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IN THIS ARTICLE

How do you spell relief for irritable bowel syndrome?

C-A-R-E-F-U-L-L-Y

Many treatment options lack strong evidence for their efficacy. Others have proven efficacy, but restricted use

Practice recommendations

- Little or no diagnostic testing is required to make an accurate diagnosis of irritable bowel syndrome (IBS) in patients younger than 50 without alarm symptoms (**C**).
- IBS can develop and persist as a consequence of an episode of gastroenteritis (**B**).
- Tell patients with IBS that it has a physiologic basis and that psychosocial stressors aggravate the already painful and dysfunctional bowel, but do not cause the chronic dysfunction (**B**).
- Alosetron and tegaserod have proven efficacy, but are available only through limited access programs (**A**).
- Promising newer therapies for IBS include probiotics and a chloride-channel opener, as well as locally acting, non-absorbable antibiotics for small intestinal bacterial overgrowth-associated IBS (**B**).

Strength of recommendation (SOR)
A Good-quality patient-oriented evidence
B Inconsistent or limited-quality patient-oriented evidence
C Consensus, usual practice, opinion, disease-oriented evidence, case series

"I've always had some stomach pain," says Mary Jane, a 36-year-old patient, whom you are seeing for the first time. "But this is becoming unmanageable."

You see from Mary Jane's chart that she has been to your group practice twice over the last few years with complaints of diarrhea that were diagnosed as gastroenteritis. She tells you that after each visit, it got "a little better," but it "never really went away."

She also tells you that her stomach bothers her a few days every month, but that it feels a little better after she defecates. She says that she thinks she may be sensitive to certain foods.

"Things are getting worse," she tells you. "The bloating, pain, and diarrhea have gotten to the point that I can't go anywhere without worrying where the nearest bathroom is."

"I've already had my gallbladder and appendix removed," she says, "but I still feel lousy."

On exam, Mary Jane appears to be in good health. She is afebrile and has a normal abdominal exam, except for very mild diffuse tenderness. She tells you that she has not traveled to any locations where access to clean food or water is suspect. Her stool is heme negative. Urine dip is negative and she is not pregnant.

"Do you know what's the matter with me?" she asks you. "Or do I need to see a specialist?"

No need for a specialist

Your patient meets the criteria for irritable bowel syndrome (IBS) set by Rome III, an international panel of experts in the field of functional gastrointestinal disorders. She's had recurrent abdominal pain/discomfort for at least 6 months, and she's had symptoms at least 3 days a month for the last 3 months (**TABLE 1**).[1]

Mary Jane tells you that she is relieved to finally get a diagnosis, having struggled for some time with stomach pain that never really went away. Her experience is not unusual: The wide range of concomitant gastrointestinal and extraintestinal symptoms in IBS patients make the initial diagnosis difficult.[2,3] She's also relieved to learn from you that contrary to popular belief, IBS has a physiologic basis and that psychosocial stressors merely aggravate an already painful and dysfunctional bowel. (See **"Irritable bowel syndrome: Not just a functional disorder"**[4–7] on page 102.)

We have a number of treatment options to offer patients like Mary Jane, including alosetron, tegaserod, lubiprostone, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants, as well as complementary therapies (such as probiotics) and behavioral therapy. But before we review the evidence behind the different options, let's take a look at the factors that may be at work in IBS, and the things you'll want to pay special attention to during your assessment.

TABLE 1

Is it IBS? Rome III criteria provide guidance[1]

- Recurrent abdominal pain or discomfort with onset at least 6 months before diagnosis.
- Symptoms must have occurred for at least 3 days per month in the past 3 months and must have been associated with 2 or more 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.

Infection, bacterial overgrowth may play a role

Between 4% and 26% of patients contract IBS for the first time after gastroenteritis.[8] Tissue from patients with post-infectious IBS shows chronic mucosal lymphocytosis[9,10] associated with enterochromaffin cell hyperplasia.[11] Spiller et al[12] noted these changes, as well as an increase in gut permeability, for more than 1 year after the resolution of *Campylobacter* enteritis. Using prednisolone for early intervention suppressed T-cell lymphocyte counts but not IBS symptoms.[13]

The role of bacterial overgrowth in IBS is controversial. Pimentel et al[14] reported that 78% of 202 IBS patients had small intestinal bacterial overgrowth. After treatment, almost half no longer met the Rome criteria for IBS and showed a statistically significant improvement in diarrhea and abdominal pain but not in straining, urgency, or bloating.

A second study from the same group demonstrated that 84% of 111 consecutive IBS patients had small intestinal bacterial overgrowth compared with 20% of healthy controls. Thirty-five percent of the IBS patients treated with neomycin had improved composite scores compared with 11.4% of those receiving placebo.[15]

Correlation between small intestinal bacterial overgrowth and Rome criteria for IBS has not been replicated by other centers, and other investigators who have looked into this relationship have suggested that small intestinal bacterial overgrowth is not associated with IBS.[16,17]

Genetics and the environment may also be at work

Familial clustering of IBS is commonly seen.[3,18] Several studies have suggested a genetic role but a recently published comprehensive review suggests that the

FAST TRACK

Up to 26% of patients contract IBS for the first time after gastroenteritis

THE JOURNAL OF FAMILY PRACTICE

Irritable bowel syndrome: Not just a functional disorder

The discovery of physiological differences between IBS patients and control groups suggests that IBS entails significant underlying neuroenteric dysfunction wherein both function *and* physiology are altered.[4,5] The endogenous release of serotonin (5-HT) initiates sensory, secretory, and motor signals within the enteric nervous system by binding to a variety of serotonergic receptors as well as stimulating afferent signals to the spinal cord and brain.[4,6,7]

Studies by multiple groups using human subjects or human tissue demonstrate physiologic differences between IBS patients and controls which include:[5,7]

- increased enterochromaffin cell numbers, specifically in post-infectious IBS
- a decrease in mRNA for TPH-1, an enzyme that synthesizes 5-HT
- significant differences in the 5-HT content of enterochromaffin cells
- decreased expression of the serotonin reuptake transporter protein that helps regulate serotonin signaling.

Significant disruption of 5-HT signaling is found in IBS patients compared with controls and more work is underway to better understand the relationship between physiologic dysfunction and symptoms.

FAST TRACK

You can diagnose IBS with few—if any—diagnostic tests, as long as there are no alarm symptoms or red flags

evidence of genetic susceptibility to IBS is modest, if present at all.[19]

Research tells us that the environment also plays a role; specifically, psychological stress is related to IBS symptoms. In one GI referral practice, women with diagnoses of functional disorders had experienced a high frequency of abuse.[20]

Abuse history is also associated with more severe symptoms, worse daily function, greater psychological distress, and poor health outcome.[21] Removal of these stressors provides significant relief to the patient, but IBS still exists in the absence of significant psychosocial pressures.

Few tests (if any) are needed for diagnosis

IBS historically has been a diagnosis of exclusion, but this is no longer the case. You can make the diagnosis with few—if any—diagnostic tests, as long as there are no "red flag" findings or alarm symptoms (**TABLE 2**[1,22,23]). In particular, surgery is not required to make a diagnosis, nor will it improve a patient's condition, yet the incidence of abdominal and pelvic surgery in IBS patients is 87% greater, and cholecystectomy three-fold higher, than in the general population.[24]

While taking a history, you will of course ask about the patient's altered bowel habits. In addition, though, you will need to:

Ask about personal and family history of inflammatory bowel disease (IBD), colon cancer, celiac disease, pregnancy, recent overseas travel or camping exposure to parasites or contaminated food and water, and history of recent gastroenteritis.[25]

Ask about alarm symptoms and red flags. Red flags on your examination include any focal positive physical findings, such as peritoneal signs, heme-positive stool, abdominal mass, or pelvic findings. Alarm symptoms that the patient may talk about include things like significant weight loss.

Red flags are based on observational data but have become the accepted standard of practice.[1,22,23,26] Extensive testing, including the routine use of blood tests, stool studies, and imaging, however, is not required.[22,25] If you have any doubt about history or findings, your diagnostic testing should focus on the issue in question.

When warranted by the presence of alarm symptoms or family history, you may need to schedule a colonoscopy to rule out IBD, tumors, or melanosis coli, which can be caused by excessive use of laxatives. Screening colonoscopy is the standard of care for all patients older than 50, regardless of symptoms.

Key in on food concerns. If specific foods aggravate symptoms, further investigation or a dietary exclusion trial may be helpful; however, even patients with proven lactase deficiency experience little or no bloating after drinking 240 mL milk.[1,27] You may want to test for celiac disease if

indicated by clinical features such as diarrhea, local prevalence, or family history. Routine testing of celiac disease, however, is not supported by the evidence.[28,29]

Many treatment options, limited quality research

Few pharmaceutical compounds have been tested and proven effective in reproducible, high-quality, double-blind, placebo-controlled trials (**TABLE 3**).[1,29–43] In addition, no alternative or complementary therapies have been proven in quality clinical trials to date (**TABLE 4**).[39,44–46,50] Behavioral therapy has shown benefit, but lacks double-blind, placebo-controlled trial data required for a level A strength of recommendation (SOR) (**TABLE 5**).[1,47,48] That said, there are various options that can help patients with IBS—specifically, those who have IBS with diarrhea, IBS with constipation, IBS with mixed bowel habit (where stools are reported as >25% hard or lumpy and >25% loose or watery[1]), or IBS with unspecified bowel habit.

IBS with diarrhea

Options all have "but" clauses

Alosetron, the 5-HT_3 receptor antagonist, has demonstrated efficacy in women (specifically) with IBS with diarrhea and has a grade A treatment recommendation from the American College of Gastroenterology.[29,30] Given the concerns about severe constipation and ischemic colitis, alosetron was withdrawn from the market in November 2000 but was reintroduced in June 2002 under a limited-use program for patients with severe IBS with diarrhea, in whom standard therapy has failed (SOR: **A**). Research has since shown that IBS patients have a greater risk for ischemic colitis than the general population.[49]

Loperamide, a μ-opioid receptor agonist, which does not cross the blood-brain barrier, can be started at bedtime or in the morning at 2 mg and slowly titrated daily to effect. The effect, however, is limited to the bowel habits (SOR: **B**).[38]

TABLE 2

These red flags and alarm symptoms should prompt further evaluation[1,22,23]

PATIENT PRESENTATION
Age of onset >50 years
Fever
Nocturnal symptoms
Blood in stools
Anemia
Weight loss >10% body weight
Profuse or large volume of diarrhea
Family history of inflammatory bowel disease or cancer
PHYSICAL EXAMINATION
Fever
Fecal blood
Organomegaly
Jaundice
Positive physical findings such as peritoneal signs or focal abdominal tenderness

Anticholinergics can be used for abdominal pain or discomfort, particularly in patients with IBS with diarrhea. Despite their lengthy history and broad use in IBS populations, limited evidence supports their efficacy, and many are not available in the US (SOR: **B**).[35,36]

Tricyclic antidepressants (TCAs) exert their effects by blocking the muscarinic receptors. TCAs can provide relief to patients with severe or refractory pain but perceived social stigma associated with taking antidepressants can be a barrier to this therapeutic approach (SOR: **B**).[36,41]

IBS with constipation

Laxatives, lubiprostone are options

Osmotic laxatives such as polyethylene glycol or lactulose can improve constipation. Despite widespread over-the-counter and prescription use, however, evidence is lacking for their efficacy and tolerability in IBS (SOR: **B**).[39]

Lubiprostone, a ClC2 chloride-channel opener, improved individual symptoms scores in 50 patients with IBS with constipation compared with placebo

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Tricyclics can provide relief to patients with severe or refractory pain

TABLE 3

Pharmacologic options for IBS

TREATMENT	CLINICAL EFFICACY*	SOR	COMMENTS
5-HT$_3$ receptor antagonist (alosetron)[1,29,30]	**IBS with diarrhea** Global symptom relief, improvement in individual symptom measures, improved quality of life scores (NNT=7)	A	Drug available through limited access program
5-HT$_4$ receptor agonist (tegaserod)[1,29,31]	**IBS with constipation** Global symptom relief, improvement in individual symptom measures, improved quality of life scores (NNT=14)	A	Marketing suspended on March 30, 2007;[32] limited temporary access program makes drug available through FDA[33]
Antibiotics (neomycin, rifaximin)[34]	**IBS / IBS with diarrhea** Global symptom relief, improvement in bowel habits for IBS with diarrhea	B	May benefit a subset of IBS patients with small intestinal bacterial overgrowth. Other research groups have not replicated results to date in IBS patients. Rifaximin produces most durable results
Anticholinergics/calcium channel blockers (hyoscyamine, dicyclomine, mebeverine, otilonium bromide, pinaverium bromide)[35,36]	**IBS** Improvement in abdominal pain (NNT=4–15)	B	Long history of use in IBS patients; however, little credible evidence to support use or efficacy in relief of global IBS symptoms. Best evidence with calcium channel blockers and anticholinergics comes with agents not available in US: mebeverine, otilonium bromide, and pinaverium bromide
Bulking agents (ispaghula husk, polycarbophil)[35,36]	**IBS with constipation** Improvement in bowel habits (NNT=2.2–3.5)	B	Improvement in bowel habits, but no significant difference vs placebo for other measures; may aggravate bloating and abdominal pain
Chloride-channel receptor agonist, ClC2 (lubiprostone)[37]	**IBS with constipation** Global symptom relief, improvement in individual symptom measures	B	Indicated for chronic constipation; pending FDA review of data for IBS with constipation indication
Loperamide[1,38]	**IBS with diarrhea** Improvement in bowel habits (NNT=3–5)	B	Reduction in diarrhea, but no better than placebo in global relief of symptoms or pain
Osmotic laxatives (polyethylene glycol, lactulose)[1,39,40]	**IBS with constipation** Improvement in bowel habits (NNT=2–4)	B	Lacks randomized controlled trials in IBS. Improvement in bowel habits, but no significant difference vs placebo for other measures; may aggravate bloating and abdominal pain
SSRIs (citalopram, fluoxetine, paroxetine)[35,41–43]	**IBS / IBS with constipation** Improvement in abdominal pain and quality of life scores (NNT=3–6)	B	Limited and inconclusive data; diarrhea common side effect on beginning therapy. Start with low dose, increase as needed; may be useful for IBS with constipation patients, but it's uncertain if effect is on the enteric nervous system, central nervous system, or both
Tricyclic antidepressants (TCAs)[35,41]	**IBS / IBS with diarrhea** Improvement in abdominal pain (NNT=3)	B	May increase constipation, does not produce global relief of symptoms, and patients experience poor tolerability (effect on gut function occurs predominantly with lower doses). Hypothesized to modify central-enteric nervous system communication

* We did not calculate NNT endpoints on studies of poor quality, those with a small number of patients, or in cases where results were not reproducible in a consistent fashion or were not published in manuscript form.

IBS, irritable bowel syndrome; SOR, strength of recommendation; NNT, number needed to treat; FDA, Food and Drug Administration; SSRI, selective serotonin reuptake inhibitor.

in a small phase II dose-ranging study (SOR: B).[37]

Tegaserod, a partial 5-HT$_4$ receptor agonist, facilitates neurotransmission in the gut that is involved in motility and secretion and produces global symptom relief.[31] The American College of Gastroenterology gave tegaserod a grade A recommendation for the treatment of women with IBS with constipation.[29]

TABLE 4

Complementary and alternative therapies for IBS

TREATMENT	CLINICAL EFFICACY	SOR	COMMENTS
Acupuncture[44]	No proven benefit	C	Poor-quality trial with heterogeneous interventions, controls, and outcomes measured
Chinese herbal therapy[45]	Reported improvement in global symptoms and pain	C	Very few high-quality clinical trials. Mixtures vary, content unknown, and some mixtures can be toxic. Unknown which herbs might produce benefit
Herbal therapy (*Curcuma xanthorrhiza, Fumaria officinalis*)[45]	No proven benefit	C	Tested in quality clinical trial; no efficacy over placebo
Peppermint oil (colpermin)[39, 50]	Improvement in abdominal pain	B	Lacks data on global symptom improvement; mechanism of action is similar to that of calcium channel blockers
Probiotics (*Bifidobacterium infantis, Lactobacillus, B animalis*)[46]	Global symptom relief and improvement in individual symptom measures	B	Preliminary trials encouraging, but differences in trial design, probiotic dose, strain, as well as unpredictable symptom response, has not yielded consistent evidence. No quality of life improvement seen in early studies

SOR, strength of recommendation

On March 30, 2007, Novartis Pharmaceuticals agreed to stop selling tegaserod maleate (Zelnorm) because a safety analysis found a higher chance of heart attack, stroke, and worsening chest pain that could become a heart attack in patients treated with Zelnorm, compared with those receiving placebo.[32] In July 2007, the FDA announced that it would permit restricted use of the drug in patients who meet strict criteria, have no known or pre-existing heart problems, and who are in critical need of the drug.[33]

Polycarbophil and **ispaghula husk** are the only fibers to have demonstrated any significant benefit in clinical trials for constipation,[35] but may make pain and bloating worse (SOR: B).

SSRIs and **low-dose benzodiazepines** are an option for patients who have coexisting psychological illness.[41] There is limited evidence for SSRI treatment (citalopram, paroxetine), either alone or in combination with additional treatments (SOR: B).[35,41–43]

IBS with mixed/unspecified bowel habit

Consider therapy

Cognitive behavioral therapy or other standard psychotherapy may be beneficial in many IBS patients (SOR: B).[1,48]

Peppermint oil for IBS is efficacious in recurrent abdominal pain compared with placebo and anticholinergic agents (SOR: B).[39,50]

Hypnosis has had a therapeutic impact on patients with IBS, even those whose conditions were refractory to other forms of therapy (SOR: B).[47]

Certain probiotic therapies have shown improvement in global symptoms and may prove to be promising therapeutic agents (SOR: B).[46]

Acupuncture has shown no proven efficacy in IBS (SOR: C).[44]

Some Chinese herbal medicines may improve the symptoms of IBS. Positive findings from trials should be interpreted with caution, though, due to inadequate methodology, small sample sizes, and lack of confirming data. In addition,

FAST TRACK

Hypnosis has had a therapeutic impact on patients with IBS—even those whose conditions were refractory to other forms of therapy

TABLE 5

Hypnotherapy and psychotherapy for IBS

TREATMENT	CLINICAL EFFICACY	SOR	COMMENTS
Hypnotherapy[47]	Global symptom relief, improvement in individual symptom scores	B	Trials, though many, were of poor quality, but did show significant benefit. A large, randomized placebo-controlled trial is needed to demonstrate benefit
Psychotherapy (Cognitive behavioral therapy, biofeedback)[1,48]	Global symptom relief, improvement in individual symptom scores (NNT=1–2)	B	Significant reduction in symptoms, but did not eliminate them. To maximize the likelihood of success, biofeedback techniques should be administered by a trained professional. Recommended as part of an overall treatment plan

SOR, strength of recommendation; NNT, number needed to treat.

herbal remedies may contain unknown substances that can pose serious risk for adverse events and drug interactions (SOR: C).[45]

Antibiotics for IBS patients with small intestinal bacterial overgrowth can provide some relief, according to Pimentel and colleagues,[14] but other groups have not been able to duplicate these findings. Rifaximin in IBS and IBS-like symptoms has shown a sustained benefit (SOR: B).[34]

Exercise or dietary therapies have no proven benefit in otherwise healthy IBS patients (SOR: C).[1]

FAST TRACK

Comorbid psychological conditions do not cause symptoms, but can contribute to pain

Set realistic goals, address patient fears

When caring for a patient with IBS, it's important to set and discuss realistic goals. Be sure to address patient concerns, as well. IBS patients are frequently frustrated by a lack of diagnostic findings and may worry about being labeled as having a psychological disorder rather than having a true GI abnormality. This concern, especially if the patient feels that the physician is not adequately addressing her (or his) symptoms, may exacerbate the already troublesome IBS symptoms.

Assure your patient that comorbid psychological conditions do not cause symptoms, but can contribute to pain and bowel dysfunction. Consider the possibility of behavioral therapy, if indicated by patient history.

Advise the patient that the initial approach you are taking to alleviate her (or his) symptoms may provide significant improvement. Manage expectations appropriately and be open to discussion about what the patient may need to alleviate both physiologic and psychologic stressors that perpetuate symptoms. Family practitioners, not specialists, are ideally suited to address the patients' needs and expectations as they are the ones who know the patients' histories, personalities, and families best.[1] Tell the patient that rather than hoping for a cure, the goal for the both the physician and patient should be to achieve symptom relief.

Mary Jane finally gets some relief

After speaking with Mary Jane and doing a thorough exam, you reassure her that her symptoms meet the criteria for the diagnosis of IBS, and that research indicates that she can safely be treated for the disorder.

You tell your patient that you'd like to begin treatment by putting her on loperamide—2 capsules at onset of diarrhea and 1 capsule after each diarrheal episode to a maximum of 8 capsules a day and a low-dose amitriptyline (25 mg at bed-

time). You explain that the tricyclic should provide her with some relief by modifying the way the nervous system of the intestine communicates with the brain.

Two months later, during a follow-up visit, Mary Jane tells you that the medications are providing her with relief, but when she feels particularly stressed at home, she notices that her symptoms flare up. You and she discuss the benefits of cognitive behavioral therapy, and you provide her with the names of some therapists in the area. You suggest that she consult her health plan and make some phone calls to identify a provider that she feels comfortable with.

You advise her to schedule another follow-up visit in 3 months so that you can see how the therapy is working. You also tell her to call any time she experiences significant pain or any symptoms that are persistent or worrisome to her. ■

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FAST TRACK

Rather than hoping for a cure, the goal should be to achieve symptom relief

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FAST TRACK

FPs—not specialists—are ideally suited to address IBS patients' needs