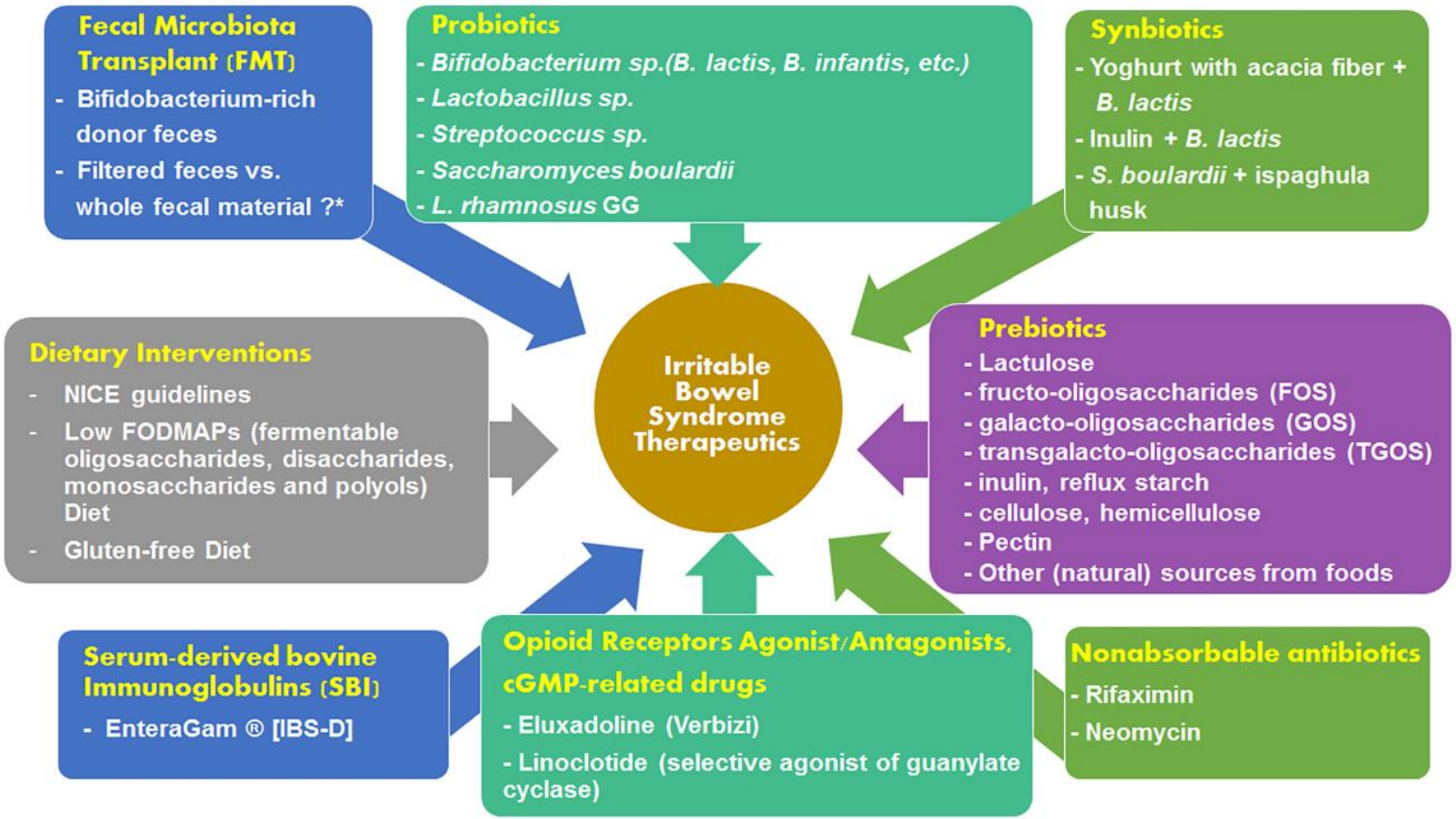
- Furthermore, this response can be blunted by the administration of a CRF receptor antagonist with no effect on the hypothalamus-pituitary-adrenal axis .

RECOMMENDATIONS

- Initial management: Establishment of the clinician-patient relationship and continuity of care are critical to the management of all patients with IBS.
- In patients with mild and intermittent symptoms, we suggest not using pharmacologic therapy for initial management.
- We begin with lifestyle and dietary modification (eg, exclusion of gas-producing foods; and in select cases, lactose and gluten avoidance) and a trial of psyllium in patients with IBS-C.

- In patients with mild to moderate symptoms who fail to respond to lifestyle and dietary modification and in patients with moderate to severe symptoms of IBS that affect quality of life, we use pharmacologic therapy as adjunctive treatment.

- Since IBS presents as a complex of symptoms, pharmacologic treatment should be based on the predominant symptom with incremental changes in therapy at two- to four-week intervals.


Fecal Microbiota Transplant (FMT)
- Bifidobacterium-rich donor feces
- Filtered feces vs. whole fecal material ?*
Probiotics
- Bifidobacterium sp.(B. lactis, B. infantis, etc.)
- Lactobacillus sp.
- Streptococcus sp.
- Saccharomyces boulardii
- L. rhamnosus GG
Synbiotics
- Yoghurt with acacia fiber + B. lactis
- Inulin + B. lactis
- S. boulardii + ispaghula husk
Dietary Interventions
- NICE guidelines
- Low FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) Diet
- Gluten-free Diet
Irritable Bowel Syndrome Therapeutics
Prebiotics
- Lactulose
- fructo-oligosaccharides (FOS)
- galacto-oligosaccharides (GOS)
- transgalacto-oligosaccharides (TGOS)
- inulin, reflux starch
- cellulose, hemicellulose
- Pectin
- Other (natural) sources from foods
Serum-derived bovine Immunoglobulins (SBI)
- EnteraGam ® [IBS-D]
Opioid Receptors Agonist/Antagonists, cGMP-related drugs
- Eluxadoline (Verbizi)
- Linoclotide (selective agonist of guanylate cyclase)
Nonabsorbable antibiotics
- Rifaximin
- Neomycin

TREATMENT: FROM CHOICE BASED ON SYMPTOMS TO STRATEGY BASED ON PATHOPHYSIOLOGICAL MECHANISMS

- The widespread availability of noninvasive clinical tests that can appraise the mechanisms responsible for symptom generation in IBS provides the opportunity to advance the practice from treatment based on symptoms to individualization of treatment guided by pathophysiology and clinically identified biomarkers.

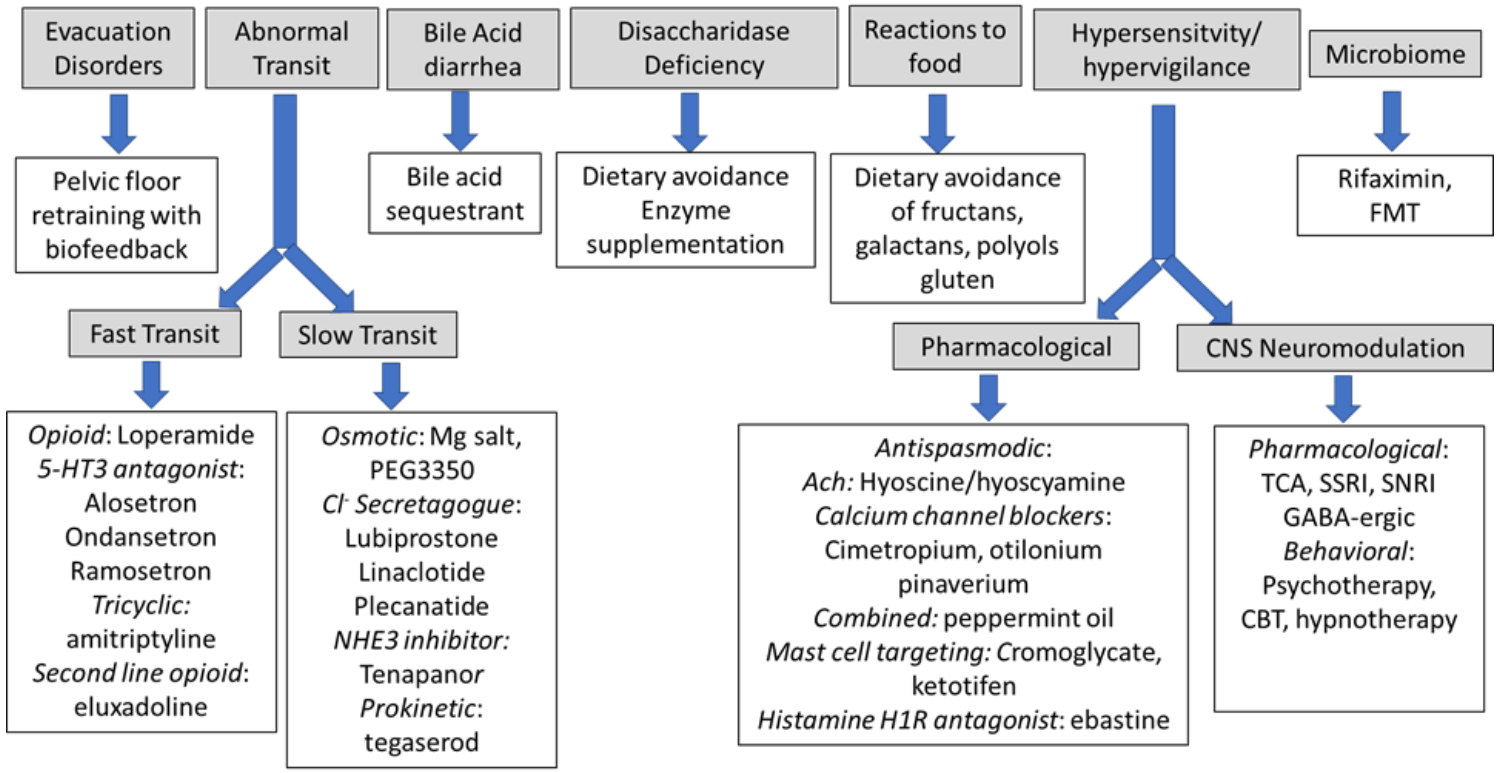
Table 2. Symptom specific pharmacological treatment for IBS.

Predominant symptom	Treatment
Pain and flatulence	- Antispasmodics (Diciclomine 10-20 mg 4 times a day, Otilonium 40-80 mg 2-3 days, Mebeverine 135 mg 3 times a day). - Peppermint oil (enteric coating capsules, 250-750 mg 2-3x / day). - Tricyclic antidepressant (Desipramine 25-100 mg, Amitriptyline 10-50 mg qhs, Paroxetine 10-40 mg qd, Sertraline 25-100 mg qd, Citalopram 10-40 mg qd). - Activators of the chloride channel (Lubiprostone 8 µg 2x day) Ag Guanylate cyclase C agonists (Linaclotide 290 mg 4x per day). - 5-HT 3 antagonists (Alosetron 0.5-1 mg twice daily, Ondansetron 4-8 mg 3 times daily). - Avoid milk, dairy products, grains and vegetables.
Constipation	- Regular physical activity. - Diet high in fiber (25 to 30 g / day) preferably soluble fibers plus increase in water intake. - Psyllium (up to 30 g / d in divided doses). - Osmotic laxatives PEG (17-34 g / d). - Channel activator channels (Lubiprostone 8 µg 2x day). - Guanylate cyclase C agonists (Linaclotide 290 mg 4 times a day). - Tegaserod 6 mg twice daily, before meals, for 4-6 weeks.
Diarrhea	- Anti-diarrheic analogous to opioids (Loperamine 2-4 mg - maximum 16 mg / day). - Diet poor in FODMAPs. - Seque Bile salt sequestrants (Colestyramine 2 g 2-3x day, Colestipol 2 g 2-4x / day and Colesevelan 625 mg 2-4x / day). - Probiotics. - Antibiotics (Rifamixin 550 mg 3 times a day for 14 days). - 5-HT 3 antagonists (Alosetron (0.5-1 mg twice daily; Ondansetron (4-8 mg 3 times daily). - Antagonist and mixed opioid agonist (Eluxadolin 100 mg).
Alternating with diarrhea and constipation	- Mixed treatment.

Application of pathophysiology - actionable biomarker approach to managing patients with IBS

Pathophysiology	**Diagnostic test**	**Actionable biomarker**
Evacuation disorders	Anorectal manometry, balloon expulsion, ? defecography	Spastic pelvic floor or descending perineum
Transit	Radiopaque markers, scintigraphy, wireless motility capsule	Accelerated transit at 24h or delaye transit at 48h on scintigraphy
Sensation and central nervous system hypervigilance	Rectal sensation to balloon distension, e.g., during anorectal manometry (ARM)	Rectal sensation recorded during ARM as symptoms: first sensation, gas, urge, pain
Psychosocial factors	HAD, IBS-QOL, PAC-SYM, PAC-QOL	Anxiety, depression, general pain conditions
Bile acid diarrhea	Serum 7αC4, primary or total bile acids (single or 48h stool), 75-SeHCAT retention	Increased bile acid synthesis or excretion
Disaccharidase deficiency	Lactose-hydrogen breath test, duodenal biopsy measurements of disaccharidases	Lactose and sucrose intolerance wit objective test results
Coeliac disease	TTG-IgA, anti-gliadin IgA	Diagnostic tests for coeliac disease
Local immune reactions to foods or mucosal inflammation	Fecal calprotectin, careful dietary history, specific inquiry on fructans and galactans, consider gluten intolerance	Colonoscopy for microscopic colitis experimental studies, screen for HLA DQ2/8 with gluten intolerance in absence of proven celiac disease
Microbiome	N/A	N/A

Therapeutic choices guided by pathophysiology and biomarkers



- The availability of several noninvasive clinical tests can appraise the mechanisms responsible for symptom generation in IBS.

