IBS

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Epidemiology

- **Irritable bowel syndrome is a common functional gastrointestinal disorder that manifests as abdominal pain or discomfort and diarrhea or constipation, or both.**

- **The definition of IBS has evolved over time, from a diagnosis of exclusion to the symptom-based diagnostic criteria including Manning, Rome I, Rome II, and Rome III criteria.**

Epidemiology

- **IBS accounts for 10% to 15% of primary care visits**

  25% to 50% of gastroenterology referral visits

- **Only limited proportion of subjects suffering from IBS seek medical attention for this condition.**

- **Prevalence rates in various studies have varied between 3 and 32 per 100.**

Epidemiology

Table 1
Prevalence of irritable bowel syndrome in Western countries

First Author,[Ref.] Country	Year	N	Case Definition	% IBS Overall	% IBS Men	% IBS Women
Talley,[4] USA	1987	835	Manning 2	15.8	15.8	18.2
			Manning 3	12.8	12.1	13.6
Hahn,[13] USA	1989	42392	Manning 2	3	—	—
			Rome I	12		
Drossman,[14] USA	1990	5430	Rome I	9.4	7.7	14.5
Saito,[15] USA	1992	643	Manning 3	15.7	13.5	17.7
			Rome I	8.4	8.4	8.4
Mearin,[9] Spain	2001	2000	Manning	10.3		
			Rome I	12.1		
			Rome II	3.3	1.9	4.6
Brommelaer,[16] France	2002	8221	Manning	2.5	1.7	3.1
			Rome I	2.1	1.4	2.8
			Rome II	1.1	0.9	1.3
Thompson,[17] Canada	2002	1149	Rome II	12.1	8.7	15.2
Boyce,[18] Australia	1997	2910	Manning	13.6		
			Rome I	4.4	4.4	9.1
Jones,[7] England	1992	1620	Manning	21.6	18.7	24.3
Agreus,[19] Sweden	1988	1290	Rome I	12.5	—	—
Wilson[20] UK	2003	4807	Rome II	8.1	—	—
Hungin,[21] Europe (UK, France, Germany, Italy, Holland, Belgium, Spain, Switzerland)	2003	41984	Overall	9.6	7.1	12
			Manning	6.5		
			Rome I	4.2		
			Rome II	2.9		
Kennedy,[22] UK	1998	3179	Manning 3	17.2	10.5	22.9
Icks,[7] Germany	2002	1281	Patient report	12.5	—	—
Kay,[8] Denmark	1994	4581	Symptom criteria	6.6	5.6	7.7
Heaton,[24] UK	1992	1896	Manning 3	9.5	5.0	13.0
			Manning 2	21.6	18.7	24.3
Hillila,[11] Finland	2004	3650	Manning 2	16.2	13.1	19.2
			Manning 3	9.7	8.3	11.2
			Rome I	5.5	5.1	6.1
			Rome II	5.1	5.1	5.3
Jung,[25] USA	2004	2273	Rome III	11	8	14
Olafsdottir,[26] Iceland	1996	1336	Manning 2	31	—	—
	2006	799	Rome III	10		
			Manning 2	32		
			Rome II	5.0		
			Rome III	13		

Epidemiology

- **The incidence rate :**
  - **196 cases per 100,000 person-years in study on American population**
  - **200 to 300 per 100,000 people in a study from Europe.**
- **If only half seek care, the observed incidence can be doubled to 400 per 100,000 per year and then multiplied by a 20-year disease duration to get a prevalence of 12%.**

Demographic predictors of IBS

- **The odds of having IBS are higher in women.**
- **More prevalent in younger patients.**
- **More prevalent in lower socioeconomic groups.**

Resource use in IBS

- **Burden of illness studies estimate that there are 3.6 million physician visits in the United States annually for IBS**
- **IBS care consumes over $20 billion in both direct and indirect expenditures.**
- **Patients with IBS consume over 50% more health care resources than matched controls without IBS.**

Resource use in IBS

- **Much of the cost of care in IBS arises from sequential and redundant diagnostic tests, invasive procedures, and abdominal operations.**
- **patients with IBS are three times more likely than matched controls to undergo cholecystectomy**
- **Nearly 25% of colonoscopies performed in patients younger than 50 years of age are for IBS symptoms**

Resource use in IBS

- **Employees with IBS are absent 3% to 5% of the work-week, and report impaired productivity 26% to 31% of the week, rates that exceed those of non-IBS control employees by 20%.**
- **Patients with impaired productivity have more extraintestinal comorbidities : chronic fatigue syndrome, fibromyalgia, interstitial cystitis, and more disease-specific fears and concerns.**

Quality of life

- **IBS patients have the same physical HRQOL as patients with diabetes, and a lower physical HRQOL compared with patients who have depression or gastroesophageal reflux disease.**

- **The health utility of severe IBS is similar to that of Class 3 congestive heart failure and rheumatoid arthritis.**

Quality of life

- **This HRQOL decrement can be severe enough to raise the risk of suicidal behavior is some cases.**

- **Data from several studies indicate that in patients with IBS, HRQOL decreases in parallel with increasing symptom severity.**

Overlap with Other Functional Gastrointestinal Disorders

- **Many population-based and clinical studies have reported the associations with other diseases, specifically other FGIDs.**

- **GERD and symptomatic bronchial hyper-responsiveness occurred more frequently together with IBS than expected.**

Overlap with Extra intestinal Disorders

- **IBS patients make 2 or 3 times as many non-GI health care visits as control subjects.**
- **Non-GI nonpsychiatric disorders documented to be associated with IBS include:**
  - **chronic fatigue syndrome (51%)**
  - **chronic pelvic pain (50%)**
  - **temporomandibular joint disorders (64%)**

Overlap with Extra intestinal Disorders

- **In referred patients with IBS, psychiatric disorders have also been reported to be very common: especially major depression, anxiety, and somatoform disorders.**

Natural history of IBS

- **IBS is considered a chronic stable disorder that may wax and wane for years.**
- **Substantial symptom fluctuation among the GI symptom complexes with increasing prevalence over time.**
- **IBS is not associated with any increase in mortality.**

Table 5 | Development of IBS, retained, lost and developed in 10 years

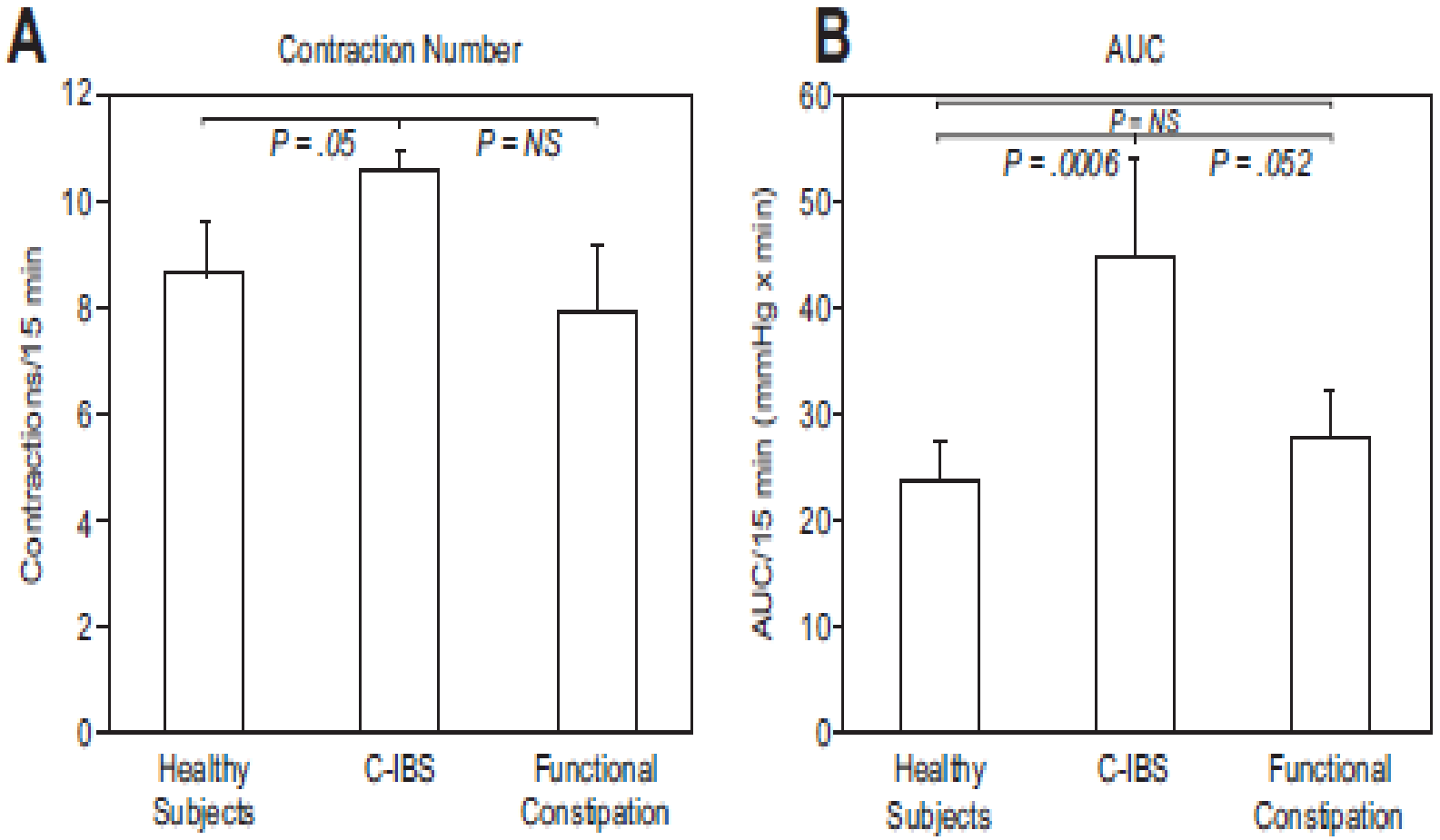
	n	Never IBS (%)	Lost IBS (%)	Retained IBS (%)	Developed IBS (%)
Manning	674	56.2	12.2	19.1	12.5
Self-report	621	74.9	8.5	8.2	8.4
Rome III	749	81.4	5.7	4.3	8.7

Pathophysiology

- **Multifactorial and varies from patient to patient.**
- **Disturbances of motor function in the small intestine and colon and smooth-muscle dysfunction in other gut and extraintestinal regions.**
- **Abnormalities of sensory function in visceral and somatic structures, which may relate to peripheral sensitization or altered central nervous system processing of afferent information.**

Pathophysiology

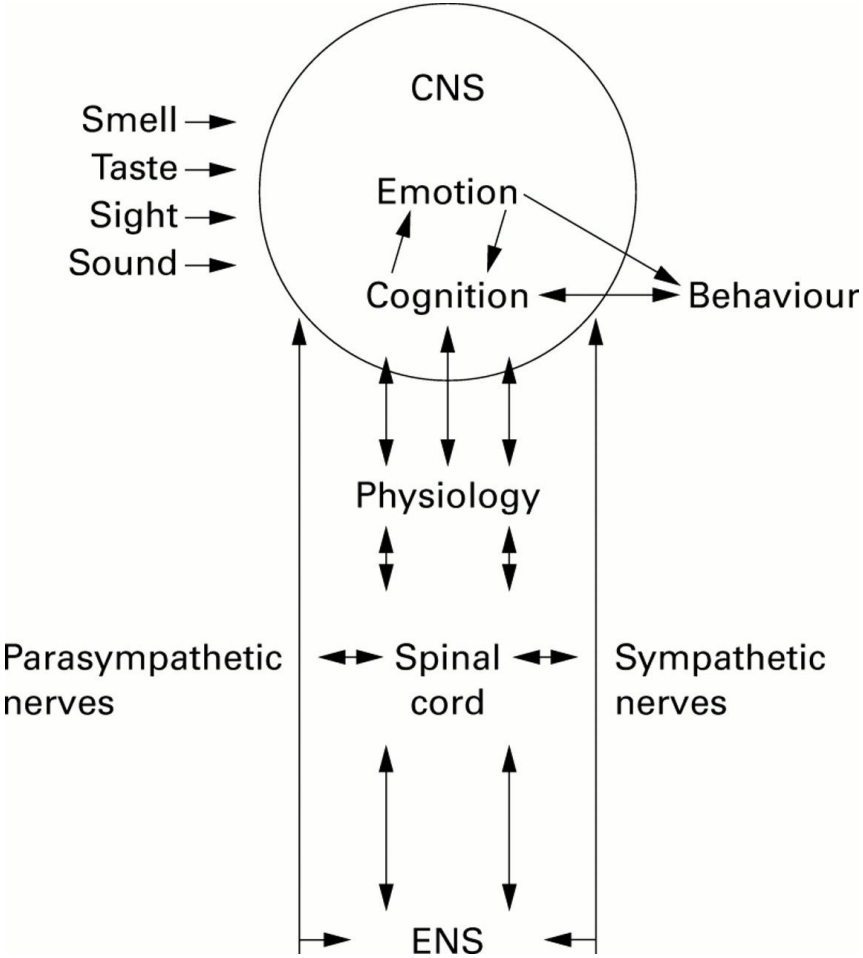
Motor dysfunction



Altered visceral sensory activity

- **Alterations in visceral and somatic perception are prevalent in IBS but have uncertain roles in inducing the different symptoms of this disorder.**
- **Some patients with IBS experience normal physiologic events, not normally perceived by healthy individuals, as being uncomfortable or painful**

Pathophysiology



Brain-gut interactions

- **Results from PET and fMRI investigations taken suggest that patients with IBS show significant disruptions of CNS activity related to attention, arousal, emotional, and autonomic responses to gut stimulation.**
- **CNS imaging studies have shown alterations in brain structure in IBS**
- **Evoked potential recordings in functional dyspepsia and IBS show shorter waveform latencies and increased waveform amplitudes, consistent with defects in visceral afferent pathways.**

Psychosocial distress

- **Numerous studies confirm a high degree of psychosocial dysfunction in IBS.**
- **Psychiatric disturbances can be shown in most patients with IBS in tertiary practice, but also in patients managed in primary care and in individuals with IBS who do not seek care.**
- **Rates of suicidal behavior are increased 2- to 4-fold in IBS.**

Psychosocial distress

- **Exposure to wartime early in life increased the risk of developing IBS in another investigation.**
- **Increases in patients with IBS compared with healthy controls have been reported for:**

major depression
somatization disorder
generalized anxiety disorder
panic disorder
neuroticism
PTSD
phobias
hypochondriasis
hostility
concealed aggression
suppressed anger

