AGA Technical Review on Irritable Bowel Syndrome

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The irritable bowel syndrome (IBS) is part of the larger group of functional gastrointestinal (GI) disorders that, despite differences in location and symptom patterns, share common features with regard to their motor and sensory physiology, central nervous system (CNS) relationships, and the approach to patient care.[1] IBS is a functional bowel disorder characterized by symptoms of abdominal pain or discomfort that is associated with disturbed defecation.[2] This disorder is highly prevalent and can be associated with significant emotional distress, impaired health-related quality of life (HRQL), disability, and high health care costs. Psychosocial factors, although not part of IBS per se, have an important role in modulating the illness experience and its clinical outcome.[3]

Knowledge of the pathophysiology of IBS and the diagnosis and management of patients has previously been hampered by few well-designed investigations, a lack of diagnostic precision, and an absence of specific treatments. In the last 5 years, since publication of the previous AGA Technical Review on IBS,[4] there has been a notable increase in basic, mechanistic, and clinical investigations that has improved our understanding of this disorder and its physiological and psychosocial determinants. The adoption of multinational symptom-based criteria,[1] particularly for clinical research studies, has increased diagnostic precision, and within clinical practice, may lead to a reduction in unneeded diagnostic studies. Finally, treatment methods have evolved toward use of more integrated multicomponent pharmacological and behavioral strategies based on the severity of, and psychosocial factors, influencing the patient's symptom pattern.

This technical review updates our previous report.[4] Based on a critical review and analysis of the existing literature, we address: (1) the epidemiology and impact of the disorder, (2) its pathophysiological determinants, (3) the role of psychosocial factors in symptom experience and behavior, (4) the diagnostic approach, and (5) recommendations for treatment.

Definition and Classification

The Rome classification system[1] characterizes the IBS in terms of multiple physiological determinants

contributing to a common set of symptoms rather than a single disease entity. It is defined as a "group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habit, and with features of disordered defecation."[2,3] Table 1 lists the recently revised Rome II diagnostic criteria for IBS.[1]

Epidemiology

Prevalence

Table 2 gives the prevalence estimates for IBS from population surveys among American, European, and Australia/New Zealand adults. These prevalence estimates vary due to the diversity of definitional criteria and to differences in the specific questions used to elicit the information. There is also evidence that survey recall rates for reporting bowel symptoms are frequently inaccurate[5] and are strongly influenced by anxiety.[6]

The data from Table 2 may be summarized as follows: (1) the prevalence of IBS is greater in women; (2) the first presentation of patients to a physician is between the ages of 30 and 50 years, and there is a decrease in reporting frequency among older subjects; and (3) the prevalence seems to be similar in whites and blacks, but may be lower in Hispanics. Sandler's analysis of the NHANES data[27] shows a 5-fold greater prevalence of IBS in whites than blacks. However, this was based on self-report rather than symptom criteria or may have been influenced by limited access to health care by blacks. The overall prevalence was 2.9%. However, epidemiological studies of non-European American and non-Western ethnic groups are limited and may be confounded by cultural influences. Available studies suggest that IBS seems to be as common in Japan, China, South America, and the Indian subcontinent as it is in

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Table 1. Rome II Diagnostic Criteria for Irritable Bowel Syndrome[3]

At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has 2 of 3 features:
1. Relieved with defecation; and/or
2. Onset associated with a change in frequency of stool; and/or
3. Onset associated with a change in form (appearance) of stool.

Symptoms that cumulatively support the diagnosis of IBS:
1. Abnormal stool frequency (for research purposes, "abnormal" may be defined as greater than 3 bowel movements per day and less than 3 bowel movements per week);
2. Abnormal stool form (lumpy/hard or loose/watery stool);
3. Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation);
4. Passage of mucus;
5. Bloating or feeling of abdominal distention.

NOTE. The diagnosis of a functional bowel disorder always presumes the absence of a structural or biochemical explanation for the symptoms.

Western countries.[3] There are limited data to address incidence rates.

Symptom Features

In the short term (weeks to months), the symptoms of IBS occur frequently. In a study of 59 patients in the United States, England, and the Netherlands, the majority reported at least one GI symptom on over one half of the days, and pain was reported one third of the time.[7] Symptom episodes (defined as a period of symptoms bounded by symptom-free days) occurred 12.4 times during the 12 weeks of observation and averaged 5 days/episode.

Over a longer period of time (years), the symptoms of IBS wax and wane. When the prevalence of IBS is examined in the same population at 2 time points separated by 12 months[8] or 5 years,[9] the point prevalence remains almost unchanged. However, up to 40% of subjects reporting symptoms at time 1 lose them at time 2, only to be replaced by new cases at time 2.

Health Care Utilization and the Health Care Burden

In the United States, up to 70% of persons with IBS symptoms do not seek medical attention.[10,11] This may relate to cultural factors,[12] the presence and degree of pain,[13–17] and psychological disturbance.[14,18] However, these rates are also influenced by access to health care. In the United States, where up to 40% of patients do not have easy access to health care, the consulting rate is 46%,[17] whereas in Australia, where health care access is close to 100%, the consulting rate is 73%.[19] IBS accounts for 12% of patients seen in primary care prac-

tice and is the largest diagnostic group seen in GI practice. Two surveys of AGA members[20,21] undertaken 10 years apart show that functional GI disorders comprised respectively 41% and 35% of symptomatic outpatients' diagnoses, and IBS was the most frequent of the functional GI diagnoses.

Patients with IBS, when compared with persons with IBS not seeking health care or persons without bowel symptoms, have more non-GI complaints and consult physicians more for these symptoms.[13,22,23] Female patients with IBS are 3 times as likely to receive a hysterectomy[24] and report more surgical procedures such as appendectomies.[25] In the U.S. Householder Study,[17] persons with IBS visited physicians 1.64 times in the year before the survey for GI and 3.88 times for non-GI complaints, compared with 0.09 and 1.77 times, respectively, for persons without bowel symptoms.

Although most persons with IBS do not consult physicians, the cost to society in terms of direct medical expenses and indirect costs, such as work absenteeism, is considerable: (1) they miss 3 times as many work days as those without bowel symptoms (13.4 days vs. 4.9 days) and are more likely to report that they are too sick to work (11.3 % vs. 4.2 %)[17]; (2) there are between 2.4 and 3.5 million physician visits annually for IBS in the United States,[26,27] during which 2.2 million prescriptions are written[27]; and (3) they incur health care costs of $4044 (1995 dollars), compared with $2719 for those without IBS over the previous year.[23] In a comprehensive assessment of burden of illness for GI illnesses in the United States, IBS was second only to esophageal reflux disease in its prevalence (15.4 million people) and was associated with $1.6 billion in direct and $19.2 billion in indirect costs.[28] By adding 3.5 million people suffering from chronic diarrhea, the prevalence for lower functional bowel disorders nears that of gastroesophageal reflux disease.[28] These data have important implications with regard to the need to identify treatments that can help improve HRQL and associated costs to society among a very large clinical population.

Pathophysiology of IBS Symptoms

The physiological mechanisms responsible for abdominal pain and altered bowel habits occur in healthy control subjects and in persons with IBS. Symptoms can occur in response to a disruption of functioning of the GI tract from an infection, dietary indiscretions (e.g., increased fat or alcohol intake), lifestyle changes (e.g., traveling or vigorous physical activity), or psychologic stress. Among college students and hospital employees, 71% reported that stresses affected their bowel pattern,

Table 2. Epidemiological Studies of IBS in Western Countries Using Symptom Criteria

