CME

Severity in Irritable Bowel Syndrome: A Rome Foundation Working Team Report

Douglas A. Drossman, MD[1], L. Chang, MD[2], N. Bellamy, DSc[3], H.E. Gallo-Torres, MD[4], A. Lembo, MD[5], F. Mearin, MD[6], N.J. Norton[7] and P. Whorwell, MD, FRCP[8]

OBJECTIVES: **The concept of severity in irritable bowel syndrome (IBS) is clinically recognized and operative in diagnostic decision making and treatment planning. Yet, there is no consensus on its definition, and there are limited data on the prevalence of severity subgroups, its medical and psychosocial determinants, and its association with other health status measures. The aims of the Rome Foundation Working Team Committee were to summarize current research, to develop a consensus of understanding on this concept, and to make recommendations for its use in research and clinical care.**

METHODS: **In 2006, a multinational committee of clinical investigators with expertise in IBS and/or psychometric research methods undertook a systematic review of the literature relating to severity in IBS. Owing to limited data, the Foundation commissioned three clinical studies to better characterize the concept of severity in IBS, and summary information and recommendations for future research and clinical care were developed.**

RESULTS: **The main findings were: (i) severity in IBS is defined as a biopsychosocial composite of patient-reported gastrointestinal and extraintestinal symptoms, degree of disability, and illness-related perceptions and behaviors; (ii) both visceral and central nervous system physiological factors affect severity; as severity increases, the central nervous system provides a greater contribution; (iii) severity is related to and influences health-related quality of life and health behaviors and also guides diagnostic and therapeutic clinical decision making; (iv) severity can be subcategorized into clinically meaningful subgroups as mild (~40%), moderate (~35%), and severe (~25%), and this provides a working model for use in future research and clinical care.**

CONCLUSIONS: **Future work is required to understand more precisely the factors contributing to severity and to develop a valid patient-reported instrument to measure severity in IBS.**

Am J Gastroenterol 2011; 106:1749–1759; doi:10.1038/ajg.2011.201; published online 12 July 2011

INTRODUCTION

This Rome Foundation Working Team Report addresses current understanding of the concept of severity in irritable bowel syndrome (IBS), the most recognized and the most studied of functional gastrointestinal (GI) disorders (FGIDs) (1,2). The committee was charged to summarize current research and to make recommendations as to how the concept of severity should be integrated in investigative studies and be applied in the diagnosis and care of patients with IBS in clinical practice. Although the primary focus of this document relates to IBS, when possible references to other FGIDs are made. This knowledge of severity in FGIDs can be a starting point to later understand the role of severity with these disorders as well.

The need to understand severity in IBS is based on several factors:

Severity in IBS and FGIDs is determined by symptom reports and behaviors rather than by blood tests or histopathological markers in the bowel. It is necessary that FGIDs be understood from the

[1]UNC Center for Functional GI and Motility Disorders, Chapel Hill, North Carolina, USA; [2]UCLA: Center for Neurobiology of Stress, Los Angeles, California, USA; [3]Centre of National Research on Disability and Rehabilitation Medicine, The University of Queensland, Brisbane, Queensland, Australia; [4]Food and Drug Administration, Division of Gastrointestinal and Coagulation Drug Products, Bethesda, Maryland, USA; [5]Beth Israel Deaconess Medical Center, Harvard University, Cambridge, Massachusetts, USA; [6]Institute of Functional and Motor Digestive Disorders, Centro Médico Teknon, Barcelona, Spain; [7]International Foundation for Functional Gastrointestinal Disorders, Milwaukee, Wisconsin, USA; [8]Gastroenterology Department, Wythenshawe Hospital, Manchester University, Manchester, UK. **Correspondence:** Douglas A. Drossman, MD, UNC Center for Functional GI and Motility Disorders, Bioinformatics Building CB 7080, Chapel Hill, North Carolina 27599-7080, USA. E-mail: drossman@med.unc.edu
Received 9 December 2010; accepted 17 May 2011

patient's personal experience of ill health. Patients make decisions about taking medications, reducing work or social activities, and seeking health care based on their perceived illness severity. Clinicians do not always, but should weigh the patient's symptom reports and behaviors to make diagnostic and treatment decisions. Finally, investigators assessing the patient's clinical state need to use questionnaires that are anchored to patients' self-perceptions of the condition. Thus, it would be helpful to have guidance as to how to understand and quantify severity from the patient's perspective.

Categories of severity can influence diagnostic decisions and treatment planning. Clinicians make diagnostic and treatment decisions based on the patient's perceived severity. With milder symptoms, little or no diagnostic testing may be performed (primarily to further assess "red flags") and treatments involve dietary and lifestyle modifications or over-the-counter medications. However, when symptoms have greater levels of severity, diagnostic testing increases and can be extensive, and multiple prescription treatments are often used. The availability of certain treatments, such as the serotonergic agents, alosetron and tegaserod, are limited to severe, refractory cases. The caveat is that if we rely solely on patient reports of severity, on occasion, unnecessarily intensive investigations or treatments can occur. For example, patients may report symptoms with great desperation and physicians in response may make judgment errors ("furor medicus") (3) and overdo diagnostic studies or treatments. Thus, patient reports, although critical to understand severity, must be considered within a larger biopsychosocial context when making diagnostic and treatment decisions. This may involve integrating patient reports with other clinical measures such as daily functional status or concurrent psychosocial features (see below). Once severity is assessed in its most accurate context, diagnostic and treatment options are more precise.

Categorizing patients with IBS into clinically meaningful subgroups of severity has not yet been formalized. The Rome classification system specifically addresses symptoms in terms of diagnostic categories but not severity. The first effort to categorize severity into meaningful subgroups was published almost 20 years ago when Drossman and Thompson (2,4) proposed subcategorizing IBS into mild, moderate, and severe based on certain clinical features. When severity is "mild," patients have low-intensity infrequent symptoms and good health-related quality of life (HRQOL) and may not seek health care, and epidemiological studies of individuals with mild IBS indicate that many have never been to a physician (5). When severity is "moderate," there is more persistent and discomforting symptoms with some impaired HRQOL, reduced socializing, and some work absenteeism. In Western cultures, health-care visits occur, often to primary care physicians with perhaps occasional referrals to GI specialists. When IBS is "severe," the symptoms are more frequent, even persistent, and of greater intensity, and associated with marked function impairment, psychosocial comorbidities, and health-care referrals to specialists.

Although these concepts have been well accepted over the last two decades, the categories were based on personal experience of the authors rather than from scientific data. In fact, the authors' initial report of patients being 70% mild, 25% moderate, and 5% severe seems to underestimate the prevalence of severe IBS based on current studies (6). Furthermore, no provision was made to quantify the clinical features to systematically categorize them in any standard manner. In addition, without having a standard categorization, we are unable to determine the natural history of severity in IBS: whether patients shift between mild to severe or continue in one category. Thus, standards are required to accurately assess severity, place them into meaningful subgroups, validate them, and determine their prevalence and natural history.

Severity needs to be understood within a psychosocial context. As self-reported severity increases, there is a concurrent increase in physical and psychosocial distress, comorbidities, and maladaptive coping strategies. This in turn affects health status including frequent physician visits, and referrals to gastroenterologists and surgeons often at major medical centers where more diagnostic testing or invasive treatments may occur (7,8). Thus, it is important to understand the influence of psychosocial factors on severity reporting and *vice versa*. The consequences can ultimately affect clinical decision making and the clinical outcome including treatment.

A better understanding of severity in IBS will help third party payers and regulatory agencies to establish guidelines for treatment. One example is the requirement to use alosetron only for patients with severe IBS-D (IBS with diarrhea), based on standards specified by the FDA (Food and Drug Administration). However, this definition of severe IBS-D is not fully recognized by clinicians and investigators, and standardized definitions would be helpful to establish full consensus among all interested parties.

All of these factors highlight the importance of a clearer understanding of severity in IBS and the FGIDs; yet to date, there is no consensus for assessing and defining IBS severity (6). With this in mind, the Rome Foundation Working Team on Severity in IBS was charged to address the following aims: (i) to define severity in IBS, (ii) to identify the factors, both physical and psychosocial, contributing to severity, and (iii) to make recommendations regarding the use of severity measures in research and clinical practice. Individuals were selected for this working team based on their academic accomplishments in the area of severity assessment in IBS and FGIDs. One individual was selected for his expertise in instrument development and severity assessment outside the field of gastroenterology, another who had experience working in the area of severity as part of a regulatory agency, and one individual who was able to serve as a patient advocate, given the recognized need for patient definitions of severity. We were unable to identify individuals with expertise in symptom severity who worked in geographical areas outside Western Europe and the United States.

THE NATURE OF SEVERITY

Although severity is understood primarily from the patient, it can begin with the underlying physiological bases for symptom development, its intensity, and affective contributions. IBS is a disorder of dysregulated brain–gut homeostasis, which has systemic effects derived from peripheral and central influences that interact mutually. For example, increased motility or visceral afferent firing can generate and amplify GI symptoms based on their intensity and

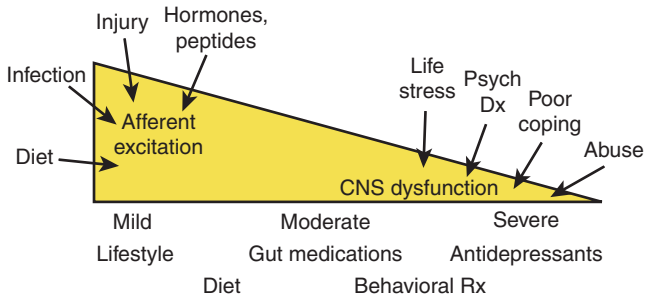

Figure 1. Relation of peripheral (afferent excitation) to central nervous system (CNS dysfunction) to prevalence and severity of IBS. The triangle represents the point prevalence of IBS; therefore, severe IBS as shown on the right comprises a smaller proportion of the IBS population. Most patients with mild-to-moderate IBS have symptoms related to peripheral- or gut-related factors (e.g., post-infectious visceral hypersensitivity, dietary factors, dysmotility, bowel injury, hormonal factors). For patients with more moderate-to-severe symptoms, there is an increasing frequency of psychosocial difficulties (e.g., trauma, abuse, life stress, psychiatric comorbitidies, poor coping) that contributes to central upregulation of pain, presumed to be at the level of the anterior cingulate cortex. In addition, as noted treatments for IBS shift from addressing gut dysfunction for mild-to-moderate symptoms to centrally targeted treatments such as antidepressants and behavioral interventions. CNS, central nervous system; Dx, diagnosis; IBS, irritable bowel syndrome; Psych, psychosocial; Rx, treatment.

this can increase psychological distress. Psychological distress in turn may increase symptom intensity, and conversely psychological methods such as hypnosis or even distraction can decrease symptom intensity (1,9). Thus, severity needs to be understood from a biopsychosocial framework that involves increased peripheral signal intensity and central dysregulation.

With this understanding, depending on physiological and psychosocial contributions, severity will differ among individuals and also within the same individual over time. Those with IBS who have multiple exposures to GI insult such as infection or surgery may have a greater propensity to develop more severe symptoms with additional events and this can be modulated by central regulatory factors (10). Similarly, individuals with a previous history of emotional trauma, such as sexual or physical abuse, may interpret and experience visceral sensations from IBS in a more noxious manner and this will be associated with greater severity of symptoms later in life (11). Factors associated with patient reports of severity include the nociceptive contribution, the degree of disability, poor HRQOL, psychological distress, culture, ethnicity, and possibly comorbid conditions (2). In general, it is hypothesized that patients with mild-to-moderate IBS often have more peripherally generated symptoms with gut-based features (i.e., relieved by defecation worse with eating, intermittent, crampy abdominal pain), whereas patients with more severe and painful IBS tend to have more noxious, continuous, and severe symptoms with psychosocial and somatic comorbidities, thus reflecting the greater central nervous system contribution to their illness experience (see **Figure 1**) (12).

Furthermore, this concept applies across various medical conditions, such as fibromyalgia, chronic fatigue syndrome,

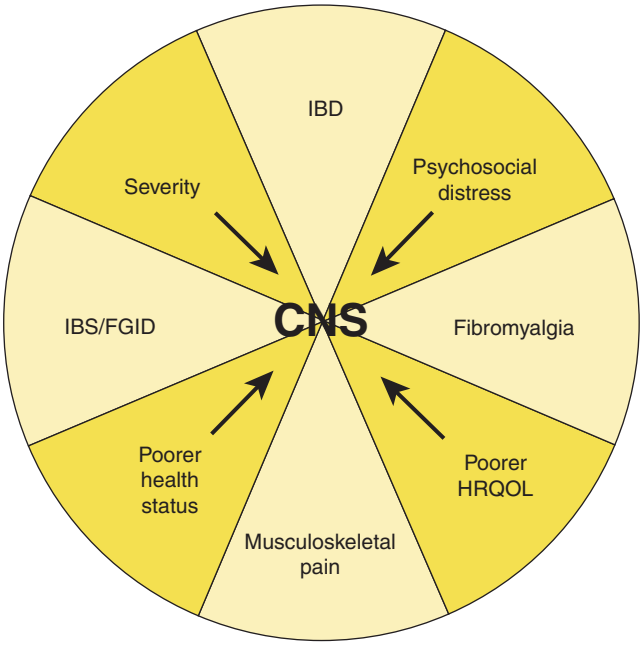

Figure 2. Relation of peripheral to central (CNS) activity contributing to pain symptoms and health status in visceral and somatic medical disorders. The IBS triangle shown in **Figure 1** is also represented here on the left, and also seen are other medical disorders given as examples (yellow triangles). The relative prevalence of peripheral to central influences on pain and symptom severity are also displayed. As the severity of these conditions become greater, there is an increasing contribution of CNS factors, similar to **Figure 1**. Greater severity is associated with increased psychosocial distress, poorer health status, and poorer health-related quality of life. Thus, patients with the most severe symptoms share psychosocial features and often share comorbidities. FGID, functional gastrointestinal disorder; HRQOL, health-related quality of life; IBS, irritable bowel syndrome.

inflammatory bowel disease, or other chronic pain conditions, so much that when a condition is severe, it is associated with more symptoms of greater intensity due to loss of central "filtering" of visceral and somatic afferent input ("disinhibition") (12). Thus, there is a clinical association of severity with psychosocial and medical comorbidities for all functional conditions (see **Figure 2**).

Given this understanding, severity in IBS and other FGIDs can be seen as a multi-determined concept that integrates peripheral and central biological processes as they affect symptoms. It is this level of complexity that makes it so challenging to fully understand and quantify severity. Unfortunately, studies from the existing literature as summarized below have not adequately recognized the nature of severity from this more comprehensive perspective.

SUMMARY OF PREVIOUS PUBLICATIONS RELATING TO SEVERITY IN IBS

The Working Team Committee in their literature review noted that the most comprehensive evidence-based assessment of severity in IBS was published in 2005 by Lembo *et al.* (6). Consistent with the Working Team's conceptualization above, this review noted: Severity must be understood from a broader multi-component construct that would include HRQOL, psychosocial factors,

health-care utilization behaviors, and burden of illness associated with IBS. Individual symptoms, such as abdominal pain, were considered important factors of severity but are insufficient to fully embody the severity concept. Thus, the paper clarified that severity is not defined solely as intensity of IBS symptoms, but rather reflects more generally the "illness" of IBS: the patient's personal experience of ill health incorporating symptom intensity along with attributions and perceptions resulting from multiple biopsychosocial factors. Some of the key features of this paper are noted:

1. IBS is a chronic FGID that ranges in severity from mild and intermittent to severe and continuous.
2. The published prevalence of severe IBS ranges from 3 to 69% and averages considerably more than the original estimate of 5% (4).
3. Individual symptoms are important but not sufficient to explain severity.
4. Severity is multi-dimensional, being influenced by the intensity of GI and extraintestinal symptoms, HRQOL, comorbidities, psychosocial factors, degree of disability, and illness behaviors. However, the relative contributions of each are unknown.
5. IBS severity has clinical implications: It affects HRQOL and health behaviors and guides diagnostic evaluation and treatment.
6. Severity is also affected by whether it is assessed by the patient or physician, as well as by the type of measurement scale used.

EVALUATION OF SEVERITY IN IBS

There are few studies that have attempted to measure severity in IBS in any standardized manner. Given the heterogeneity of symptoms, a global assessment or a compilation of multiple symptoms and behaviors have often been used. The components of severity have either been determined by investigators and physicians or are intrinsically determined by patients when they self-rate their severity. Severity for IBS and other FGIDs has been generally assessed in two ways: (i) use of a simple grading scale for individual symptoms, e.g., mild, moderate, severe, very severe pain (either reported by patient or physician) or (ii) a composite of multiple symptoms or behaviors, e.g., abdominal pain, along with stool frequency, stool consistency, urgency, and impact on HRQOL, health-care utilization, and level of disability. Most of the research in assessing the severity of FGIDs has been performed in IBS (**Table 1**).

Standardized physician rating of severity measures

There are two multi-component physician-based measurement tools for severity of (6):

The Functional Bowel Disorder Severity Index (FBDSI) (13) assesses severity based on patient pain behaviors: the presence and intensity of pain and the number of health-care visits. It was developed by assessing a large number of patient-related clinical features and then using them to predict physician ratings of patient severity at different medical centers in the United States, Canada, and the United Kingdom. A regression analysis predicting physician-rated severity identified only three significant variables: (i) the amount of pain present today, (ii) a diagnosis of functional abdominal pain syndrome (chronic or frequently recurring pain), and (iii) the number of physician visits in the previous 6 months. These three variables produced a numerical score for severity that was categorized into subgroups: a score of ≤36 for mild illness, 37–110 for moderate illness, and ≥111 for severe symptoms. The FBDSI has construct validity and it demonstrates known groups' discriminant validity by differentiating IBS non-patients from IBS patients and IBS patients who also have fibromyalgia (14). It also shows concurrent validity by the scale's ability to correlate with psychological distress and illness behavior. For example, patients rated as severe by the FBDSI have been shown to have increased psychological symptoms, health-care utilization, maladaptive coping skills, and poorer physical functioning. The measure is most often used to stratify patients by severity category or as a way to quantify severity in a linear manner for multivariate analyses (7,13), but the nature of the questions do not make it responsive to change over a short period of time.

IBS Severity Scoring System (IBS-SSS). A second disease severity measurement tool for IBS was the IBS-SSS (15). This scale evaluates primarily the intensity of IBS symptoms during a 10-day period: abdominal pain, distension, stool frequency and consistency, and interference with life in general. The IBS-SSS calculates the sum of these 5 items each scored on a visual analog scale from 0 to 100. Although the IBS-SSS uses patient-rated intensity of IBS symptoms, the determination of severity by the scoring system was originally anchored to a physician's assessment of patient severity. With regard to concurrent validity, a European study found that greater symptom severity in IBS outpatients when measured by the IBS-SSS was associated with poorer HRQOL (16). The IBS-SSS is also responsive to treatment. In one study (17), there was a 37-point reduction in the IBS-SSS score over 1 year ($P=0.01$) in an uncontrolled study evaluating response to cognitive-behavioral therapy; this reduction was associated with a significant reduction in the Work and Social Adjustment and the Hospital Anxiety and Depression scale. In another study (18), patients who had a >50% reduction in symptoms following hypnotherapy had an IBS-SSS mean score reduction of 139, which is considerably in excess of the 50-point reduction in IBS-SSS considered indicative of a responder. Finally, in an acupuncture clinical trial, changes in the IBS-SSS scores were comparable with other commonly used measures of improvement in IBS trials (19). Notably, most studies confirming the responsiveness of the IBS-SSS to symptom change have been trials aiming at evaluating behavioral interventions; hence, future work is required to assess responsiveness in clinical trials using pharmacological agents. Nevertheless, the data suggest that the IBS-SSS could be used for selecting symptomatic patients for clinical trials and for measuring response to treatment (6).

When comparing the two measures, some general observations can be made (6): both measures are relatively easy to use, have reasonable psychometric validity and reproducibility, and can therefore be used to assess severity in research and clinical care. For research

Table 1. Studies which have measured severity of IBS

Study	FGID	Patient population	Severity measure	Components	Findings
Validated severity instruments					
Drossman (13)	FBD with abdominal pain (Rome I criteria)	Four centers: three university-referral sites and one community health-care center (*n*=270), 77% F	FBDSI (based on physician's severity rating)	(i) Amount of pain for today (ii) Diagnosed as FAPS (iii) # Doctor visits in past 6 months	Three variables were best predictors of physician's rating of severity of patient's FBD
Francis (15)	IBS (*n*=61) and controls (*n*=40)	University outpatient clinic (*n*=61), 78% F	IBS-SSS (0–500, based on investigator's rating of severity)	(i) Two items on presence of abdominal pain and bloating (ii) Four VAS of intensity of pain, bloating, relief w/BM, impact on HRQOL (iii) # Days with symptoms in past 10 days	Determined cutoffs for scores for those rated as mild, moderate and severe. Found to be reproducible and sensitive to change
Studies using validated severity instruments or other investigator-determined severity measures					
Drossman (7)	FBD (83% IBS)	Two tertiary care centers (*n*=211), 100% F	FBDSI	(i) Amount of pain for today (ii) Diagnosed as FAPS (iii) # Doctor visits in past 6 months	More severe FBD is associated with increased psych symptoms, health care utilization, maladaptive coping and poorer physical functioning and QOL.
Sperber (14)	IBS patients (IBS only: *n*=50, *n*=25 IBS and FS), IBS non-patients (*n*=21)	GI clinic	FBDSI	(i) Amount of pain for today (ii) Diagnosed as FAPS (iii) # Doctor visits in past 6 months	IBS patients have more severe FBDSI than IBS non-patients and healthy controls. IBS patients with FS had most severe scores. More severe scores were associated with worse overall well-being and extraintestinal symptoms
van der Horst (22)	IBS (ICHPPC-2 criteria)	(i) PCP practices (*n*=109), 80% F (ii) Outpatient university clinics (*n*=86), 65% F	Severity score (0–9)	(i) Frequency of abdominal complaints (0–3) (ii) Interference with daily activity (0–3) (iii) Avoidance of behavior (0–3)	Higher severity score and large number of additional complaints, and low stress attribution score in the outpatient clinic patients
Coffin (16)	IBS (Rome II)	Non-hospital GI outpatient clinics (*n*=858), 68.9% F	IBS-SSS (0–500): <75: remission 75–175=mild, 175–300=moderate >300=severe	(i) Two items on presence of abdominal pain and bloating (ii) Four VAS of intensity of pain, bloating, relief w/BM, impact on QOL (iii) # Days with symptoms in past 10 days	Significant correlation between symptom intensity and changes in HRQOL. