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Irritable Bowel Syndrome: Modern Concepts and Management Options

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ABSTRACT

Irritable bowel syndrome is the most common functional gastrointestinal disorder, manifesting as abdominal pain/discomfort and altered bowel function. Despite affecting as many as 20% of adults, a lack of understanding of etiopathogenesis and evaluation strategies results in diagnostic uncertainty, and in turn frustration of both the physician and the patient. This review summarizes the current literature on the diagnosis and management of irritable bowel syndrome, with attention to evidence-based approaches. A 4-step treatment strategy that has been used successfully in our tertiary referral practice is presented and should lead to successful therapeutic outcomes in the majority of patients with irritable bowel syndrome.
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KEYWORDS: Diagnosis; Irritable bowel; Pathophysiology; Treatment

The functional gastrointestinal disorders represent chronic gastrointestinal conditions with altered bowel sensitivity and motility.[1] Irritable bowel syndrome is the most common functional gastrointestinal disorder, manifesting as abdominal pain/discomfort and altered bowel function.[2]

DEMOGRAPHICS, DISEASE BURDEN, AND CLINICAL PRESENTATION

Irritable bowel syndrome has a prevalence of 1% to 20% worldwide, although up to 75% affected individuals never seek care.[3-6] In North America, irritable bowel syndrome prevalence is 5% to 10%, affecting any age, and is 3 to 4 times more common in women. Irritable bowel syndrome health-related quality of life is similar to that of those with asthma and worse than that of those with chronic liver disease.[7-9] Irritable bowel syndrome leads to $1.6 billion in direct medical costs and $19 billion in indirect costs annually.[10-12]

Diagnostic criteria for irritable bowel syndrome have been proposed, including the Manning[13] and Rome criteria (most recently Rome III, Table 1).[1] These criteria, intended primarily as irritable bowel syndrome research tools, have sensitivities of 62% to 96%.[14] Although irritable bowel syndrome diagnostic criteria perform variably across studies,[15,16] they are more robust (95% positive predictive value in one study) in the absence of red flag symptoms.[17] Irritable bowel syndrome can be further categorized into constipation-predominant, diarrhea-predominant, or mixed patterns (Table 2).[2] Organic causes for symptoms must be excluded, especially in older populations. Alarm features prompting further investigation include weight loss, fever, hematochezia, older age, and family history of gastrointestinal malignancy.[16] On physical examination, peritoneal signs, ascites, masses, and hemoccult positive stool also constitute alarm signs.[18]

Mood disorders and nongastrointestinal functional pain syndromes (eg, fibromyalgia, migraine) are present in up to two thirds of patients with irritable bowel syndrome,[19,20] whereas somatization (perceptive symptoms across multiple systems) occurs in 40%.[21] Multiple medication intolerances or adverse effects frequently are encountered in patients with irritable bowel syndrome.

ETIOPATHOGENESIS

Both peripheral (gut-based) and central (eg, abnormal brain responses to peripheral bowel signals) pathophysiologic

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mechanisms play an etiopathogenetic role,[22,23] although no single mechanism can explain all irritable bowel syndrome cases.[12] Inflammation, infection, gut motility, and brain-gut axis disturbances all partially explain symptom triggering or perpetuation; enhanced visceral sensitivity from upregulation of bowel sensation and greater afferent nerve signaling also participate in irritable bowel syndrome pathogenesis. Sensitization of afferent neural pathways allows physiologic gut stimuli to produce pain or motor symptoms.[23-25] Visceral hypersensitivity can be reproduced experimentally using rectal balloon distention in some patients.[26] As a symptom-based diagnosis, multiple conditions may mimic irritable bowel syndrome. Some of these (ie, celiac disease) are common enough to warrant routine diagnostic testing (see "Diagnostic Strategy"). Less common conditions, such as bile acid diarrhea, microscopic colitis, and pancreatic insufficiency,[27-31] require a clinical suspicion to invoke the appropriate diagnostic approaches.

CLINICAL SIGNIFICANCE

- Advances in the understanding of irritable bowel syndrome pathophysiology have been made in recent years.
- These insights inform a treatment strategy for the management of irritable bowel syndrome.
- The implementation of this approach will yield favorable treatment outcomes in the majority of patients with irritable bowel syndrome.

Alterations in gut secretory and motor function can manifest as meal-triggered diarrhea, resulting in rapid small-bowel transit.[32,33] Neurotransmitters such as serotonin are key in regulating and modulating intestinal transit, through serotonin type 3 (5-HT3) and 4 (5-HT4) receptors;[34] treatment strategies targeting serotoninergic receptors have proven effective.

Intestinal inflammation and the microbiome are emerging factors in irritable bowel syndrome etiopathogenesis.[22,35] Although overt small bowel bacterial overgrowth may initiate irritable bowel syndrome symptoms,[36] lesser degrees of bacterial colonization may be sufficient to produce irritable bowel syndrome-like symptoms.[37,38] Infectious gastroenteritis may trigger microinflammation ("post-infectious irritable bowel syndrome"), and up to one third of irritable bowel syndrome cases follow acute gastroenteritis[39]; conversely, only 7% to 30% patients with acute gastroenteritis develop irritable bowel syndrome.[40] Psychologic distress is an important cofactor when persistent functional symptoms follow enteric infection.[41,42]

Abnormal brain activation responses to noxious rectal stimulation on functional neuroimaging are present in some irritable bowel syndrome cases.[43-45] The brain regions implicated (eg, anterior cingulate, insula) also are responsible for affective responses;[23] these observations offer strong evidence for aberrant brain neurocircuitry in irritable bowel syndrome.

Many patients with irritable bowel syndrome perceive food to be important symptom triggers;[46] dietary intolerances, particularly lactose, are present in one third of patients with irritable bowel syndrome.[47] Deficiencies of other disaccharidases (sucrose, maltase) can lead to diarrhea,[29] and fermentable oligosaccharides, disaccharides, monosaccharides, and polyols can yield methane, hydrogen, and carbon dioxide production implicated in bloating.[48-50] Osmotically active carbohydrate by-products precipitate fluid secretion and enhance intestinal contraction, leading to diarrhea. Evidence for the role of gluten exposure in irritable bowel syndrome is mixed; controlled studies have failed to indict gluten in the absence of celiac disease, whereas other reports suggest contribution to symptoms.[51,52] In addition to amplifying visceral pain pathways, psychologic states influence illness and health care-seeking behaviors. Comorbid mood disorders or

Table 1 Diagnostic Criteria* for Irritable Bowel Syndrome

Recurrent abdominal pain or discomfort† at least 3 d/mo in the last 3 mo associated with ≥2 of the following:
1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

Supporting symptoms (not required for diagnosis but helpful in confirming IBS presentation): a) abnormal stool frequency (<3 bowel movements per week or >3 bowel movements per day); b) abnormal stool form; c) defecation straining; d) urgency (feeling of incomplete evacuation); e) passage of mucus; f) bloating

IBS = irritable bowel syndrome.
*Criteria fulfilled for the last 3 mo with symptom onset at least 6 mo before diagnosis.
†Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 d/wk during screening evaluation for subject eligibility.

Table 2 Subtyping Irritable Bowel Syndrome by Predominant Stool Pattern

1. IBS with constipation—hard or lumpy stools* ≥25% and loose (mushy) or watery stools† ≤25% of bowel movements‡
2. IBS with diarrhea—loose (mushy) or watery stools† ≥25% and hard or lumpy stool* ≤25% of bowel movements‡
3. Mixed IBS—hard or lumpy stools* ≥25% and loose (mushy) or watery stools† ≥25% of bowel movements‡
4. Unsubtyped IBS—insufficient abnormality of stool consistency to meet criteria for IBS with constipation, diarrhea, or mixed‡

IBS = irritable bowel syndrome.
*Bristol Stool Form Scale 1-2 (separate hard lumps like nuts [difficult to pass] or sausage-shaped but lumpy).
†Bristol Stool Form Scale 6-7 (fluffy pieces with ragged edges, a mushy stool or watery, no solid pieces, entirely liquid).
‡In the absence of use of antidiarrheals or laxatives.

somatization portend a several-fold higher likelihood of developing functional gastrointestinal disorders[19] with more severe symptoms, lower health-related quality of life, and higher treatment refractoriness.[53-55]

Finally, convincing evidence exists for a genetic basis to irritable bowel syndrome; despite this, no single genetic defect reliably accounts for all cases. Genetic polymorphisms predict endophenotypes, such as inflammatory and infectious triggering, symptom burden, and visceral hypersensitivity.[56,57] Gene−gene interactions and environmental influences probably are key to genetic predispositions.[58,59] **Figure 1** illustrates the complex interplay of environmental, psychologic, and physiologic factors in irritable bowel syndrome pathophysiology via a biopsychosocial model.[60,61]