Source	Group characteristics	Sample size	Age (yrs)	Diagnostic criteria	% IBS Total	% IBS Females	% IBS Males
Talley et al.[15]	Olmsted County, MN white = 99%	N = 835 Response = 82%	50 Range 30–64	≥3 Manning Sx ≥2 Manning Sx	12.8 17.0	13.6 18.2	12.1 15.8
Heaton et al.[16]	English urban white = 99%	N = 1896 Response = 72%	Female 25–69 Male 40–69	≥3 Manning Sx	9.5	13.0	5.0
Jones and Lydeard[225]	Southern English mostly white	N = 1620 Response = 71%	20–90	≥2 Manning Sx	21.6	24.3	18.7
Drossman et al.[17]	U.S. householder white = 95% female = 51%	N = 5430 Response = 66%	49 ± 16	Rome I	9.4	14.5	7.7
Kay et al.[9]	Copenhagen sex stratified	N = 3608 Response = 79%	Age stratified	Altered bowel habits and pain relieved by defecation	6.6	7.7	5.6
Zuckerman et al.[226]	El Paso, TX white = 36% Hispanic = 64% female = 66%	N = 905 Response = 99%	30.5 ± 9.3	Drossman criteria	16.9 Hispanics 21.8 white	21.7 26.5	7.1 13.9
Taub et al.[227]	U.S. college students black = 26.9% female = 62%	N = 1344 Response = 87%	21.2 ± 5.6	≥3 Manning Sx	16.9 black 15.0 white	19.1 18.0	9.7 9.1
Osterberg et al.[228]	Stockholm	2707 (54)	31.5 (31.3–31.8)	Rome I	10.6	13.3	7.4
Boyce et al.[229]	Sydney	2910 (72)	43.8 (43.2–44.3)	Manning Rome I Rome II	13.6 4.4 6.9	17.2 6.4 9.2	9.8 2.2 4.6
Talley et al.[230]	Dunedin	890 (86)	Longitudinal study (ages 3–26)	≥2 Manning Rome II	12.7 4.3	14.6 5.3	10.8 3.3
Thompson et al.[231]	Canada	1149 (57)	Weighted age sample (18 to >64)	Modif Rome II Rome I	12.1 13.5	15.2 18.1	8.7 8.5

and 54% reported that stress led to abdominal pain or discomfort.[10]

Abnormal Motility in Patients With IBS

Table 3 details the studies of altered GI motility in IBS and is summarized below. The differences between IBS patients and healthy controls are quantitative rather than qualitative.

Motility observations in the stomach, small intestine, colon, and rectum are qualitatively similar to those in healthy controls. Moreover, only 25%–75% of IBS patients exhibit the motility "abnormalities" listed in Table 3, which are considered to differentiate IBS from healthy controls. These motility parameters cannot be used as diagnostic markers.

In the ileum, colon, and rectum, IBS patients show an exaggerated response to a variety of provocative stimuli including meals, distention, stress, cholecystokinin, neostigmine, and corticotropin-releasing hormone injection. No corresponding pattern of hyper-reactivity has been shown in the proximal small intestine and stomach, where the response to stress (inhibition of contractions) differs from the response to meals (increase in contractions).

There is no consensus on the patterns of motility responsible for diarrhea and constipation, although accelerated transit is seen in diarrhea and slowed transit is seen in constipation. Among IBS patients exhibiting diarrhea and abdominal pain, there are significantly more high-amplitude propagating contractions, which are of higher amplitude than those observed in healthy controls, and these high-amplitude propagating contractions are more likely to be associated with a sensation of pain.

Motility abnormalities may interact with low sensory thresholds to produce symptoms: delayed transit of gas causes greater abdominal perception in IBS,[29] and IBS patients are more likely than healthy controls to perceive the occurrence of normal migrating motor complexes.[30]

Visceral Hypersensitivity in IBS

In 1973, Ritchie first reported that IBS patients have pain at lower volumes and pressures when a balloon is inflated in the bowel.[31] This seminal observation has been replicated by a number of research laboratories,[31–36]

Table 3. Studies of Altered GI Motility in IBS

Motility Parameter	Comments	Study
Stomach		
	Delayed emptying, greater for solids	Van Wijk et al.[232]; Evans et al.[233]; Caballero-Plasencia et al.[234]
	Anger inhibits antral motility	Welgan et al.[235]
	Electrogastrogram abnormal in 1/4 of IBS with comorbid dyspepsia, but only 8% without dyspepsia	Leahy et al.[236]
Small intestine		
Discrete clustered contractions	Increased frequency, duration of DCCs; DCCs associated with pain	Kumar and Wingate[237]; Kellow et al.[238]; Schmidt et al.[239]; Simren et al.[240]
	No increase in DCCs	Gorard et al.[241]
	Increased DCCs following CRH	Fukudo et al.[242]
Prolonged propagating contractions	No increase in frequency, but PPCs associated with pain in IBS	Kellow and Phillips[243]
Migrating motor complex	Increased frequency of MMCs	Kellow and Phillips[45]
	Normal frequency of MMCs	Gorard et al.[241]
Phasic contractions	Duodenal and jejunal contractions suppressed by stress	Kellow et al.[244]
	Greater increase in ileum with distention, fatty meal and CCK	Kellow and Phillips[243]
	More retrograde duodenal and jejunal contractions	Schmidt et al.[239]; Simren et al.[240]
Small bowel transit	Delayed in IBS-C; accelerated in IBS-D	Cann et al.[245]; Lu et al.[246]
	Accelerated in IBS-D	Vassallo et al.[247]
	Impaired transit of infused gas resulting in discomfort/pain	Serra et al.[29]
	IBS patients more likely to perceive occurrence of MMCs	Kellow et al.[30]
Colon and rectum		
Phasic contractions	No difference from control at rest, but greater increase following rectosigmoid distention	Whitehead and Drescher[248]
	Greater increase after meal	Rogers et al.[249]
	Greater increase with stress	Welgan et al.[111]; Fukudo and Suzuki[250]
	Greater increase with neostigmine	Fukudo and Suzuki[250]
	Increased number and amplitude of HAPCs in colon; increased phasic motility in descending colon and response to intravenous CKK	Ladabaum et al.[251]
	Greater increase with CRH	Fukudo et al.[242]
Myoelectric activity	Increased long spike bursts with diarrhea; irregular short spike bursts with constipation	Bueno et al.[252]
Compliance and tone	Normal compliance in IBS	Whitehead et al.[248]
	Normal fasting and postprandial tone in descending colon	Vassallo et al.[253]
	Increased fasting muscle tone in rectum	Whitehead et al.[254]; Blomhoff et al.[255]
Colonic transit	Delayed in IBS-C; accelerated in IBS-D	Cann et al.[245]
	Whole gut and colonic transit accelerated in IBS-D, but normal in IBS-C	Horikawa et al.[256]

DCC, discrete clustered contractions; CRH, corticotropin-releasing hormone; CCK, cholecystokinin; HAPC, high-amplitude propagated contractions; IBS-C, constipation predominant IBS; IBS-D, diarrhea-predominant IBS; MMC, migrating myoelectric complex; PPC, prolonged propagated contractions.

and the threshold to report pain is below the normal range in 50%–70% of IBS patients. Consistent with the concept of enhanced perception of visceral events are observations that IBS patients are more likely than controls to notice intestinal contractions[37] and gas,[29] and their pain thresholds are correlated, albeit weakly, with the amount of clinical pain they experience.[32,38,39]

Enhanced perception of visceral events is documented throughout the GI tract, including the esophagus,[40] stomach,[41] duodenum,[42–44] and ileum.[45] However, IBS patients do not show somatic hypersensitivity to pain[42,46,47] and may have elevated[48,49] somatic pain thresholds.

One study[32] noted that when combining other measures of pain sensitivity, such as the intensity with which the pain sensation is described and the location and size of the somatic referral area, up to 95% of patients show evidence of visceral hypersensitivity. The investigators concluded that visceral hypersensitivity might be a biological marker for IBS, although this interpretation has been challenged.[38]

Inflammation

Preliminary evidence for a possible alteration in gut immune function in IBS comes from both unselected

Table 4. CNS Modulation of Gut Sensations

Central mechanism	Targets of modulation	Resulting mechanism of sensitization
Autonomic nervous system	Gut effector cells (enterochromaffine cells, immune cells, smooth muscle cells, ICCs)	Modulation of peripheral afferent nerve terminal excitability
Descending bulbospinal pathways (inhibitory, facilitatory)[88]	Dorsal horn of spinal cord	Central (spinal sensitization)
Ascending arousal systems[83,89]	Prefrontal and anterior cingulate cortex	Hypervigilance

ICCs, interstitial cells of Cajal.

and so-called postinfectious IBS (PI-IBS) patients. In unselected patients, increased numbers of mast cells in the muscularis externa of the colon[50] and the ileal and colonic mucosa[51,52] have been reported. Increased cellularity of the colonic mucosa and lamina propria has also been described in unselected IBS patients using semi-quantitative microscopy.[53] In patients with intractable IBS, lymphocytic infiltrates of the myenteric plexus were reported,[54] and most recently, preliminary evidence for increased iNOS (nitric oxide synthetase) expression was described.[55] For subgroups of IBS, these findings suggest there is an up-regulation of gut immune function. However, methodological deficiencies exist, including the influence of the bowel preparation, the classification of the patients, and the nonquantitative analysis of gut cells. Further studies are needed to explore these intriguing findings.

Further support for a possible role of altered gut immune function in IBS comes from recent studies in PI-IBS patients.[56–59] A subset of IBS patients associate the development of IBS symptoms with the onset of gastroenteritis.[60–62] In recent prospective studies, IBS-like symptoms were found in 7%–30% of patients who recovered from a proven bacterial gastroenteritis.[59] Reported risk factors included: female gender, duration of the acute diarrheal illness, and the presence of significant life stressor occurring around the time of the infection. Patients with PI-IBS were found to have a variety of functional alterations, including changes in gut motility,[63,64] epithelial function,[65,66] and an increase in colonic enterochromaffin cells.[66] In addition, evidence for increased expression of interleukin 1β messenger RNA, increased cellularity of lamina propria, and an increase in CD3$^+$ lymphocytes were reported from mucosal biopsy specimens.[66] The correlation of IBS symptoms with these observed changes has not been established. Furthermore, because the majority of patients do not develop postinfectious diarrhea and the prevalence of IBS is not higher in countries with high rates of enteric infections, further studies are required to determine if vulnerability factors (such as altered neuroimmune system responsiveness) play a role in the development

of PI-IBS in a subset of patients. In addition, psychological distress seems to be an important cofactor in determining who retains symptoms after an enteric infection.[67]

Autonomic Activity

Abnormalities in extrinsic autonomic innervation of the viscera occur in approximately one fourth of patients with functional bowel disorders.[68,69] Aggarwal et al. showed that cardiovagal dysfunction is specifically associated with a constipation-predominant subgroup of patients with IBS, whereas patients with diarrhea-predominant symptoms had evidence of sympathetic adrenergic dysfunction.[70] The role of autonomic dysfunction in IBS requires further evaluation.

Central Nervous System Modulation

In general, brain-gut interactions play a prominent role in the modulation of gut function in health and disease.[71–74] Signals from the brain to the gut assure that digestive function is optimized for the overall state of the organism (e.g., sleep vs. wake, stress vs. relaxation).[75] Conversely, signals from the gut to the brain play a role primarily in reflex regulation[76] as well as in modulation of mood states.[77] In addition, certain vagal afferent pathways can influence pain perception.[78]

The CNS modulates motility, secretion, immune function, and blood flow.[79] The emotional motor system in the brain[80] is a revised name for the limbic system and some paralimbic structures (including the medial prefrontal cortex, amygdala, and hypothalamus) communicate emotional changes via the autonomic nervous system to the gut. The CNS is also essential in the perception of events occurring within the gut. This brain-gut bidirectional communication is largely not perceived consciously. In effect, the CNS functions as a "filter" with regard to the perception of peripheral afferent signals, and the threshold for perception can vary depending on the individual's emotional and cognitive state. Most visceral afferent signals reach the brainstem and thalamus, and only a very few are consciously perceived in the cortex.[81] However, one recent study[82] suggests that low intensity signals are subliminally registered.

Modulation of visceral afferent information occurs at multiple levels from the periphery to cortical regions, as shown in Table 4. The activation of these modulatory systems is dependent on peripheral as well as central events, even though the latter seem to be dominant. For example, although acute gut inflammation results in sensitization of peripheral, spinal, and central transmission,[83] it is hypothesized that chronic inflammation may adaptively down-regulate perceptual sensitivity.[49,84,85] Stress, anxiety, or recall of aversive memories all can enhance perception of painful events,[86] whereas distraction, hypnosis, and relaxation can decrease perceptual sensitivity.[87,88] Stress-induced visceral hyperalgesia[89] may be an important mediator of visceral hypersensitivity in IBS patients. Therapeutic approaches aimed at attenuating stress responsiveness may effectively prevent the development of stress-induced visceral hypersensitivity, as well as attenuate autonomic gut responses to stress.[90,91]

Evidence for the alterations in the way the brain responds to visceral stimuli, and how this response may be altered in IBS patients, comes from recent studies using functional brain imaging techniques.[92–96] Two of the studies, using distal colonic stimulation, have shown a greater activation in IBS patients of the midcingulate cortex, a brain region concerned with attentional processes and response selection.[97,98] Modulation of this region by hypnotic suggestion was associated with changes in the subjective unpleasantness of a somatic pain stimulus in another study.[88] The extent of abnormal visceral afferent processing by the brain in IBS patients needs to be established because they may be plausible mediators of various therapeutic approaches: cognitive therapies are likely mediated via networks involving the lateral prefrontal cortex, which in turn enhance the restraining effect of the medial prefrontal cortex on the emotional motor system.[77] Hypnosis is likely to modulate attentional mechanisms (including the midcingulate cortex),[88,99] and relaxation exercises involving deep breathing techniques may alter vagal afferent input to the brain. Centrally targeted medications such as anxiolytics, low dose tricyclic antidepressants (TCAs), NK-1R antagonists, and CRF1R (corticotropin releasing factor 1R) antagonists all involve inhibitory effects on the responsiveness of the emotional motor system and provide options for future therapeutic investigations.

Role of Psychosocial Factors in IBS

Research on the psychosocial aspects of patients with IBS has yielded 4 general observations.[100]

1. *Psychologic stress exacerbates GI symptoms.* Although stressful experiences produce GI symptoms in most individuals, patients with IBS are particularly susceptible.[10] Studies of the effects of stressful life events on IBS patients are shown in Table 5. With one exception,[101] these studies suggest IBS patients report more lifetime and daily stressful events,[10,14,102–107] including severe abuse history,[108,109] than medical comparison groups or healthy controls. Furthermore, in IBS patients, stress is strongly associated with symptom onset[105,107,110] and symptom severity.[109] Even though the effects of stress on gut function are universal, patients with IBS seem to have greater reactivity to stress.[72,111] The identification of specific psychological stressors associated with exacerbation of symptoms may help in planning treatment through psychological or psychopharmacological interventions.

2. *Psychological and psychiatric comorbidity is common among patients with IBS.* A large proportion of patients with IBS and other functional bowel disorders have concurrent psychological disturbances. As shown in Table 6, when using standardized research interviews, the prevalence of a psychiatric disorder ranges from 40% to over 90% among patients with IBS/functional bowel disorders in tertiary care centers. Other psychological features identified to be greater in IBS include personality style,[14,106,112] psychological distress,[18,109,113] and altered health beliefs, cognitions, and coping style.[114–117] As indicated below, these findings are not associated with the disorder per se, but their prevalence is over-represented within the health care–seeking subset of patients.

3. *Psychosocial factors affect health status and clinical outcome.* Psychological and sociocultural factors, when present in patients with IBS, will also influence the illness experience and treatment outcome. Psychosocial factors that adversely affect health status and clinical outcome include: (1) a history of emotional, sexual, or physical abuse[109,118–121]; (2) stressful life events[104,110]; (3) chronic social stress[122] or anxiety disorder[123,124]; and (4) maladaptive coping style.[119] Some of these psychosocial influences may occur early in life. For example, increased attention by family to a child's illness complaints seems to result in delayed symptom reporting, health care seeking, and health care costs.[125–129]

Table 5. Effects of Stress on IBS Symptoms

Subjects studied	Assessment	Results	Study
102 IBS 158 UC 735 Controls	Unvalidated stress interview	More stress in IBS than in IBD or healthy controls	Mendeloff et al.[102]
20 IBS 20 IBD 20 Appendicitis	Standardized life event scale	More stressful events reported by IBS patients than controls	Fava and Pavan[103]
135 IBS 654 Controls	Self-report that stress affects bowel symptoms	72.6% of IBS and 54.4% of controls reported stress led to change in stool pattern 84.4% of IBS and 67.6% of controls reported stress led to abdominal pain	Drossman et al.[10]
36 IBS 12 Dyspepsia 16 Organic GI	Bedford College life events and difficulties interview	No relationship between stress and functional bowel disorder	Ford et al.[101]

72 IBS patients
82 IBS nonconsulters
84 Controls
	Standardized life event scale	IBS patients reported:
		    fewer negative stressful events and perceive them as less severe
		    fewer positive life events
		IBS nonconsulters reported more negative life events than controls
			Drossman et al.[14]

79 Functional 56 Organic 135 Control	Psychiatric interview based on the life events and difficulty schedule	60%–66% had experienced severe life events preceding onset of IBS vs. 25% of controls for an arbitrary time	Creed et al.[110]
206 Female GI clinic patients	Questionnaire used to detect physical and sexual abuse	Patients more likely to report physical or sexual abuse compared with patients with organic GI disorders	Drossman et al.[108]

40 IBS
32 Peptic ulcer
	Psychosocial assessment	IBS patients:
		    reported greater negative life events
		    scored higher for neuroticism and extroversion
		    not different from ulcer patients for psychiatric diagnoses
			Dinan et al.[106]

39 IBS
108 FBD
232 Controls
	Life event questionnaire given every 3 months for 1 year (5 times)	Stressful events more common in IBS
		Stress correlated with:
		    number of bowel symptoms
		    disability days
		    physician visits
		Patients and nonpatients with IBS show greater reactivity to stress than people without IBS
			Whitehead et al.[104]

239 Women in GI clinic with 1-year follow-up	Standardized abuse history interview and psychosocial/outcome questionnaires	Abuse history was associated with poorer health status and outcome with regard to:
		    pain scores
		    bed disability days
		    psychological distress
		    daily function
		    health care visits
		    lifetime surgeries
		Severe abuse history more prevalent in functional vs. organic disorders
			Drossman et al.[109]

26 IBS patients
23 IBS nonpatients
26 Controls
	Evaluated relationship between daily stress using and GI symptoms using daily diaries and LES	IBS and IBS nonpatients vs. controls
		    higher mean GI symptoms and stress
		    no difference in LES scores
		Within group both IBS and IBS nonpatients: significantly positive relationship between daily stress and daily symptoms
			Levy et al.[107]

154 Children with RAP 109 Well children	Consecutive daily telephone interviews to assess daily stressors and symptoms	More frequent daily stressors than well children Association between daily stressors and symptoms was stronger for patients with RAP than well children	Walker et al.[105]

LES, life event survey; RAP, recurrent abdominal pain.

Table 6. Prevalence of Psychiatric Disorder in Functional Bowel Disorder/IBS Using Standardized Research Psychiatric Interviews

Number of subjects	Instrument for psychiatric disorder	Functional bowel disorders	Organic gastrointestinal disorder	Healthy controls	Study
32 (FBD)	CIS	53%	20%	—	McDonald and Bouchier[257]
79 (FBD)	PSE	42%	18%	—	Craig and Brown[258]
44 (IBS)	PSE	42%	6%	8%	Ford et al.[101]
37 (FBD)	CIS	57%	6%	—	Colgan et al.[259]
48 (IBS)	CIS	48%	—	—	Corney and Stanton[260]
44 (IBS)	DIS	61%	—	14%	Toner et al.[261]
68 (IBS)	DIS	56%	25%	18%	Blanchard et al.[262]
71 (IBS)	DIS	94%	65%	—	Walker et al.[263]
50 (IBS)	SCID	54%	—	—	Irwin et al.[264]

FBD, functional bowel disorder (e.g., consecutive nonorganic gastrointestinal disorders in the clinic); CIS, clinical interview schedule; PSE, present state examination; DIS, diagnostic interview schedule for diagnostic statistical manual (DSM-IIIR and DSM-IV); SCID, structured clinical interview for DSM-IIIR and DSM-IV.

4. *Psychosocial factors influence which patients consult physicians*. This tends to overestimate the true prevalence of psychosocial disturbance when evaluating patients in referral clinical settings. In fact, persons with IBS who do not see physicians are psychologically similar to subjects without bowel complaints.[14,18,130]

IBS Can Lead to Impaired HRQL

HRQL addresses the psychological and social consequences of having IBS. It incorporates the patient's perceptions, illness experience, and functional status.[131] Several self-administered questionnaires to study HRQL now exist for GI disorders[132] and IBS.[133] To date, 2 IBS-specific instruments have been shown to be responsive to change.[134,135]

The data show that patients with functional GI disorders have poorer functional status (Sickness Impact Profile) than those with organic GI diagnoses.[109] In addition, patients with IBS have significantly poorer HRQL (SF-36) than the general population or of patients with gastroesophageal reflux disease, and have selected impairments in HRQL relative to patients with diabetes and end-stage renal disease.[136] However, the degree of impairment also relates to the population being studied: nonpatients with IBS have HRQL scores (SF-36) that are intermediate between referred IBS patients (who were similar to patients with congestive heart failure) and normal controls.[137] When using IBS-specific questionnaires, patients show the lowest scores related to interference with activity, food avoidance, and health worry concern (IBS quality of life).[138] Moreover, quality of life improves in relation to changes in pain severity and daily function after psychological or antidepressant treatment.[134] When compared with patients having other GI conditions, physical, emotional, and social role functions and energy (IBS quality of life) were poorer.[139]

Figure 1 provides a conceptual model on the role of psychosocial factors on illness and outcome in IBS. Early life factors influence later psychosocial experiences, physiologic functioning, and susceptibility to developing IBS. Therefore, a psychosocial stressor, interpreted from previous experiences, may produce symptoms primarily through changes in intestinal function, central amplification of normal gut signals, or a combination of these factors. The combined and integrated effects of altered physiology and the person's psychosocial status via the brain-gut axis affects how the symptom is experienced, the individual's illness behavior, and ultimately the outcome. Furthermore, the clinical outcome will, in turn, affect the severity of the disorder. Therefore, while psychosocial factors are not etiologic to IBS, they are rele-
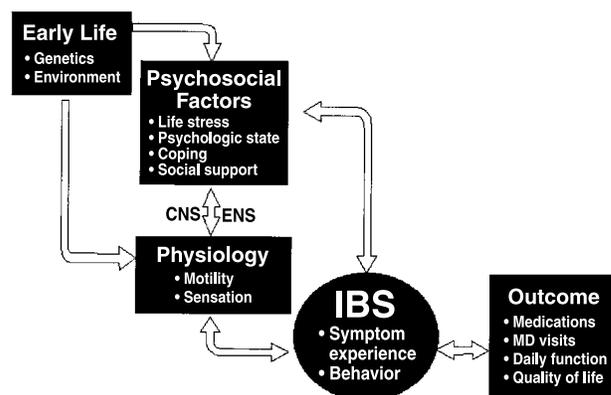
IBS - Conceptual Model

Figure 1. A conceptual model depicting the relationship between early life, psychosocial factors, physiology, symptom experience, and behavior and outcome. See text for details.
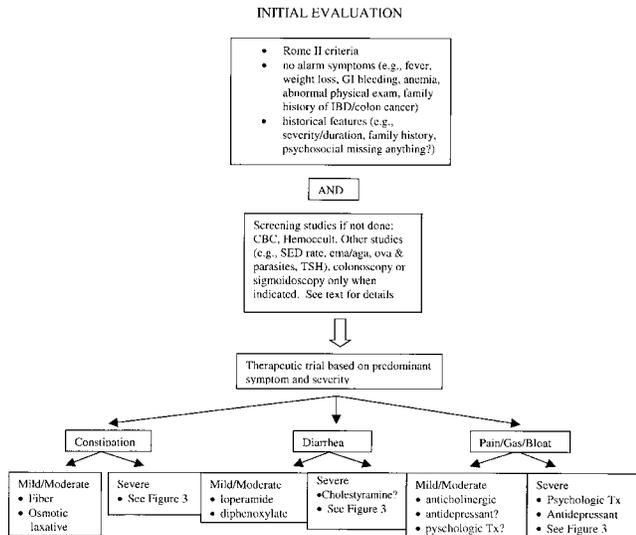
Figure 2. Initial evaluation by the gastroenterologist for patients with IBS.

vant to understanding the patient's adjustment to IBS, the clinical outcome, and the plan of treatment.

Diagnosis

Symptom-Based Criteria

A diagnosis is based on identifying positive symptoms (e.g., Rome criteria) consistent with the condition (Table 1), and excluding, in a cost-effective manner, other conditions with similar clinical presentations, which may include organic or other functional (e.g., functional diarrhea or bloating, pelvic floor disorders, or slow transit constipation with associated abdominal discomfort relieved with defecation) disorders.[3,140] Any needed tests, as suggested by "alarm features," should be discussed with the patient and set up at the first encounter. When "alarm features" such as weight loss, refractory diarrhea, and family history of colon cancer are excluded, the specificity of the symptom-based Rome I criteria for IBS exceeds 98% and hence, the risk of missing organic disease is low.[141]

Evaluation

A physical examination should be performed on the first visit and on subsequent visits as needed. This is done to exclude findings not consistent with IBS (e.g., enlarged liver, abdominal mass, signs of bowel obstruction) and to meet the patient's expectations of a thorough evaluation. A pelvic examination is often indicated for lower abdominal/pelvic symptoms and/or if there is a change in menstrual pattern. A rectal examination, particularly for patients reporting symptoms of incontinence or dyschezia, can help to identify a lax sphincter or

paradoxical pelvic floor muscle contraction. This may require anorectal testing of pelvic floor muscle function.