- The basic molecular mechanisms contributing to these pathophysiology are increasingly recognized, offering opportunities to intervene with medications directed specifically to food components, receptors and potentially the microbiome.

- the opportunity to advance the practice from treatment based on symptoms to individualization of treatment guided by pathophysiology and clinically identified biomarkers.

Psychotropic drugs

- Antidepressants are useful for IBS.
- TCA and SSRI are recommended for patients with IBS depending on the pathophysiology, taking into consideration side effects.
- Anxiolytics are useful for treating IBS.
- Relieving anxiety is related to improving the symptoms of IBS in highly anxious patients.
- Anxiolytics should be used for a short period while taking into account the risk of dependency.

- Antidepressants have analgesic properties independent of their mood improving effects .

- TCAs, via their anticholinergic properties, also slow intestinal transit time, which may provide benefit in diarrhea-predominant IBS.

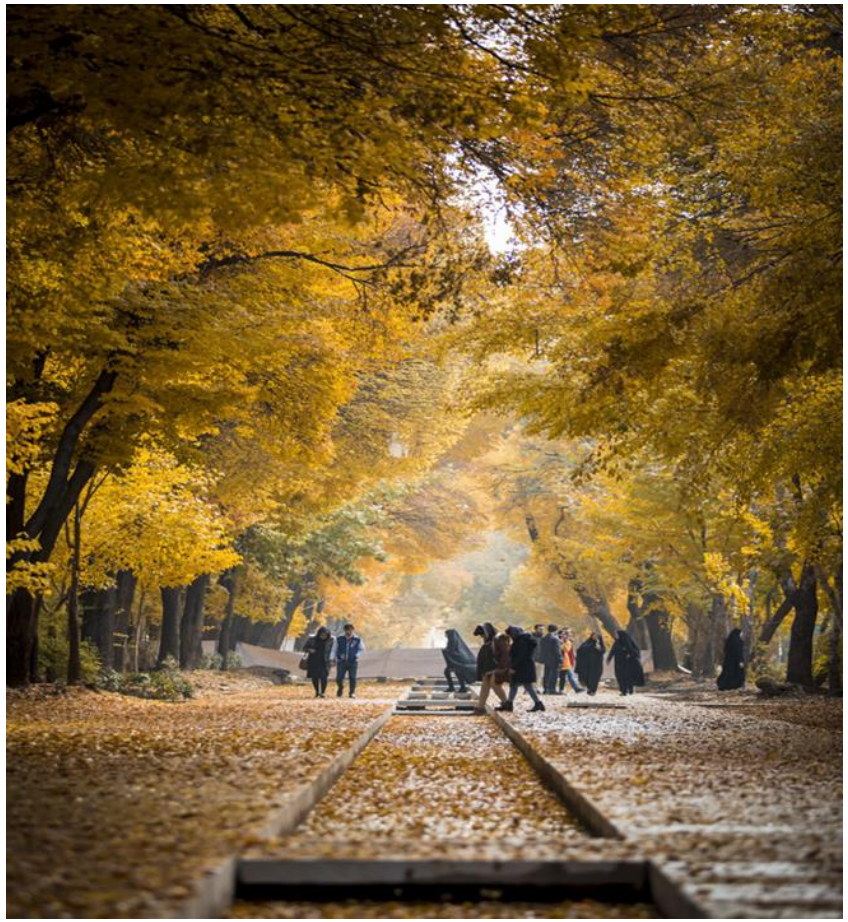
- Amitriptyline, nortriptyline, desipramine, and imipramine can be started at a dose of 10 to 25 mg at bedtime.

- For the treatment of abdominal pain in IBS, antidepressants should be started at low doses.

- There is little evidence for the usefulness of antipsychotics or mood stabilizers in patients with IBS.

- Anti-psychotics and mood stabilizers may be used in IBS patients to control abdominal pain or mental state in severe refractory cases.

- Psychotherapy is effective in treating patients with IBS, include:
  - CBT
  - relaxation
  - hypnotherapy
  - mindfulness-based stress reduction (MBSR)
  - stress management
  - psychodynamic therapy



Have a good time