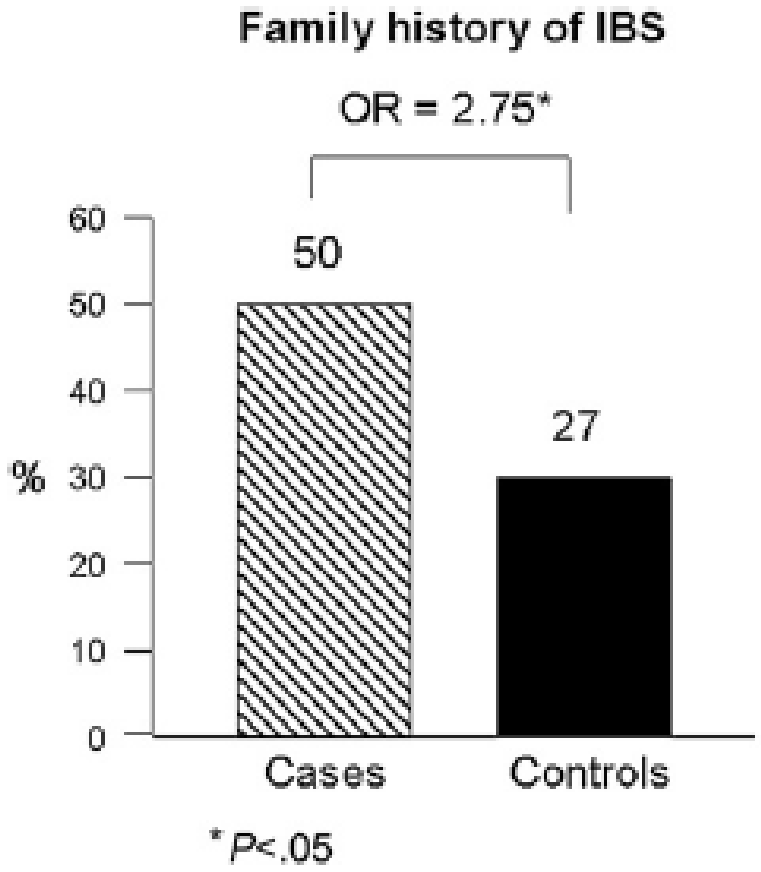
Role of Stress

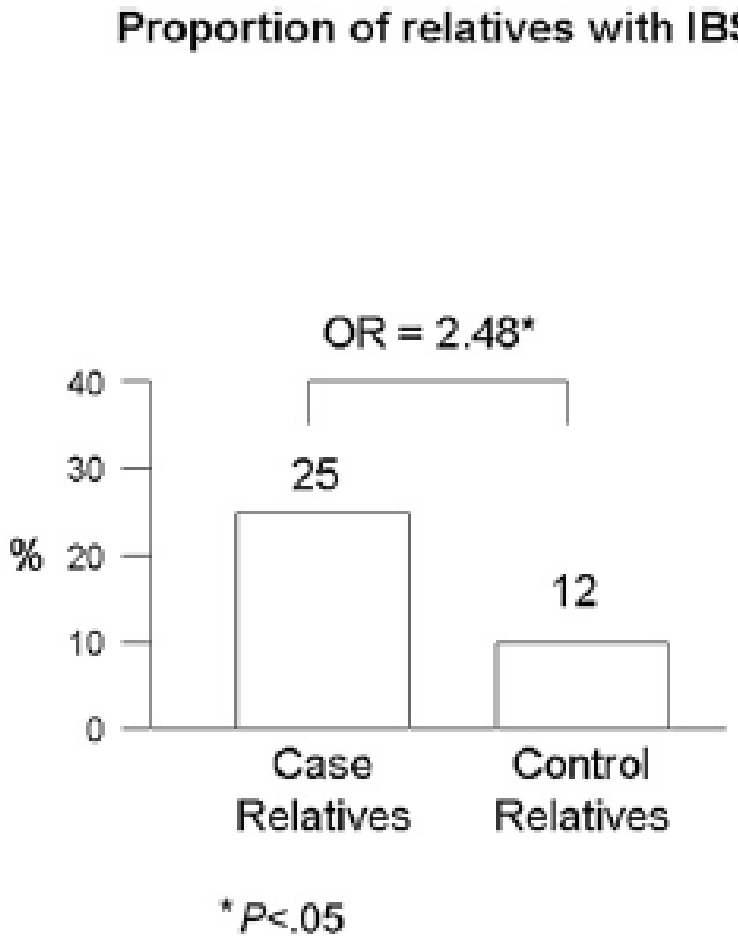
- **Psychiatric disturbances usually predate or occur concurrently with the onset of bowel symptoms, indicating that emotional illness is not a consequence of IBS.**
- **IBS shows a strong association with reports of psychological stress.**
- **Previous stressful life events, such as loss of a parent, marital difficulties, maladaptive family interactions, and career changes, are more common in patients with IBS than in healthy individuals or patients with organic disease**

Psychosocial distress

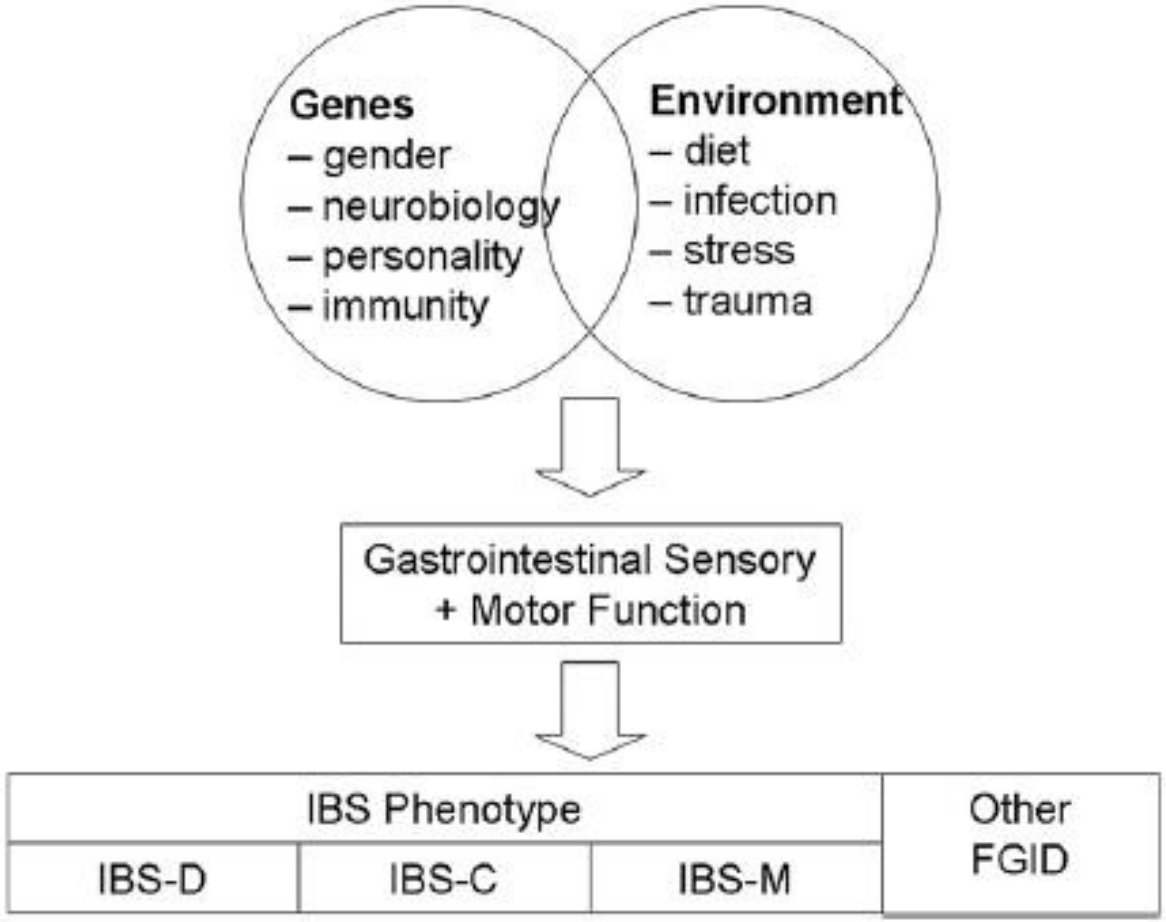
- **Sleep disturbances are reported by most patients with IBS.**
- **IBS has been associated with histories of sexual and/or physical abuse including verbal aggression, exhibitionism, sexual harassment, sexual touching, and rape**

The Role of Genetics in IBS

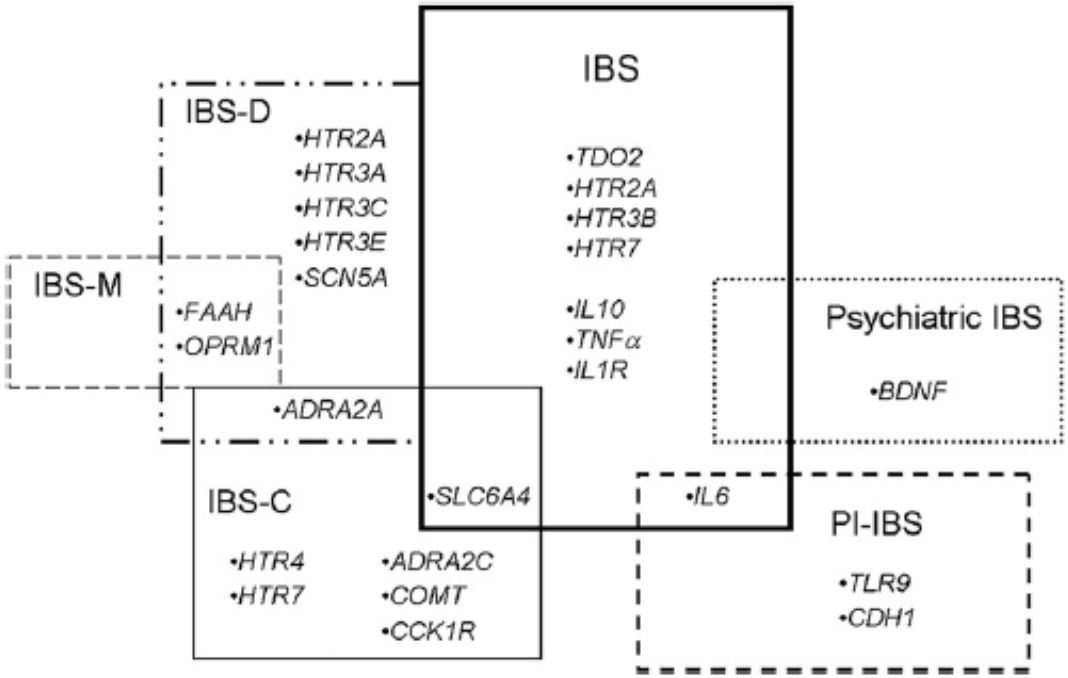




The Role of Genetics in IBS



Summary of positive gene associations, by IBS type and subtype



Food and IBS

Food and IBS

- Patients associate their symptoms with the ingestion of certain foods, combinations of foods, or a meal itself.
- More than 60% of IBS patients report worsening of symptoms after meals, 28% of these within 15 minutes after eating and 93% within 3 hours.
- Many patients identify specific trigger foods :most commonly dairy, fructose, wheat products, and caffeine.
- There is little evidence that IBS patients with food-related complaints are suffering from a true FA

Elimination diets

- Response rates to exclusion diets have ranged from 15% to 71%.
- Dairy products, wheat, and eggs the most commonly implicated food items.

Inflammation and Microflora

- The human intestinal tract is composed of more than 500 different species of bacteria.
- By adulthood most humans reach an established balance of type and numbers of bacteria that is unique to a given individual.
- There is growing evidence that supportes a new hypothesis for IBS based on alterations in intestinal bacterial composition.

Inflammation and Microflora

- Gut microbes interact with the gut mucosal immune system through innate and adaptive mechanisms.
- Altered flora can lead to changes in the intestinal epithelial barrier.
- Neuroimmune and pain modulation pathways may be influenced by the flora.
- Changing flora can increase food fermentation and subsequent intestinal gas production.
- Bile acid malabsorption can result from expansion of gut flora into the small bowel

Inflammation and Microflora

- Culture studies have consistently demonstrated a paucity of *Lactobacillus* and *Bifidobacterium.*
- Balb/c mice infected with a probiotic *L acidophilus* strain had elevated expression of several intestinal pain receptors that led to decreased visceral sensitivity.

Postinfectious IBS

- Numerous studies have shown that IBS can be precipitated by an episode of acute gastroenteritis.
- 10% of subjects who have AGE develop IBS, with a summary odds ratio of 6 to 7.
- The 2 most significant of these are duration/severity of gastroenteritis and female sex.

Antibiotic Treatment of IBS: Support for a Gut Flora Hypothesis

TARGET 1 and TARGET 2: In these studies, rifaximin was effective in improving IBS based on abdominal pain, stool consistency, bloating, and the primary outcome measure of global relief.

Probiotics in IBS

- It seems reasonable that probiotics should restore a “healthy” gut microbiota and alleviate IBS symptoms.
- Unfortunately, the numerous controlled trials of probiotics in IBS have shown mixed results.
- The data are strongest for *Bifidobacterium* and *Lactobacillus* strains.

Diagnosing IBS

Box 1
Differential diagnosis of suspected IBS

- IBS
- Celiac disease
- Disaccharide maldigestion
- Food intolerance
- Small intestine bacterial overgrowth
- Bile acid malabsorption
- Chronic pancreatitis
- Enteric neuropathy or myopathy
- Gastrointestinal infection
- Inflammatory bowel disease (IBD)
- Thyroid dysfunction (hyper or hypo)
- Malignancy
- Metabolic disease
- Medication side effects
- Other functional gastrointestinal disorders

Symptom-Based Diagnostic Criteria for Irritable Bowel Syndrome

Rome II criteria[6]

Symptoms present for at least 12 weeks in 1 year (need not be consecutive). Patient must experience abdominal pain with at least 2 of the following features:

- Relieved by defecation
- Onset of pain associated with change in stool frequency
- Onset of pain associated with change in stool form

Rome III criteria[7]

Symptoms present for at least 3 days per month in the last 3 months (with symptom onset at least 6 months previously) with at least 2 of the following features:

- Pain improved with defecation
- Onset of pain associated with change in stool frequency
- Onset of pain associated with change in stool form

Diagnosing IBS

- Most patients who fulfill Rome III suffer with IBS.
- Because the condition is so common, there are likely many patients who do not fulfill symptom-based criteria but end up with a diagnosis of IBS.

Diagnosing IBS

- The most recent guidelines encourage clinicians to make a positive diagnosis of IBS based on a thorough history, using symptom-based criteria and considering the presence or absence of specific alarm features.

- In the absence of alarm features, routine use of diagnostic imaging studies, blood tests, or stool studies are not advised.

Alarming clinical or historical features

Box 2
Classic alarm features to note in suspected IBS

Unintentional weight loss

Iron deficiency anemia

Family history of IBD

Family history of CRC

Family history of celiac disease

Rectal bleeding

Nocturnal diarrhea

Data from Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. An evidence-based systematic review on the management of irritable bowel syndrome. Am J Gastroenterol 2009;104(Suppl 1):S1–35.

Diagnosing IBS

Table 2
Pretest probability and prevalence of frequently excluded organic diseases in patients with IBS and population norms

Disease	Prevalence Among Patients with IBS (%)	Prevalence Among General Population (%)
Colitis/IBD	0.51–0.98	0.3–1.2
Colorectal cancer	0–0.51	0–6
Thyroid dysfunction	4.2	5–9
Gastrointestinal infection	0–1.5	N/A
Lactose maldigestion	38	26
Celiac disease	0.4–4	0.7

Routine Blood Tests

- CBC, CMP, TFT, ESR and CRP are often ordered on initial evaluation of patients with suspected IBS.
- In patients in tertiary centers, the likelihood of identifying organic disease with routine laboratory tests seems to be no greater in patients with IBS (and absent alarm features) than in the general population.

Testing for Celiac Disease

- The prevalence of celiac disease in individuals with suspected IBS was computed to be 4 times greater than in non-IBS controls.
- The ACG IBS Task Force recommended testing for celiac disease in patients presenting with nonconstipated IBS symptoms.
- The tests include EMA or TTG levels.

Colonoscopy

- Recommendations of the ACG IBS Task Force are to perform colonoscopy in patients with IBS older than 50 years and those with alarm features.
- When colonoscopy is performed in patients with suspected IBS-D random mucosal biopsies Should be preformed to rule out microscopic colitis.

Breath Testing SIBO or Carbohydrate Maldigestion

- Bloating is one of the most common symptoms associated with IBS, occurring in more than 75% of patients .
- Known symptom improvement from antibiotic and probiotic therapy.
- Association of IBS-like symptoms with lactose or fructose ingestion.
- Whether or not a correlation exists between IBS and SIBO remains controversial.

Breath Testing SIBO or Carbohydrate Maldigestion

- The ACG Task Force indicated that there is insufficient evidence to support the routine use of breath tests for SIBO.
- In patients reporting food-related symptoms, trials of lactose- or fructose-restricted diets are a rational and pragmatic therapeutic approach.

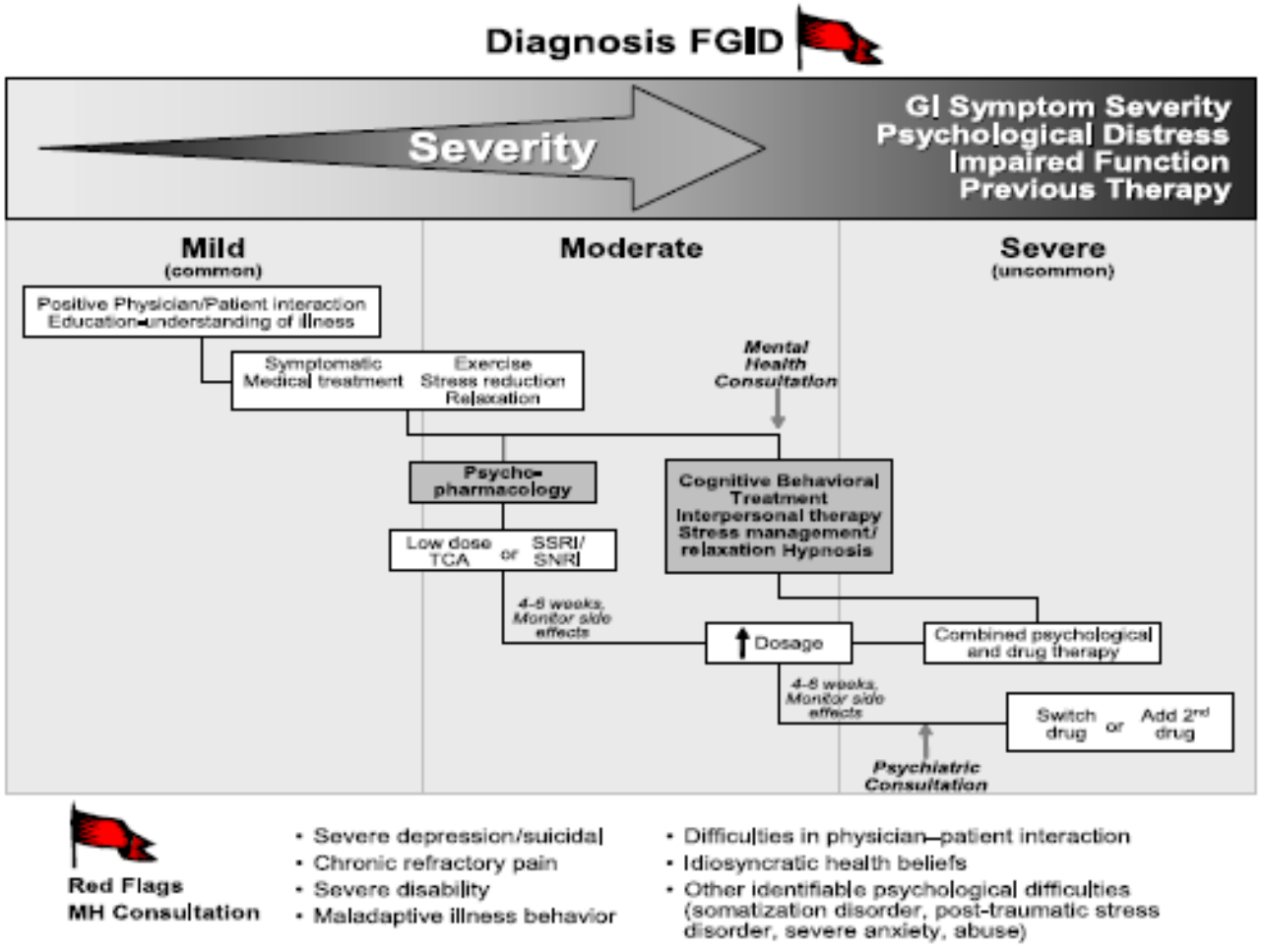
Stool Studies

- The ACG IBS Task Force does not recommend the routine use of stool studies to evaluate for infectious causes of IBS symptoms in the absence of a relevant travel history or specific alarm features (severe uncontrollable diarrhea, hematochezia, weight loss).

Stool Studies

- Several neutrophil-derived proteins excreted in the feces, such as lactoferrin and calprotectin, are highly sensitive and specific markers of inflammatory activity in the gut.
- Because of the high negative predictive value of these tests in ruling out intestinal inflammation, clinicians use them as a noninvasive screen for IBD in their patients with typical IBS symptoms.