DIAGNOSTIC STRATEGY

Laboratory and invasive testing are minimized, because repetitive investigations are costly and reinforce illness behavior. History alone without alarm symptoms yields likelihood ratios of 3 to 5 favoring irritable bowel syndrome.[14,62] Complete blood counts, erythrocyte sedimentation rate, and fecal occult blood tests may be appropriate early in evaluation. A bland physical examination (abdomen without peritoneal signs or palpable masses; no concerning extra-abdominal findings), a consistent history, and normal laboratory results yield robust post-test probability of irritable bowel syndrome.[18] The history should gauge any temporal association with medications or food as symptom triggers, recent changes in anatomy (gastric or intestinal surgery, cholecystectomy), exposures (travel, children), or gastrointestinal infections (enteritis, *Clostridium difficile*). With a 4% overlap between celiac disease and irritable bowel syndrome, celiac testing is a cost-effective strategy.[63,64] Hydrogen breath tests for bacterial overgrowth (~50%) are inadequate to predict responses to antibiotics[65,66]; therefore, empiric antibiotics may be a more cost-effective strategy when used judiciously. Testing for carbohydrate intolerance should be reserved for ambiguous cases or when further education and dietary monitoring may enhance symptom control.[67]

Colonoscopy is considered in patients aged more than 50 years as part of routine colon cancer screening and in patients with alarm features.[68] Melanosis coli indicating laxative use and microinflammatory disease can be identified during colonoscopy. Endoscopy is unnecessary in young patients with classic irritable bowel syndrome symptoms.[69]

IRRITABLE BOWEL SYNDROME TREATMENT

This section will offer guidance on the treatment of irritable bowel syndrome, emphasizing an evidence-based approach

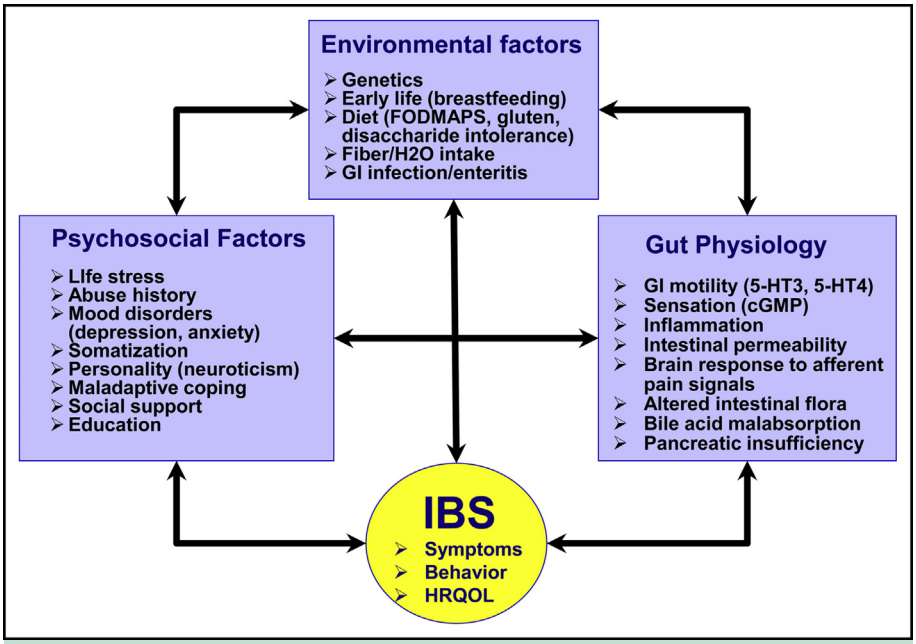

Figure 1 A biopsychosocial model of irritable bowel syndrome pathophysiology. Irritable bowel syndrome is thought to be a multifactorial disorder, deriving from a potential multitude of etiopathogenic factors, including environmental, psychologic, and physiologic factors. This model highlights the complex, often bidirectional interplay of these factors in the experience of irritable bowel syndrome symptoms. cGMP = cyclic guanosine monophosphate; 5-HT3 = serotonin type 3; 5-HT4 = serotonin type 4; FODMAPS = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; HRQOL = health-related quality of life; IBS = irritable bowel syndrome.