Two algorithms applicable to the evaluation of patients with IBS seen in primary care settings have recently been presented.[142] Figures 2 and 3, as summarized below, provide an algorithm for patients presenting to gastroenterologists.

In general, if Rome criteria are fulfilled, "alarm signs" or "red flags" are not present, and screening studies from the referring physician are negative, further testing is not needed. Screening studies are recommended when certain historical information is present[143]: (1) short symptom duration or worsening severity and trajectory of symptoms, (2) demographic features (e.g., onset in an older patient), (3) family history (e.g., colon cancer or inflammatory bowel disease), and (4) no concurrent psychosocial difficulties or symptom behaviors (particularly the absence of comorbid psychosocial features or health care seeking). We recommend a complete blood count and a stool hemoccult for screening purposes. A sedimentation rate (particularly in a younger patient), serum chemistries, thyroid-stimulating hormone (TSH), and stool for ova and parasites can be ordered based on symptom pattern, geographic area, and relevant clinical features (e.g., predominant diarrhea, areas of endemic infection). However, studies do not generally support a role for these tests without supportive clinical features.[144] A colonoscopy is recommended for patients over age 50 (due to higher pretest probability of colon cancer), but in younger patients, performing a colonoscopy or sigmoidoscopy is determined by clinical features suggestive of disease (e.g, if there is significant diarrhea) and may not be indicated. There has been growing interest in the use of antiendomysial (ema) and antigliadin (aga) antibodies to diagnose celiac sprue.[145–147] However, such testing
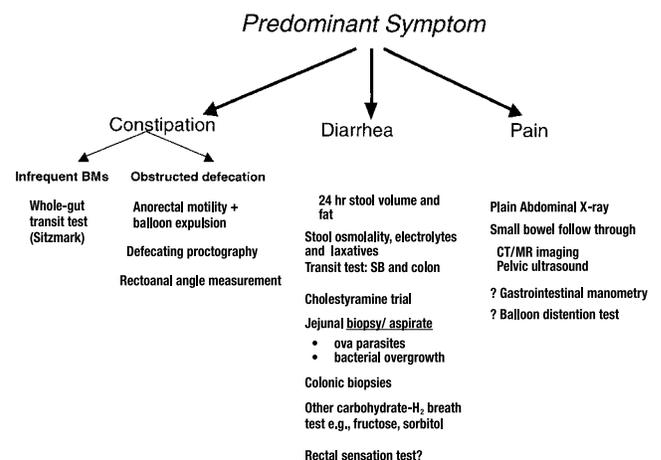

Figure 3. Diagnostic evaluation based on symptom subtype after initial treatments are insufficient to control patient's symptoms.

must be put into a clinical perspective as determined by presence of symptom pattern, ethnicity, and other clinical features suggestive of the disease.[143]

In many cases, the therapeutic trial can be undertaken before further diagnostic studies are done and will depend on the symptom subtype and its severity (Figure 2): for constipation, fiber, or an osmotic laxative; for diarrhea, loperamide, or diphenoxylate-atropine and possibly cholestyramine; and for pain/gas/bloating, an anticholinergic, or, if more severe, antidepressant or psychologic treatment may be considered. It needs to be emphasized that patients presenting with typical symptoms and no "alarm" signs are rarely found to have another diagnosis,[144,148] supporting the benefit of ongoing care and symptomatic management rather than continued diagnostic evaluation.

If initial treatment fails, or certain clinical features emerge requiring further evaluation, we recommend the algorithm indicated in Figure 3. Many of these studies are performed by gastroenterologists in specialty centers.

In patients with infrequent bowel movements, whole gut transit study by Sitzmark technique or a plain radiography (to evaluate for obstructive signs or fecal retention) is indicated. When symptoms of dyschezia or incomplete evacuation are prominent, suggesting obstruction to defecation, or when the physical examination discloses poor pelvic floor relaxation with straining, further anorectal testing is indicated. This includes anorectal motility testing with balloon expulsion (to evaluate for pelvic floor dyssynergia) or defecography (to evaluate for enterocele or rectocele).

If diarrhea is persistent, other tests to consider include: 24-hour stool volume and fat; if increased (>400 mL/day), electrolytes and laxative screen; and small bowel biopsy for *giardia lamblia* or sprue and colonic biopsy for microscopic colitis. On occasion, transit tests of the small bowel and colon can help evaluate the severity of the motility component of the diarrhea. A therapeutic trial of cholestyramine may also be considered, particularly if symptoms developed or worsened after a cholecystectomy. A jejunal biopsy and aspirate can be done to obtain samples to assess malabsorption (e.g., sprue), or to obtain an aspirate for giardia or for bacterial overgrowth. Colonic biopsies can be considered to evaluate for collagenous or lymphocytic colitis, although the findings may not lead to instituting more effective treatments. Finally, when postprandial symptoms of bloating and gaseousness accompany the diarrhea, a breath H_2 study to exclude bacterial overgrowth can be considered.[149]

The persistence of pain-predominant symptoms or severe bloating usually requires plain abdominal radiography during an acute episode to exclude bowel obstruction, an increased gastric air bubble from aerophagia, and/or other abdominal pathology. If negative, additional imaging studies (e.g., small bowel radiography, computerized tomography scan, pelvic ultrasonography) may be recommended, particularly when there are other symptoms or signs present (e.g., vomiting, weight loss, abdominal mass, irregular menses, abnormal chemistries). A balloon distention test may confirm rectal or colonic visceral hypersensitivity, although this test is usually done for investigative purposes.

Treatment

The treatment strategy is based on the nature and severity of the symptoms, the correlation of IBS symptoms with food intake and/or defecation, the degree of functional impairment, and the presence of psychosocial difficulties and psychiatric comorbidity affecting the course of the illness. Table 7 provides a practical framework, supported by recent empiric evidence[150] for differentiating patients into subgroups of severity based primarily on patient pain reports and behaviors.[22,151,152] In general, milder symptoms relate primarily to visceral hyperactivity and/or hypersensitivity and are commonly treated symptomatically with pharmacological agents directed at the gut, whereas more severe symptoms are associated with greater levels of psychosocial difficulties and illness behaviors and often require psychological/behavioral and antidepressant medications.

The most frequently seen group of IBS patients have mild symptoms. They are usually cared for in primary care practices, usually maintain normal daily activities, have little or no psychosocial difficulties (although they may experience symptom exacerbations with stress), and are not high health care users. Treatment involves education, reassurance, and dietary/lifestyle changes. A smaller proportion of patients have moderate symptoms

Table 7. Spectrum of Clinical Features Among Patients With IBS

Clinical feature	Mild	Moderate	Severe
Estimated prevalence	70%	25%	5%
Practice type	Primary	Specialty	Referral
Correlation with gut physiology	+++	++	+
Symptoms constant	0	+	+++
Psychosocial difficulties	0	+	+++
Health care use	+	++	+++
Illness behavior	0	+	+++
Psychiatric diagnoses	0	+	+++

0, Generally absent; +, mild; ++, moderate; +++, marked. Data from Drossman.[265]

that are usually intermittent, although at times disabling. Symptoms may be associated with considerable symptom-related distress, and historical symptoms are associated with greater physiological gut reactivity (e.g., worse with eating, relieved by defecation). Treatments involve gut-acting pharmacological agents (e.g., anticholinergics, antidiarrheals, newer GI treatments, etc.), and if more persistent, possibly low-dose TCAs and/or psychological treatments. Finally, only a very small proportion of patients with IBS have severe and sometimes refractory symptoms. These symptoms predominate among patients seen in referral centers; these patients frequently have more severe, often constant pain symptoms, psychiatric comorbidity (e.g., depression, anxiety disorders), and psychosocial difficulties (history of sexual/physical abuse, poor coping) associated with high health care use rates. These patients require antidepressant medication and possibly mental health or pain center referral, along with an ongoing relationship with the primary care physician to provide psychosocial support through brief, regular visits.[153]