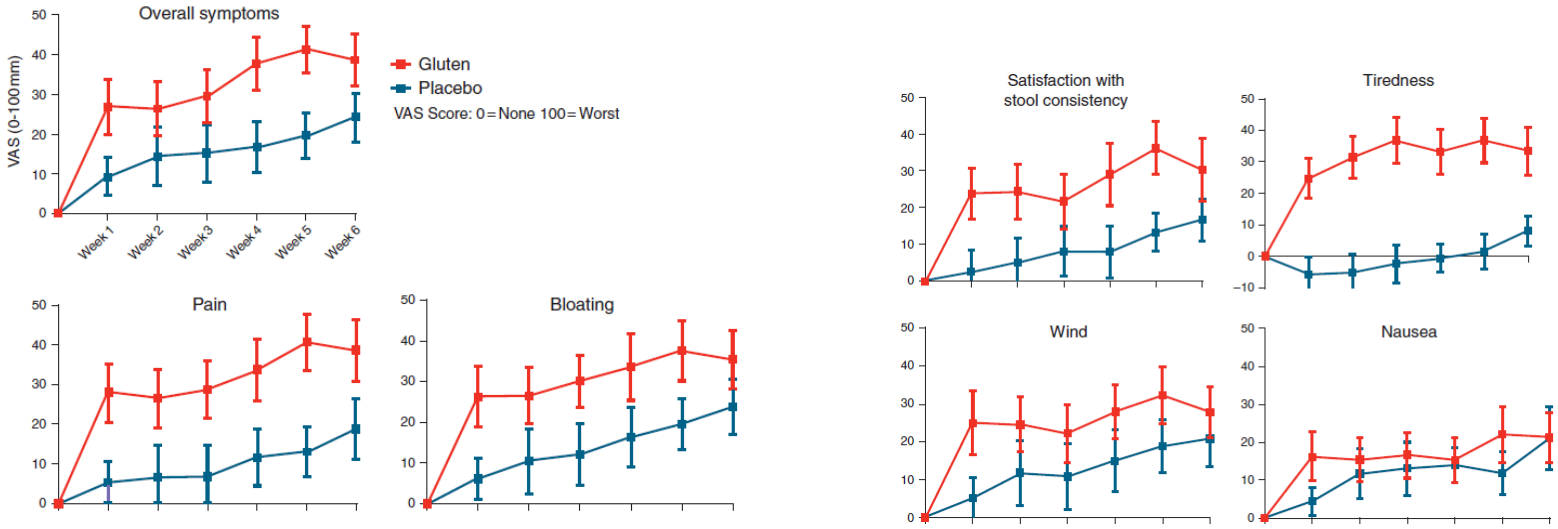
Treatment


Diagnosis FGID
Severity
GI Symptom Severity
Psychological Distress
Impaired Function
Previous Therapy
Mild
(common)
Moderate
Severe
(uncommon)
Positive Physician/Patient interaction
Education-understanding of illness
Symptomatic
Medical treatment
Exercise
Stress reduction
Relaxation
Mental Health Consultation
Psycho-pharmacology
Low dose TCA
or
SSRI/ SNRI
Cognitive Behavioral Treatment
Interpersonal therapy
Stress management/ relaxation Hypnosis
4-8 weeks, Monitor side effects
Dosage
Combined psychological and drug therapy
4-8 weeks, Monitor side effects
Switch drug
or
Add 2nd drug
Psychiatric Consultation
Red Flags
MH Consultation
• Severe depression/suicidal
• Chronic refractory pain
• Severe disability
• Maladaptive illness behavior
• Difficulties in physician–patient interaction
• Idiosyncratic health beliefs
• Other identifiable psychological difficulties (somatization disorder, post-traumatic stress disorder, severe anxiety, abuse)

Gluten Restriction

Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease: A Double-Blind Randomized Placebo-Controlled Trial

Jessica R. Biesiekierski, B Appl Sci[1], Evan D. Newnham, MD, FRACP[1], Peter M. Irving, MD, MRCP[1], Jacqueline S. Barrett, PhD, BSc, MND[1], Melissa Haines, MD[1], James D. Doecke, BSc, PhD[2], Susan J. Shepherd, B Appl Sci, PhD[1], Jane G. Muir, PhD, PGrad Dip(Dietetics)[1] and Peter R. Gibson, MD, FRACP[1]



FODMAP Restriction

- *F*ermentable *O*ligo-, *D*i-, and *M*ono-saccharides *A*nd *P*olyols diet.
- Family of poorly absorbed, short-chain carbohydrates, which are highly fermentable in the presence of gut bacteria.

Table 3
Foods rich in FODMAPs by category

FODMAP	Fructose	Polyols	Lactose	Fructans and Galactans
High FODMAP food sources	Apples, pears, watermelon, honey, fruit juices, dried fruits, high-fructose corn syrup	Sugar alcohols (sorbitol, maltitol, mannitol, xylitol, and isomalt), stone fruits, avocado, mushrooms, cauliflower	Milk (cow, goat, sheep), yogurt, soft cheeses (ricotta, cottage)	Wheat, rye, garlic, onions, artichokes, asparagus, inulin, soy, leeks, legumes, lentils, cabbage, Brussels sprouts, broccoli
Alternative lower FODMAP food sources	Citrus, berries, bananas, grapes, honeydew, cantaloupe, kiwifruit	Sweeteners, such as sugar, glucose, other artificial sweeteners not ending in "-ol" (sucralose, aspartame)	Lactose-free dairy products, rice milk, hard cheeses	Starches, such as rice, corn, potato, quinoa. Vegetables, such as winter squash, lettuce, spinach, cucumbers, bell peppers, green beans, tomato, eggplant

All nonprocessed meats are generally low in FODMAPs.

FODMAP Restriction

- The low FODMAP diet differs from most other elimination diets in that no initial attempts are made to identify specific culprit foods.
- In persons who respond to the full elimination phase, specific FODMAP food groups are sequentially reintroduced, allowing determination of the particular foods that the patient cannot tolerate.

Peripherally Acting Therapies for the Treatment of Irritable Bowel Syndrome

- Most of these peripheral acting agents are primarily targeted at individual symptoms.
- The evidence supporting the use of these agents in IBS is largely anecdotal.
- Serotonergic agents and the chloride channel activator lubiprostone have shown efficacy in treating symptoms of IBS.

Fiber supplements and laxatives

- Dietary fiber supplements represent a heterogeneous group of complex carbohydrates that are resistant to hydrolysis during digestion.
- These non-digested products result in increased stool bulk and water content, effectively decreasing stool consistency and increasing stool frequency.

Fiber supplements

- The results of the 6 trials comparing psyllium and ispaghula with placebo were pooled, yielding a total of 321 patients with IBS, with 161 in the treatment arm.
- 52% of patients treated with psyllium had persistent IBS symptoms after treatment compared with 64% of those receiving placebo
- RR of symptoms not improving with psyllium was 0.78 compared with placebo with a NNT of 6.

Laxatives

- The use of laxatives in the treatment of IBS-C has evolved from their known effect on the symptoms of constipation.
- Only polyethylene glycol PEG has been assessed in the treatment of IBS.
- laxatives were shown to improve stool frequency–but not abdominal pain–in one small sequential study in adolescents with IBS-C.(PEG).

Antidiarrheals

- Studies have reported accelerated small bowel and colon transit times as well as exaggerated motility patterns in those with IBS-D.

- Only loperamide has been evaluated in RCTs for the treatment of IBS.

Antidiarrheals

- The antidiarrheal agent loperamide is not more effective than placebo at reducing abdominal pain or global symptoms of IBS, but is an effective agent for treatment of diarrhea, improving stool frequency and stool consistency.

- RCTs with other antidiarrheal agents have not been performed. Safety and tolerability data on loperamide are lacking.

Antispasmodics

- Abdominal pain or discomfort is a cardinal feature of IBS.
- Observation and clinical studies have suggested that an exaggerated motility response of the small bowel and colon to environmental stimuli may be responsible for the symptoms experienced in IBS.
- For this reason antispasmodics have been and remain a mainstay of therapy for the symptoms of IBS.

Antispasmodics

- These agents are directed at those subgroups of IBS, with a predominant symptom of abdominal pain and stool patterns that are either mixed or more diarrheal in nature.

- The anticholinergic properties of these agents restrict their usefulness in clinical practice.

Antispasmodics
ACG Task Force

- Certain antispasmodics (hyoscine, cimetropium, and pinaverium) may provide short-term relief of abdominal pain/discomfort in IBS .
- Evidence for long-term efficacy is not available.
- Evidence for safety and tolerability are limited.

Antispasmodics

- These agents are likely to be most effective in those patients with IBS with a predominant symptom of abdominal pain.
- These agents can worsen constipation and should therefore be used cautiously in patients with IBS with a predominance of constipation.

Serotonergic agents

- Serotonin (5-HT) is the neurotransmitter primarily produced and stored in enterochromaffin cells located throughout the intestinal epithelium.
- 95% of total body concentration of 5-HT resides in the gastrointestinal tract.
- Acting through the intrinsic and extrinsic afferent nervous system of the GIT, 5-HT plays an important role in various aspects of gastrointestinal sensory, secretory, absorptive, and motility function.

Serotonergic agents

- **Receptor agonists of 5-HT_1** :
  improve gastric accommodation
  slow gastric emptying
  stimulate activity of the MMC
- **Receptor antagonists of 5-HT_3** :
  slow small bowel transit
  decrease intestinal secretion
  decrease colonic tone and transit.

Serotonergic agents

- **Agonists of the 5-HT_4 receptor:**

  accelerate gastric emptying

  improve gastric accommodation

  accelerate small bowel transit

  accelerate colonic transit

  decrease visceral sensation

- **No 5-HT_1 or 5-HT_4 receptor agents are approved for the treatment of IBS in the United States or Canada**

Serotonergic agents

- Alosetron is more effective than placebo at relieving global IBS in male and female patients with IBS with diarrhea.
- Potentially serious side effects include constipation and colonic ischemia.
- The benefits and harms balance for alosetron is most favorable in women with IBS-D who have not responded to conventional therapies.

Chloride channel activator

- Lubiprostone is the only chloride channel activator with FDA approval for the management of IBS-C.
- Lubiprostone in a dose of 8µg twice daily is more effective than placebo in relieving global IBS symptoms in women with IBC-S
- Lubiprostone is contraindicated in patients with mechanical bowel obstruction and should be avoided in patients with preexisting diarrhea.

Centrally Acting Therapies for Irritable Bowel Syndrome

- The use of psychotropic agents for FGIDs has grown significantly in the past 2 decades.
- Every 1 in 8 patients with IBS is offered an antidepressant.
- A recent meta-analysis showed significantly decreased relative risk of persistent IBS symptoms with antidepressant treatment.
- On average, 3 to 4 patients needed to be treated with an antidepressant to improve 1 patient's symptom.

Centrally Acting Therapies

Potential benefits for use of psychopharmacological agents in FGIDs

Central effects:

1. Alters central pain perception: analgesia or antihyperalgesia.
2. Therapeutic effects on mood: to manage general anxiety, hypervigilance, symptom-related anxiety, agoraphobia, and increased stress responsiveness.
3. Treatment of associated psychiatric disorders: depression, posttraumatic stress disorder, somatization.
4. Treatment of associated sleep disturbances.

Peripheral effects:

1. Peripheral analgesic effects: alters visceral afferent signaling.
2. Effect in GI physiology (motility and secretion) via effects on cholinergic, noradrenergic, and serotonergic pathways.
3. Smooth muscle effects on viscera, eg, gastric fundic relaxation.

Psychotropic agents

- Four major classes of psychotropic agents of interest in IBS are :

  tricyclic antidepressants

  selective serotonin reuptake inhibitors

  serotonin-norepinephrine reuptake inhibitors

  atypical antipsychotics.
- TCAs and SSRIs have been most widely studied.
- SNRIs are gaining popularity for treatment for other chronic pain conditions such as fibromyalgia and are likely to be further explored in IBS and other FGIDs.

Tricyclic Antidepressants

Recent studies on use of TCAs in IBS

Citation	Drug	Sample	Study Design	Outcome
Drossman et al,[30] 2003	Desipramine	Women; moderate to severe IBS (n = 431)	12 weeks Multicenter, comparator-controlled RCT	Per-protocol analysis: desipramine superior to placebo; intention-to-treat analysis: not significant. With dosages up to 150 mg, there is no relationship between total dose or plasma level and the clinical response.[30]
Otaka et al,[39] 2005	Amitriptyline	Refractory Functional Dyspepsia (n = 14)	4 weeks Double-blind RCT	Amitriptyline showed 66.7% efficacy in famotidine-failed group and 75.0% efficacy in the mosapride-failed group.
Morgan et al,[40] 2005	Amitriptyline	Women with severe IBS (n = 19)	4 weeks RCT	During stress, amitriptyline reduced pain-related cerebral activations in the perigenual ACC and the left posterior parietal cortex.
Vahedi et al,[41] 2008	Amitriptyline	IBS-D (n = 50)	8 weeks Double-blind RCT	Lower incidence of loose stool and feeling of incomplete defecation. Increased report of "loss of all symptoms" compared with placebo (68% vs 28%).
Bahar et al,[42] 2008	Amitriptyline	Adolescent IBS (n = 33)	13 weeks Double-blind RCT	Improved overall quality of life. Reduction in IBS diarrhea. Improved abdominal pain.
Abdul-Baki et al,[43] 2009	Imipramine	IBS (n = 107)	12 weeks RCT	Higher global symptom relief. Improvements in SF-36 scales.

Abbreviations: ACC, anterior cingulate cortex; IBS, irritable bowel syndrome; RCT, randomized controlled trial; TCA, tricyclic antidepressant.

Selective Serotonin Reuptake Inhibitors

Recent studies on the use of SSRIs in IBS

Citation	Drug	Sample	Study Design	Outcome
Creed et al,[31] 2003	Paroxetine	Severe IBS (n = 257)	3 months Multicenter Parallel RCT	Improved physical component of SF-36 (QOL) scale. Decreased health care costs at 1-year follow-up. Decreased severity and number of days in pain.
Kuiken et al,[28] 2003	Fluoxetine	IBS (n = 40)	6 weeks Double-blind placebo-controlled RCT	Improved abdominal pain score (53% vs 26%) showing trends toward significance. Patients on fluoxetine were more likely to continue with the drug (84% vs 37%). Significant reduction in abdominal pain in patients with gut hypersensitivity.
Tabas et al,[32] 2004	Paroxetine	IBS (n = 110)	12 weeks Double-blind placebo-controlled RCT	Improved overall well-being. Increased desire to continue medication. Less IBS-related anxiety. Decreased food avoidance. Benefit seen in nondepressed.
Vahedi et al,[33] 2005	Fluoxetine	IBS-C (n = 44)	12 weeks Double-blind RCT	Decreased abdominal discomfort and bloating. Increased frequency of bowel movements and decreased stool consistency. Insignificant reduction in the mean number of symptoms per patient.

Selective Serotonin Reuptake Inhibitors

- SSRI's improve global well-being and some GI-specific symptoms.
- SSRI's have anxiolytic properties and can target social phobia, agoraphobia, and symptom-related anxiety.
- may augment the analgesic effects of other agents (TCAs);

  Treat psychiatric comorbidities.

  Diarrhea may be a side effect, and SSRIs may benefit patients with constipation.

Serotonin-Norepinephrine Reuptake Inhibitors

- The SNRI's may potentially be as effective as the TCAs, owing to their dual blockade of reuptake of NE and 5HT receptors.
- Duloxetine is the only SNRI agent that has been studied for the treatment of IBS.
- Duloxetine (60 mg daily dosage) appeared to be effective for pain, severity of illness, quality of life, loose stool, work and family disability, and anxiety.

Atypical Antipsychotics

- Are beneficial in lower dosages for patients with FGIDs because of their analgesic properties (alone or in synergism with antidepressants) and their sedative and anxiolytic effects.

Centrally Acting Therapies

Class effects of psychotropic agents

	TCAs	SSRIs	SNRIs
Agents	Amitriptyline Imipramine Doxepin Desipramine Nortriptyline	Fluoxetine Sertraline Paroxetine Citalopram Escitalopram	Duloxetine Venlafaxine
Dose range	10–50 mg 10–200 mg (Desipramine)	10–40 mg 25–100 mg (Sertraline)	30–90 mg (Duloxetine) 75–225 (Venlafaxine)
Potential benefits			
Peripheral pain modulation	++	?	++
Central anti-nociception	+++	+	+++
Anxiolysis			
Motility			
Visceral pain	+	+++	+
Sleep	++	+	?
Psychiatric comorbidities	+++ ++ ++ (high doses)	? — +++	? ? +++
Adverse effects	Sedation Constipation Dry mouth/eyes Weight gain Hypotension Sexual dysfunction	Insomnia Diarrhea Night sweats Weight loss Agitation Sexual dysfunction	Nausea Agitation Dizziness Fatigue Liver dysfunction
Time to action	Few days–2 weeks (low doses) 2–6 weeks (high doses)	4–6 weeks	4–6 weeks
Efficacy	Good	Moderate	Not well studied
Dose adjustments	Required	Usually Not	Required

Behavioral therapies

"You won't get me to sit on the couch and discuss my obsession until I straighten things up, Dr. Hunter."

Behavioral therapies

- Establish a rational model of illness: reframe maladaptive beliefs.
- Reduce overresponsiveness to stress, eg, stress and autonomic reactivity.
- Reduce or modify maladaptive psychological responses: catastrophizing, symptom-specific anxiety, shame/guilt.
- Reduce or modify maladaptive behaviors, eg, agoraphobia, seeking diagnostic studies.

Behavioral therapies

- CBT has a direct effect on global IBS symptom improvement, independent of its effects on distress.

- Symptom benefit with CBT may be mediated through changes in neural activity of cortical-limbic regions that subserve hypervigilance and emotion regulation.

Relaxation Training

- Relaxation techniques are to train patients to counteract physiologic squeal of stress or anxiety.
- Five recent studies have assessed efficacy of relaxation therapy in IBS.
- Relaxation alone or in combination with CBT and other therapies can be beneficial for IBS symptoms.

Hypnotherapy

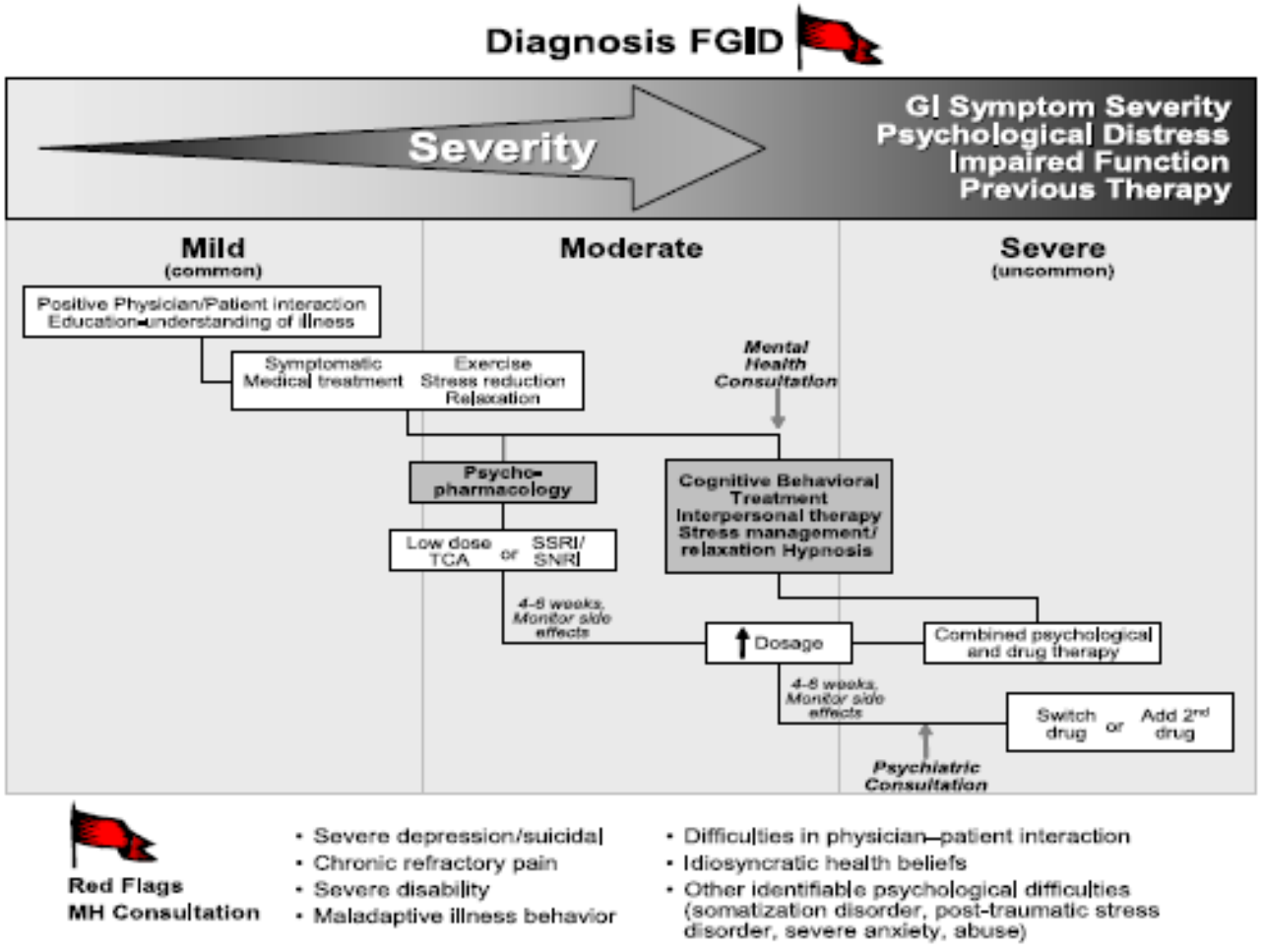
- Hypnotherapy has been shown to be effective for the treatment of IBS and a recent review concluded that hypnosis has a favorable impact on refractory IBS symptoms.

- The mechanism is unclear, although there is some evidence that it reduces gut contractility and normalizes pain thresholds after balloon rectal distension.

Complementary and Alternative Medicine for the Irritable Bowel Syndrome

- CAMs are commonly used by patients with IBS, particularly acupuncture and herbal medicines.
- Well-controlled clinical trials are lacking to support CAM use in IBS.
- Nevertheless, several treatments, particularly some probiotics and herbs (eg, peppermint oil), suggest that they may have a benefit in IBS.

Treatment


Diagnosis FGID
Severity
GI Symptom Severity
Psychological Distress
Impaired Function
Previous Therapy
Mild
(common)
Moderate
Severe
(uncommon)
Positive Physician/Patient interaction
Education-understanding of illness
Symptomatic
Medical treatment
Exercise
Stress reduction
Relaxation
Mental Health Consultation
Psycho-pharmacology
Low dose TCA
or
SSRI/ SNRI
Cognitive Behavioral Treatment
Interpersonal therapy
Stress management/ relaxation Hypnosis
4-8 weeks, Monitor side effects
Dosage
Combined psychological and drug therapy
4-8 weeks, Monitor side effects
Switch drug
or
Add 2nd drug
Psychiatric Consultation
Red Flags
MH Consultation
• Severe depression/suicidal
• Chronic refractory pain
• Severe disability
• Maladaptive illness behavior
• Difficulties in physician–patient interaction
• Idiosyncratic health beliefs
• Other identifiable psychological difficulties (somatization disorder, post-traumatic stress disorder, severe anxiety, abuse)