where available. First, an overview of the available treatment options will be offered; subsequently, we suggest a 4-step treatment approach to irritable bowel syndrome management. The proposed implementation strategy has not been studied systematically, but has proven successful in our tertiary gastrointestinal practice composed largely of patients with severe, treatment-refractory irritable bowel syndrome. Similar strategies have been endorsed by other experts in the field.[70]

OVERVIEW OF IRRITABLE BOWEL SYNDROME TREATMENT OPTIONS

After the exclusion of disorders mimicking irritable bowel syndrome and elimination of potential symptom triggers, the cornerstone of irritable bowel syndrome management is pharmacotherapy using peripherally and centrally acting agents (Table 3). Peripherally acting agents target dominant symptoms, whereas centrally acting agents act "globally," improving pain and well-being.

Peripherally Acting Agents

Constipation-predominant Irritable Bowel Syndrome. Dietary fiber, both natural (eg, psyllium) and synthetic (eg, methylcellulose), is a simple, inexpensive option in patients with mildly constipated irritable bowel syndrome, with randomized controlled data supporting global symptom relief despite lack of superiority over placebo in meta-analysis.[71,72] However, fiber potentially worsens bloating. Simple osmotic laxatives (milk of magnesia, polyethylene glycol) are readily available over the counter. Polyethylene glycol improves bowel frequency, but not abdominal pain.[73,74] Lactulose and sorbitol have not been studied systematically in irritable bowel syndrome but are effective laxatives; bloating is a side effect, precluding use when this is a prominent symptom.[67] Although approved only for "occasional constipation," osmotic agents generally are safe for long-term use and preferable to stimulant laxatives.

Tegaserod (Zelnorm, Novartis, Basel, Switzerland) is a partial 5-HT4 receptor agonist marketed for short-term treatment of women with constipated irritable bowel syndrome.[75] However, it was withdrawn from use due to cardiovascular risk.[76] A related agent, prucalopride, is available in several countries, but not in the United States.[77]

Lubiprostone, a chloride channel type-2 activator, is a prostaglandin-E_1 derivative that triggers intestinal chloride secretion, followed by obligatory sodium and fluid transit into the lumen. Lubiprostone is approved for irritable bowel syndrome with constipation, improving bowel movement frequency and global irritable bowel syndrome symptoms.[78] Potential side effects include nausea, diarrhea, and headache. Patients with chronic liver disease may need dose reduction to a single daily dose.[79]

Linaclotide is a novel guanylate-cyclase C agonist that upregulates secretion of chloride, followed by sodium and fluid into the bowel lumen; it has been approved for constipation-predominant irritable bowel syndrome.[80,81] In 2 parallel clinical trials, linaclotide successfully improved bowel movement frequency and irritable bowel syndrome pain.[82,83] Increases in cyclic guanosine monophosphate reportedly have direct antinociceptive effects on visceral sensory nerve fibers.[84] Diarrhea is experienced by 20% treated with higher doses of linaclotide (290 μg); this diminishes with continued

Table 3 Therapeutic Approaches to Managing Irritable Bowel Syndrome

	Gut Luminal and Mucosal Therapies	Gut-Directed Regulators	Centrally Acting Agents	Adjunctive and Complementary Therapy
All Patients	Step 1	Step 2	Step 3	Step 4
Reassurance	Dietary modification (low FODMAP, lactose)	Guanylate cyclase C agents (linaclotide)	Tricyclic antidepressants (amitriptyline, nortriptyline)	Psychodynamic therapy
Limited investigation	Osmotic laxatives (PEG, lactulose, magnesium products)	Chloride channel activators (lubiprostone)	SNRI antidepressants (venlafaxine, desvenlafaxine, duloxetine)	Hypnosis
Patient-doctor relationship	Antidiarrheals (loperamide, diphenoxylate/atropine)	Serotonin modulators (alosetron)	SSRI antidepressants (citalopram, paroxetine, sertraline)	Stress reduction
	Bile binders (cholestyramine, colesevelam)	Antibiotics (rifaximin, neomycin)		
Other supportive care	Anticholinergics/antispasmodics (methscopolamine, glycopyrrolate, hyoscyamine, dicyclomine)		Other centrally acting agents (eg, gabapentin, pregabalin, antiseizure agents)	Psychiatrist consultation
	Probiotics			Psychotherapy
	Disaccharidases			Acupuncture
	Herbal therapies?			

FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; PEG = polyethylene glycol; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitors.

use; our anecdotal experience suggests lesser diarrhea if administered with meals, despite manufacturer recommendations for administration before meals. Linaclotide is not absorbed and thus has negligible concern for drug interactions or serious systemic side effects.[80,85]

Diarrhea-predominant Irritable Bowel Syndrome. The only antidiarrheal agent with randomized, controlled data supporting use in irritable bowel syndrome with diarrhea is loperamide;[86,87] diphenoxylate with atropine is a reasonable alternative.[88] Bile acid sequestrants (cholestyramine, colesevelam) are useful when diarrheal symptoms are triggered by bile acids (eg, post-cholecystectomy diarrhea) or as adjuncts.[89-91]

Anticholinergic agents are useful as needed or preemptively in irritable bowel syndrome with diarrhea and postprandial symptoms, especially abdominal pain, bloating, diarrhea, or urgency; modest benefit is reported over placebo in meta-analysis.[71] Examples include hyoscyamine, dicyclomine, and methscopolamine; the latter 2 have lesser central side effects, albeit at higher cost.[92]

Alosetron, a selective 5-HT3 receptor antagonist, improves bowel consistency and frequency in diarrhea-predominant irritable bowel syndrome; central reduction in brain activation has been suggested as an adjunct mechanism of action.[93-96] Alosetron was voluntarily withdrawn by the manufacturer because of the risk of acute ischemic colitis, but it was reapproved for chronic, severe diarrhea-predominant irritable bowel syndrome refractory to conventional therapy; currently, its use requires patient agreement and prescriber registration.[97-99]

Bile sequestrant therapy is an effective option in patients with diarrheal irritable bowel syndrome, in particular when bile acid malabsorption can be established (SeHCAT scanning, available in specialized settings; abnormal in 1% to 10% of patients with diarrheal irritable bowel syndrome).[32,100] In a systematic review, 96% of patients with severe bile acid malabsorption responded well to cholestyramine.[100] However, this medication is not particularly palatable. Colesevelam is a less well-studied and more expensive option for bile acid malabsorption. In patients in whom carbohydrate intolerance is suspected in the setting of postprandial provocation of symptoms, the initiation of disaccharidase therapy (eg, lactase, alpha-amylase) with meals may be both therapeutic and diagnostic.[30]

Centrally Acting Agents

Antidepressants are beneficial in refractory irritable bowel syndrome independently of their effect on comorbid affective disorders[101] via modulation of brain interpretation of peripheral gut signaling.[102,103] Tricyclic antidepressants (nortriptyline, amitriptyline) are the best studied antidepressants for irritable bowel syndrome; used in low doses (starting dose 10-25 mg at bedtime), they have negligible mood effects. Clinical trials have demonstrated benefit of tricyclic agents regardless of irritable bowel syndrome subtype; these medications may take weeks and several dose titrations to maximize efficacy.[71,104] The anticholinergic properties of tricyclics slow bowel transit and relieve spasm, but may be responsible for side effects (dry mouth, urinary retention); other side effects include sedation and sexual dysfunction. Switching to secondary amines (eg, despiramine) may mitigate these effects.[102]

Selective serotonin reuptake inhibitors are nearly as effective as tricyclics, with a number needed to treat of 3.5 in meta-analysis.[105] Specific agents' properties may benefit particular clinical settings; for instance, citalopram has effects on colonic tone and sensitivity, and paroxetine has anticholinergic effect useful in diarrhea. In contrast to tricyclics, selective serotonergic agents benefit comorbid affective disorders. Serotonin norepinephrine reuptake inhibitors (eg, venlafaxine) are alternative centrally acting agents, with greater pain suppression than serotonin reuptake inhibitors. Venlafaxine also has peripheral effects, inducing colonic relaxation in healthy volunteers.[106]

Antibiotics and Probiotics. Gut-specific antibiotics (eg, rifaximin, neomycin) are options when small bowel bacterial overgrowth is suspected, particularly with gas and bloat symptoms. Two large randomized, controlled studies demonstrated global benefit with rifaximin in nonconstipated irritable bowel syndrome (number needed to treat ~11),[107,108] and the effect persisted beyond the duration of use.[109] Emerging data similarly support probiotics, especially *Bifidobacteria*, *Lactobacillus*, and *Saccharomyces* species.[110,111] Although all probiotics likely are not equal in effectiveness, head-to-head comparisons are lacking.

Cognitive and Behavioral Therapies. Psychologic therapies (cognitive behavioral therapy, psychodynamic therapy) show irritable bowel syndrome benefit in global well-being (number needed to treat of 2-4).[105] High patient motivation, pain-predominant symptoms, psychiatric symptoms, and stress triggers predict good responses. Self-directed[112] and internet-based cognitive behavioral therapy[113-115] offer expanded access, yielding similar yet more cost-effective results.

Complementary and Alternative Approaches. Patients with irritable bowel syndrome frequently seek out complementary and alternative strategies.[116,117] Hypnotherapy has documented efficacy,[118] with durable symptom response and reduced health care use, and can be delivered effectively with minimal training.[119-121] Although acupuncture anecdotally provides symptomatic relief, irritable bowel syndrome severity and quality of life are not affected in well-controlled trials.[122,123]

Among herbal and homeopathic treatments, randomized controlled studies support the use of peppermint oil,[124,125] iberogast, Padma lax (Padma AG, Schwerzenback, Switzerland), Tong Xie Yao Fang, and Ayurvedic preparations (the latter two are traditional herbalist/pharmacist preparations).[126] Purity and consistency concerns limit enthusiasm

for these agents. One small trial supports regular exercise in improving irritable bowel syndrome severity scores.[127]

IRRITABLE BOWEL SYNDROME TREATMENT: A FOUR-STEP STRATEGY

In excluding confounding diagnoses, a limited evaluation is pursued early (see "Diagnostic Strategy"). If irritable bowel syndrome remains likely after evaluation, dietary and affective symptom triggers are considered; other functional disorders, psychiatric comorbidities, and drug intolerances provide corroborative evidence in support of irritable bowel syndrome and inform initial treatment selection.

Next, a specific treatment approach is selected from the 4 separate, although not necessarily sequential, treatment options (Figure 2). The initial management strategy is determined by 2 factors: symptom severity and dominant symptom (Table 4 and Figure 2).

Step 1: Gut Luminal and Mucosal Therapy

Peripherally acting agents directed at the dominant symptom may be sufficient with mild symptoms. For instance, fiber, osmotic laxatives, and polyethylene glycol can be titrated in constipated patients, whereas antidiarrheal and anticholinergic agents can be used with diarrheal predominance. Approaches that affect the diet and intestinal milieu (antibiotics and probiotics) also may be beneficial.

Step 2: Gut-directed Regulators

Newer secretagogues (linaclotide, lubiprostone) are useful with constipation, and their favorable safety profile prompt

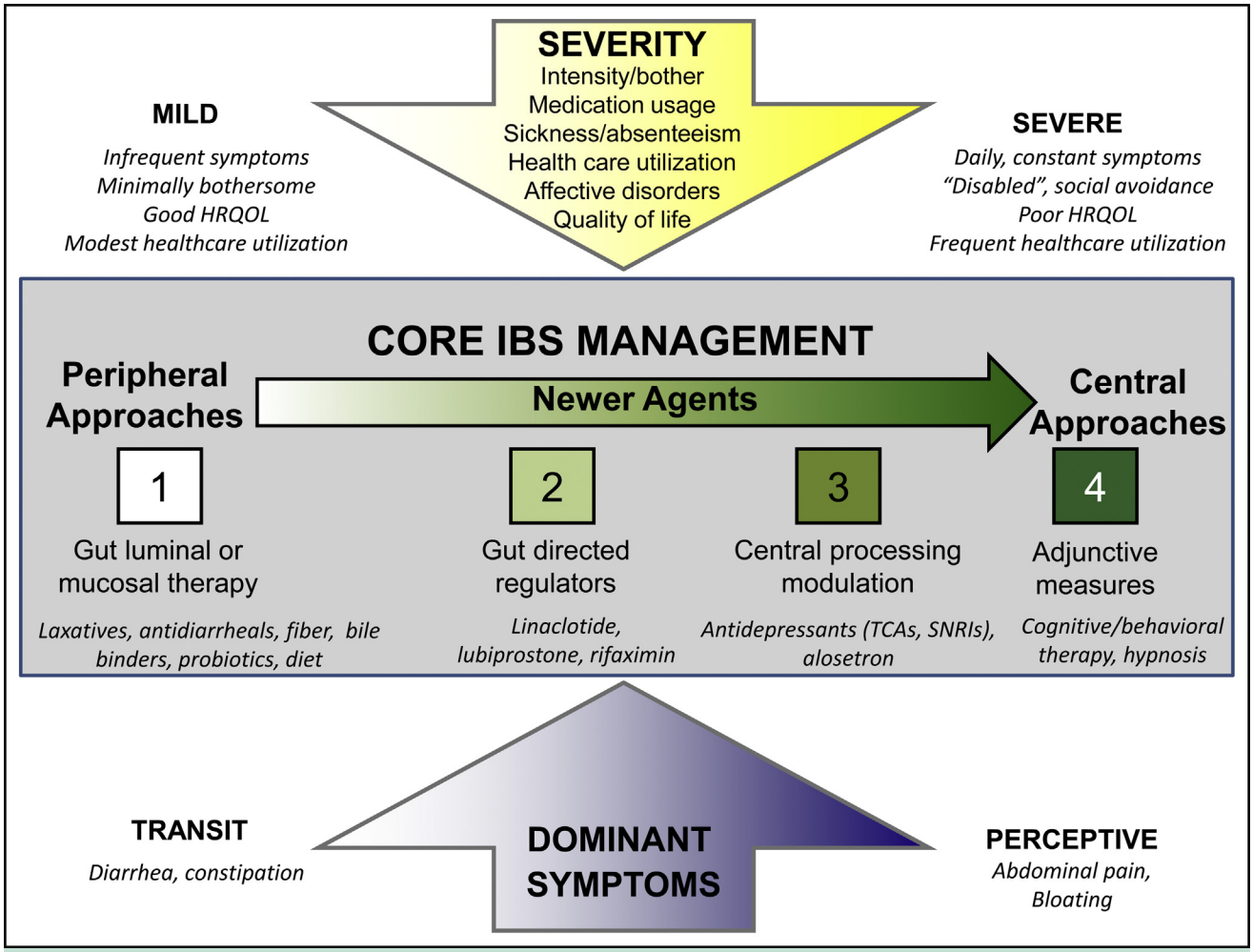

Figure 2 Overview of irritable bowel syndrome treatment strategy. Irritable bowel syndrome management involves the use of a continuum of peripheral (gut)-based and centrally acting (brain-gut) strategies. The selection of an appropriate treatment approach for a particular patient with irritable bowel syndrome considers patient severity (eg, effect on daily function/quality of life and overlapping mood disorders) and dominant symptoms (eg, transit vs pain). Patients with more straightforward, mild presentations respond well to gut-centric approaches,[1,2] whereas complex presentations are likely to achieve improvement with treatments that address central nervous system influences on symptom presentation.[3,4] HRQOL = health-related quality of life; IBS = irritable bowel syndrome.

Table 4 Irritable Bowel Syndrome Treatment Strategy: A Way Forward

1. Evaluation
   a. Consider conditions that mimic IBS (eg, celiac disease, microscopic colitis, bile acid diarrhea, pancreatic insufficiency, carbohydrate intolerances, medication side effects, postsurgical neoanatomy)
   b. Assess for the presence of alarm symptoms
   c. Evaluate for symptom triggers (eg, stressors, diet)
   d. Explore presence of other functional GI (eg, functional dyspepsia) and non-GI disorders (eg, fibromyalgia), psychiatric comorbidity, and drug intolerances
   e. Understand previous IBS treatment experiences
2. Selection of Treatment Approach (**Figure 2**)
   a. Predicated on symptom severity and dominant symptoms
   b. Symptom severity (intensity, bother, effects on quality of life)
      i. Mild symptoms, intermittent symptoms, low symptom burden: symptomatic or peripheral therapy
      ii. Moderate symptoms: centrally acting neuromodulators, especially if symptomatic therapy does not provide adequate benefit
      iii. Severe symptoms and those with comorbidities (non-GI functional disorders, psychiatric): both centrally acting neuromodulators and peripheral therapy
         a. Concurrent affective disorders need to be managed
         b. Other central therapies (cognitive and behavioral therapy, hypnosis, stress reduction) may need to be considered
   c. Dominant symptoms (diarrhea, constipation, pain, other GI symptoms)
      i. Constipation-predominant
         a. Laxatives, fiber
         b. Novel agents (linaclotide, lubiprostone)
      ii. Diarrhea-predominant
         a. Antidiarrheals
         b. Alosetron
         c. Address dysbiosis (rifaximin, probiotics)
         d. Diet (low FODMAP)
         e. Bile binders (cholestyramine, colesevelam)
         f. Disaccharidases (lactase)
      iii. Pain-predominant
         a. Antidepressants (TCAs and SNRIs preferred)
         b. Linaclotide when constipation present
         c. Avoid narcotics
3. Education/Therapeutic Alliance
   a. Inform patient about etiopathogenesis
   b. Reaffirm legitimacy of diagnosis; allay concerns about organic disease
   c. Provide information about support organizations (International Foundation for Functional Gastrointestinal Disorders)

FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GI = gastrointestinal; IBS = irritable bowel syndrome; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

early use. Pain suppression may lag behind the secretagogue effect of linaclotide by several weeks. Patients with refractory diarrhea may benefit from alosetron.

Step 3: Centrally Acting Agents

Centrally acting agents provide global syndromic benefit, complementing approaches initiated in earlier steps. Although tricyclic antidepressants have demonstrated success, contemporary antidepressants also have broad benefits. Comorbid affective disorders influence agent selection, for example, sertraline in comorbid anxiety and bupropion in comorbid depression. The side effect profile also can be targeted to the irritable bowel syndrome pattern, for example, diarrheagenic effect of sertraline and constipating effect of tricyclics. Adjunctive peripheral therapy (step 1) can overcome side effects (eg, constipation) if the agents are useful from an irritable bowel syndrome perspective. Antidepressants (particularly tricyclics, duloxetine, and venlafaxine) and psychotherapeutic approaches yield the greatest benefit in pain-predominant presentations. Severe, disabling symptoms, high nongastrointestinal symptom burdens, and psychiatric comorbidities are indications for early use of central therapies. Paradoxically, medications are tolerated poorly in these patients, and slow titration to effective doses is suggested.[54]

Step 4: Adjunctive and Complementary Therapy

When escalation of management is required, adjunctive and complementary approaches (eg, cognitive behavioral therapy, hypnosis, psychotherapy, and acupuncture) are implemented. Consultation with a health psychologist can affect coping mechanisms and reduce illness behavior. Supplementary nonpharmacologic therapies may be necessary with

specific attention to stressors and active psychiatric symptoms (step 4).

A multimodal strategy incorporating medications, nonpharmacologic options, and dietary modification often is required. Although prior treatments can be reinitiated, this may result in patient dissatisfaction; careful explanation of the intent of each recommendation (eg, advance to higher dose, longer duration of use) will maintain patient confidence and compliance.

IRRITABLE BOWEL SYNDROME OUTCOMES AND PROGNOSIS

Narcotics have no role in irritable bowel syndrome management. Physical and psychologic dependence will result, and narcotic bowel syndrome can develop; ultimately, narcotics worsen abdominal pain and constipation. The hazards of narcotic use require open discussion because durable symptom improvement with narcotics is woefully low.[128]

Irritable bowel syndrome is a lifelong condition with exacerbations and remissions; although medications should be minimized to the extent possible, treatment trials are a critical component of management, each pursued for several weeks before switching therapies. Lack of response to a particular agent does not preclude response to another medication in the same class. Patient education and reassurance are essential; strong patient-doctor relationships lead to higher patient satisfaction and fewer return visits. Concerns about the legitimacy of irritable bowel syndrome diagnoses, the low potential for organic diagnoses, and current understanding of irritable bowel syndrome etiopathogenesis should be addressed directly.

Establishing realistic expectations early is critical; the goal of irritable bowel syndrome treatment is to improve gastrointestinal symptoms and quality of life, not necessarily complete "cure." Symptom remission may allow reduction or discontinuation of medication; flares necessitate reintroduction of previously successful treatments. Through the implementation of the approaches outlined, a majority of patients with irritable bowel syndrome will experience symptom improvement.

CONCLUSIONS

Irritable bowel syndrome is a common symptom-based diagnosis, with several etiopathophysiologic mechanisms. Implementation of an informed evaluation leads to high diagnostic accuracy. Treatment strategies that consider symptom severity and dominant symptoms, using multifaceted pharmacotherapeutic and nonpharmacologic and complementary approaches, provide for effective irritable bowel syndrome management. Coupled with education, reassurance, and support, even the most challenging patients with irritable bowel syndrome will experience improvement in symptoms and quality of life.

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