General Treatment Approach

The therapeutic relationship. An effective physician-patient relationship is the cornerstone of effective treatment. Here, the physician must: (1) listen actively to determine the patient's understanding of the illness and his or her concerns, (2) provide a thorough explanation of the disorder, (3) identify and respond to the patient's concerns and expectations, (4) set realistic and consistent limits, (5) involve the patient in the treatment, and (6) establish a long-term relationship with a primary care provider.[153,154] This type of approach is associated with a reduction in health care visits[155] and improved patient satisfaction. Patients who do not feel properly informed have more health care visits.[156] Furthermore, when diagnostic and prognostic information is provided, there is also a reduction in symptoms.[157]

As with any chronic illness, it helps to determine the immediate reasons for the patient's visit. These may include: (1) everyday environmental stressors (e.g., difficulty meeting deadlines, financial or relationship problems, daily "hassles"), (2) new exacerbating factors (e.g., dietary change, concurrent medical disorder, side effects of new medication), (3) personal concern about a serious disease (e.g., recent family death), (4) psychiatric comorbidity (e.g., depression, anxiety), (5) major life events or difficulty adjusting to them (e.g., family death, abuse history), (6) impairment in daily function (e.g., recent inability to work or socialize) or (7) a "hidden agenda" (e.g., narcotic or laxative abuse, pending disability or litigation).

Education and reassurance. Education involves an iterative process in which the physician assesses the patient's level of knowledge about the disorder and provides information, verbally or in print, to enhance the patient's understanding. Patients frequently want to understand the basis for their symptoms, and, at times, seek validation that their symptoms are "real." In practice, useful statements include: "You have a common disorder where the intestine overreacts to a variety of stimuli such as food, hormonal changes, medication, and stress. These stimuli can produce spasm or stretching of the gut, enhanced sensitivity of nerves, or both. This is experienced as pain, diarrhea, constipation, bloating, or any combination anywhere in the abdomen." or "IBS is a disorder where communication between the brain and gut is not in order, so bowel disturbance may trigger symptoms of anxiety or distress, which in turn, makes your symptoms worse. We need to understand both your physical symptoms and the associated emotional distress related to it."

Reassurance should follow after the physician elicits the patient's worries and concerns, and after an adequate and generally conservative diagnostic evaluation. If reassurance is communicated in a perfunctory manner before evaluation, the patient will reject it.

Dietary modification. Although many patients may attribute their symptoms to specific food substances, the type of food does not generally contribute to symptoms. Patients are more likely to experience symptoms as a generalized effect of eating, and at times may even become conditioned to reduce eating to avoid postprandial discomfort. However, certain dietary substances may aggravate symptoms in some individuals. This might include fatty foods, beans, and gas-producing foods, alcohol, caffeine, lactose in lactose-deficient individuals, and, in some cases, excess fiber. Care should be taken to avoid an unnecessarily restrictive diet.

Although fiber has an established role in treating constipation, its value for IBS for the relief of diarrhea is controversial and not helpful for pain. In 2 randomized crossover studies of IBS patients,[158,159] the groups receiving increased fiber (15 g bran and 20 g corn fiber, respectively) and the control groups had similar degrees of symptomatic improvement.

Symptom monitoring. It helps to have the patient use a diary to monitor symptoms for 2–3 weeks to assess the time and severity of symptoms, the presence of possible aggravating factors, and the emotional and cognitive impact of the symptoms on the individual.[153,160] The diary may identify dietary indiscretions or specific stressors not previously considered, and may also give the

patient a sense of participation in the planning of care. The physician can then review and consider diet, lifestyle, or behavioral modifications with the patient. In addition, identification of maladaptive coping styles (e.g., "catastrophizing")[119] may lead to referral for psychological treatment.

Pharmacotherapy Targeted at Specific Symptoms

For pain and bloating, antispasmodic (anticholinergic) medication, particularly when symptoms are exacerbated by meals, should be considered. Meta-analyses of available studies suggest that some of these agents may be effective, although the trial methodology was inadequate by modern standards.[161] In one meta-analysis of smooth muscle relaxants in IBS,[162] 5 drugs showed efficacy over placebo: (1) cimetropium bromide (an antimuscarinic compound), (2) pinaverium bromide and (3) octylonium bromide (quaternary ammonium derivatives with calcium-antagonist properties), (4) trimebutine (a peripheral opiate antagonist), and (5) mebeverine (a derivative of beta-phenyl-ethylamine that has antimuscarinic cholinergic activity). None of these drugs underwent extensive trials in North America or received approval from the Food and Drug Administration (FDA). Notably, the commonly prescribed dicyclomine and hyosyamine were not effective in the meta-analysis. Other meta-analyses have been published with similar conclusions.[163–165] Eight trials with peppermint oil for IBS, including a meta-analysis of 5 placebo-controlled, double-blind trials, have not established a role for this treatment in IBS.[166] There are also meta-analyses on the effect of tricyclic antidepressants, which will be reviewed later.

In clinical practice, antispasmodics and anticholinergic agents are best used on an as-needed basis up to 3 times per day for acute attacks of pain or before meals when postprandial symptoms are present. Agents such as dicyclomine or mebeverine seem to retain efficacy when used on an as-needed basis, but become less effective with chronic use. Low-dose TCAs may be considered when the pain is more constant and/or disabling.

For constipation, increased dietary fiber (25 g/day) is recommended for simple constipation, although its effectiveness, based on several studies, in reducing pain in constipation-predominant IBS is mixed (see dietary modification section). If fiber is not helpful, osmotic laxatives such as milk of magnesia, sorbitol, or polyethylene glycol may be used. For diarrhea, loperamide (2–4 mg up to 4 times daily) or diphenoxylate (2.5 mg and .025 mg atropine up to 3–4 times a day) can reduce loose stools, urgency, and fecal soiling,[167] and in low doses, does not seem to affect the CNS. Cholestyramine may be considered for a subgroup of patients with cholecystectomy or bile acid malabsorption.[65]

Investigational Compounds

A novel approach to the treatment of diarrhea and pain/discomfort of IBS is based on antagonism of the $5\text{-}HT_3$ receptors. $5\text{-}HT_3$ receptors are extensively distributed on enteric motor neurons, on peripheral terminals of visceral afferent nerves, and on central locations such as the vomiting center. Antagonism of these receptors reduces visceral pain, colonic transit, and small intestinal secretion.[168] Alosetron hydrochloride, a selective $5\text{-}HT_3$ antagonist, is effective in relieving pain and normalizing bowel frequency, and reducing urgency in diarrhea-predominant female patients with IBS (effect size 12%–15%).[169] It was more effective than placebo in inducing adequate relief of pain and discomfort and improved bowel frequency, consistency, and urgency[170–172] in women with diarrhea-predominant IBS. The most common adverse event was constipation, affecting 28% of patients in clinical trials; only 10% withdrew from these studies for this symptom. A significant adverse event with an unclear relationship to alosetron is acute ischemic colitis, estimated to occur in 0.1%–1% (risk factors were not identified). The drug was withdrawn from the market in November 2000 because of these side effects, but after further evaluation was reapproved by the FDA in the spring of 2002 under restrictive guidelines to be developed for its use.

Another $5\text{-}HT_3$ antagonist, cilansetron, has demonstrated similar efficacy to that of alosetron in 2 phase II trials[173] and was effective in male patients (possibly because of a larger number of male patients studied). This drug is currently in phase III trials.

For constipation, new partial or full $5\text{-}HT_4$ agonists seem promising in the treatment of constipation or constipation-predominant IBS. The partial agonist, tegaserod, is an aminoguanidine indole, which was shown to result in global relief of IBS symptoms and constipation in females with constipation-predominant IBS.[174] The effective dose of tegaserod is 12 mg per day in 2 divided doses (6 mg twice daily). Pooled analysis of the trials to date suggests that the drug is significantly effective, with approximately a 10% advantage over placebo in the intent to treat population and up to a 14% advantage over placebo in females and those with documented constipation during the baseline run-in period. Tegaserod appears safe, with no serious adverse events reported in the clinical trials program or in open evaluation for over 6 months. An effect of tegaserod on the delayed rectifier potassium current that rarely leads to cardiac dysrhythmias has been carefully excluded; this appears to

differentiate the drug from other 5-HT_4 agonists such as the substituted benzamide, cisapride. The drug was approved by the FDA in July 2002 for females with constipation-predominant IBS symptoms.

The full 5-HT_4 agonist, prucalopride, is a benzofuran that induces strong contractions in the proximal colon in vivo in dogs[175] and accelerates colonic transit in healthy participants[176,177] and in patients with functional constipation.[74] The drug induced a significant increase in the number of spontaneous and complete bowel movements in 2 trials of patients with functional constipation.[178,179] The effects of prucalopride on abdominal pain have not been thoroughly assessed. Clinical trials have been discontinued because of carcinogenicity in animals.

Other new approaches being explored in phase II studies include: newer type 3 antimuscarinic agents, NK1 and NK3 receptor antagonists, cholecystokinin antagonists, the alpha_2 adrenergic agonists, clonidine,[180] a 5-HT_1 agonist (buspirone),[181] and a selective serotonin reuptake inhibitor (SSRI) (citalopram).[182,183] Recommendations on the use of these newer receptor-active agents with regard to being first- or second-line treatments need to be determined based on issues of efficacy, safety, and cost.

Complementary/Alternative Therapies in IBS

Several reports indicate that the public holds some skepticism toward conventional medicine and are using complementary or alternative medicine therapies more frequently in IBS than with "organic" diseases.[184–187] However, the efficacy of alternative therapies has not been established in controlled trials.[188] One exception is a placebo-controlled 16-week trial of Chinese herbal medicines that showed improved bowel symptom scores, global symptoms, and reduced IBS-related interference with life relative to placebo.[189] Notably, patients receiving individualized Chinese herbal medicine continued to report benefit beyond the actual treatment period.[189] Many herbs were used, so it is not possible to make specific recommendations.

Psychological Treatment

Psychological treatment can be considered when IBS symptoms are moderate to severe, when patients have failed to respond to medical treatments, or when there is evidence that stress or psychological factors are contributing to GI symptom exacerbations. The patient's understanding of the rationale for psychological treatment and their motivation to undertake such treatment is critical to a successful outcome. Therefore, the physician has an important role in clearly communicating why referral for psychological treatment is recommended. If

this is not done properly, patients may not accept the referral and may even feel abandoned by their physicians. Table 8 indicates that psychological treatments are frequently helpful both at reducing bowel symptoms and improving psychological symptoms.

Psychological treatment trials have methodological limitations because of the inability to blind patients or the investigators as to treatment assignment, and the difficulty of coming up with a placebo treatment that is credible, but also not effective, to patients. There are 14 randomized controlled trials (Table 8), but only 5 included placebo arms; 2 of these placebo-controlled trials were positive,[190–192] 1 showed a trend for greater bowel symptom reduction in the active treatment group,[193] and 2 showed equivalence between active and placebo arms.[194–195] Many trials have compared the active psychological intervention to continuation of standard medical therapy or merely to symptom monitoring while waiting to start therapy. However, it is probable that both these control groups are associated with a negative expectancy. Patients are only referred to these trials if they have failed medical therapy, and they are not expected to improve while they are waiting to be treated. Thus, despite a number of positive trials, there is room for doubt.

Currently, no studies indicate that one psychological intervention technique is superior to another. The symptoms associated with a favorable response are abdominal pain, diarrhea, and psychological distress.[196] Predictors of a positive response to psychological treatment[124,196] are: (1) awareness that stress exacerbates their bowel symptoms, (2) at least mild anxiety or depression, (3) the predominant bowel symptom is abdominal pain or diarrhea and not constipation, (4) the abdominal pain waxes and wanes (rather than being constant) in response to eating, defecation, or stress, and (5) the symptoms are of relatively short duration. Also, it has been proposed that patients who exhibit maladaptive coping styles or cognitions (e.g., "catastrophizing") relating to their symptoms, or perceive an inability to decrease them, may be particularly responsive to cognitive-behavioral treatment.[119,197]

Psychological treatment is initially expensive because it requires multiple, long sessions. However, its benefits persist or even increase over time,[196] and in the long run there may be a net reduction in clinic visits and health care costs,[198] which offsets the initial cost of psychological treatment.

Centrally Targeted (Psychotropic) Medications

Antidepressants and anxiolytic agents are commonly prescribed by medical physicians, whereas anti-

Table 8. Randomized Controlled Studies of Psychological Treatments With at Least 20 Subjects and Follow-up at Least 3 Months

N	Type of treatment	Comments	Study
Interpersonal psychotherapy			
n = 101	Psychodynamic therapy vs. SMT	Greater improvement in pain and bowel habits at EOT and 15 mo FU	Svedlund et al.[266]
n = 102	Interpersonal therapy vs. SMT	Greater improvement in pain, bowel habits, psychological symptoms at EOT and 12 mo FU	Guthrie et al.[196]
n = 257	Interpersonal therapy vs. SSRI vs. SMT	No differences in psychological status or bowel symptoms at EOT or 12 mo FU	Creed et al.[267]
Cognitive behavior therapy			
n = 24	Multicomponent behavior therapy vs. SMT	Greater reductions in psychological, but no difference in bowel symptoms	Bennett and Wilkinson[268]
n = 45	Summary of 5 small-scale studies of a multicomponent self-regulatory treatment	58% had primary GI symptoms reduced by at least 50%; trait anxiety had noticeable clinical utility as an individual predictor of outcome	Blanchard et al.[124]
n = 120	Multicomponent behavior therapy vs. placebo vs. SMT	No difference between active treatment and placebo; both superior to SMT	Blanchard et al.[194]
n = 20	Individual CBT vs. SMT	Reduced bowel symptoms at EOT and 3 mo FU	Greene and Blanchard[269]
n = 34	Individual CBT vs. self-help support group vs. SMT	Bowel symptoms and psychological symptoms reduced relative to placebo at EOT and 3 mo FU	Payne and Blanchard[190]
n = 45	Group CBT vs. SMT	Decreased bowel symptoms and increased ability to cope at EOT and 2 year FU	Van Dulmen et al.[270]
n = 101	Group CBT vs. education vs. SMT	CBT showed greater reductions in psychological distress and tended to show greater reduction in bowel symptoms	Toner et al.[193]
n = 24	Multicomponent behavior therapy vs. SMT	Reduced bowel and psychological symptoms at EOT and 6 mo FU	Heymann-Mönnikes et al.[271]
n = 95	CBT vs. relaxation vs. SMT	All groups equivalent	Boyce et al.[195]
Hypnosis			
n = 30	Individual hypnosis vs. placebo pill + supportive psychotherapy	Greater improvement in bowel symptoms and well-being at EOT and 18 mo FU	Whorwell et al.[191,192]
Relaxation/stress management			
n = 20	Relaxation by autogenic training vs. SMT	Decreased pain and medical clinic visits at EOT and 40 mo FU	Voirol and Hipolito[272]
n = 35	Relaxation and stress management vs. SMT	Improved bowel symptoms at EOT and 12 mo FU	Shaw et al.[273]

EOT, end of treatment; FU, follow-up; SMT, standard medical treatment; CBT, cognitive behavior therapy.

psychotics and mood stabilizers (for which there is little evidence for benefit in IBS) may be prescribed by psychiatrists consulting on patients with IBS.

Antidepressants. Several antidepressants are prescribed in IBS: TCAs (e.g., amitriptyline, desipramine, imipramine, doxepin), SSRIs (e.g., fluoxetine, sertraline, paroxetine, citalopram), or less frequently, novel antidepressants (e.g., venlaxafine, mirtazapine). The rationale includes: (1) treatment of psychiatric comorbidity (e.g., major depression, anxiety disorders usually using full therapeutic doses) associated with IBS,[199–201] (2) alteration of GI physiology (e.g., visceral sensitivity, motility, and secretion),[202–206] or (3) reduction of central pain perception arising from afferent signals in the gut.[207–209] There is also some evidence that antidepressants may be synergistic with psychological treatment for medical[210]

and psychiatric[211] disorders. They may improve the motivation for psychologic treatments, which may increase compliance with the medication. Although full antidepressant doses of TCAs are used less frequently today for the treatment of psychiatric conditions (mainly because of their high side effect rates), they are commonly prescribed in smaller doses for the treatment of a variety of chronic pain conditions and functional disorders, including IBS.[212]

Several randomized controlled trials of TCA medications in IBS have been published[100] and were evaluated in a meta-analysis.[212] Improvement in global GI symptoms against placebo was highly significant (odds ratio, 4.2; 95% confidence interval, 2.3–7.9), and there was also improvement in standardized pain scores by 0.9 SD (95% confidence interval, 0.6–1.2). Furthermore, only

Table 9. Comparison of Tricyclic and SSRI Antidepressants

	Low-dose TCA	SSRI	High-dose TCA
Compounds (dose range)	Amitriptyline (10–50 mg)	Fluoxetine (10–20 mg)	Desipramine (100–200 mg)
	Imipramine (10–50 mg)	Sertraline (25–100 mg)	Nortriptyline (100–200 mg)
	Doxepin (10–50 mg)	Paroxetine (20–40 mg)	
	Desipramine (10–50 mg)	Citalopram (20–40 mg)	
	Nortriptyline (10–50 mg)		
Potential benefits	Pain, sleep disturbance	Depression, panic, anxiety, OCD	Pain, depression, anxiety
Time to onset of therapeutic effect	Days–2 weeks	4–6 weeks	4–6 weeks
Adverse events			
	Sedation, constipation	Insomnia	Sedation
		Agitation	Hypotension Constipation
		Diarrhea	
	Dry mouth/eyes		Dry mouth/eyes
		Night sweats	Arrhythmias
	Weight gain	Weight loss	Weight gain
	Rare sexual dysfunction	Sexual dysfunction	Sexual dysfunction
Risk from overdose	Moderate	Minimal	Moderate
Efficacy	Good	Not well studied	Good
		Excellent (affective disorders)	Excellent (affective disorders)
Dose adjustment	Yes	Not usual	Yes
Cost/month	$5–20	$60–100	$10–30

OCD, obsessive-compulsive disorder.

3.2 patients needed to be treated to improve symptoms in 1 patient. In general, even though a wide range of doses were used in these studies, TCA dosages were lower than that used to treat major depression, suggesting that the therapeutic effect was largely unrelated to the TCA's antidepressant effects. The study limitations (e.g., small sample sizes, short study lengths, variable study design quality, use of outcome measures and medication dosages, large losses to follow-up, failure to assess effectiveness of blinding, whether the benefits relate to improvement in comorbid psychiatric disorders) indicate that better-designed studies are needed to determine the mechanism of benefit and the subpopulations most amenable to treatment.

Table 9 compares the TCAs and provides prescribing recommendations. In general, TCAs have more established benefit over SSRIs. Because antidepressants are used on a continual, rather than an "as needed" basis, they are usually prescribed for patients having chronic or frequently recurring symptoms. Low doses of TCAs (e.g., 10–50 mg/day) are recommended for treatment of pain and sleep difficulties associated with IBS, presumably because of their multiple receptor blocking effects (anticholinergic, antihistaminergic, antiadrenergic) in addition to their nonselective monoamine uptake inhibition (serotonin, noradrenaline).[213] Low doses of TCAs also lead to a more rapid onset of action than full doses used for treating major depression. They are also inexpensive and do not carry the potentially serious cardiovascular side effects associated with full antidepressant doses.

However, there is some evidence[203] that full dosages of TCAs may also provide benefits when lower dosages are not effective. Notable side effects to the use of high-dose TCAs include sedation, hypotension, and constipation, among others (particularly for amitriptyline, doxepin, and imipramine, over desipramine or nortriptyline), and there is a greater need for dosage adjustments and a greater risk for overdose. If used in higher doses, physicians should be aware of these risks and monitor their patient expectantly.

There are no published controlled studies on the use of SSRIs or novel antidepressants for IBS. However, studies of patients with other painful medical conditions suggest clinical benefits even in the absence of depression,[214,215] and these agents may have an advantage over TCAs for treating other comorbid psychiatric disorders (e.g., obsessive-compulsive disorder, anxiety disorders, and phobias). Furthermore, physiological studies suggest that they accelerate intestinal transit,[206] although the therapeutic value of such peripheral effects remains to be determined.

SSRIs are often prescribed particularly for older patients because of their lower side effect profile. They also are superior in treating associated emotional symptoms of anxiety, panic, obsessional behaviors, and constipation-predominant IBS. Specific agents may be considered: fluoxetine has a long half life and may be selected when poor compliance is an issue, citalopram has a low side effect profile and may prove beneficial because of peripheral effects on colonic tone and sensitivity in

IBS,[183] and paroxetine, because of its greater anticholinergic effect, may be selected for patients with diarrhea.

In addition, there are other, novel antidepressants, such as mirtazapine, which has the potentially beneficial $5\text{-}HT_3$ receptor blocking effect and is particularly indicated in the patient with poor sleep and inability to gain weight. Venlaxafine produces combined serotonin and norepinephrine uptake inhibition and has been shown to increase stimulated pain thresholds[216]; it has been suggested for treatment of certain chronic painful disorders.[217]

Anxiolytic medications (benzodiazepines or azapirones) have sometimes been prescribed for patients with IBS because of the frequent comorbidity of anxiety disorders with IBS[218] and many recognize that acute psychological distress can make bowel symptoms worse. Two small studies support the efficacy of benzodiazepines for IBS,[219,220] but the drug-placebo difference was relatively small. In view of weak treatment effects and a potential for physical dependence and interaction with other drugs, caution should be used when prescribing benzodiazepine anxiolytics, and when prescribed, it should be for a self-limited period of 1–3 weeks. More recently, there is preliminary evidence suggesting that $5\text{-}HT_1$ agonists like buspirone may have a role in decreasing GI symptoms because of their effects on relaxing visceral organs.[181,221] However, it is not clear if central or peripheral effects mediate the therapeutic effects in IBS, and further studies are needed to confirm these initial impressions.

It is important to communicate the value of centrally acting drugs in treating symptoms of IBS within the context of an effective physician-patient relationship. Several guidelines are recommended.[100,153]

Address patient perceptions and expectations for taking antidepressants. Some patients may refuse to take an antidepressant or may be noncompliant[222] because they perceive: (1) that they are being treated for a psychiatric problem, (2) that the medication may be addicting or "mind altering," or (3) they do not think the doctor accepts the symptoms as "real." These issues need to be properly addressed and clarified when they occur.

Provide a rationale for medication use that is consistent with the patient's expectations. The patient can be informed that for IBS, antidepressants act as central analgesics that work sooner, and in lower dosages, than when they are used to treat major depression.[223] The medication reduces visceral afferent activity directly or by facilitating descending inhibitory pathways that control pain; however, it can also help to treat depressive symptoms induced by the illness.[153]

Negotiate a treatment plan. The choice of a particular drug is based on: (1) the target symptoms to be treated, (2) the medication's side effect profile, (3) cost, and (4) the patient's previous experiences and preferences. The patient should be involved in making the selection of a particular medication. The patient should also be informed that benefit may occur no sooner than 3–4 weeks (although benefit can occur sooner), and that side effects, if they occur, tend to diminish in 1–2 weeks. TCAs start with lower dosages (e.g., 25–50 mg) and work up to full therapeutic (150 mg) dosages over several weeks. With SSRIs, only one pill is all that is usually required. Treatment is continued for 6–12 months before tapering, and dosage adjustments are usually mutually determined.

Continue phone contact with the patient to assess compliance and side effects. Because the benefit of the medication will not occur for several weeks, and because side effects occur immediately, it helps to have an initial phone contact with the patient during the first week of treatment (and possibly repeat the phone call 2–3 weeks later). This is done to make decisions about possible dose or medication changes, and if needed, to help motivate the patient to continue the medication. The response to the treatment is not based only on symptom reduction, but also by improvement in daily function, quality of life, and emotional state. If side effects occur, it is best to hold the same dosage or reduce it, and only if required, to switch to another medication (preferably within the same class).[224]

Consider alternates if treatment response is suboptimal. When symptoms are refractory, switching to a different class of antidepressant may be considered. Occasionally, a low-dose TCA can be combined with an SSRI[213]; there is evidence to suggest an augmenting effect of combining psychological treatment with an antidepressant.[211]

Conclusions

There is sufficient evidence to conclude that IBS is an important medical disorder with significant impact on those afflicted with regard to symptom severity, disability, and impaired quality of life. Furthermore, the burden to society in terms of direct health care costs and indirect effects including work absenteeism exceeds that of most GI disorders. The authors believe that a compelling need exists for investigations that address the mechanisms for these effects through basic studies, as well as pharmacological and behavioral treatment trials to help ameliorate the suffering of patients so afflicted. Meanwhile, there is some empiric evidence for a diag-

nostic and hierarchical treatment approach based on predominant symptom type, its severity, and associated clinical and psychosocial features.

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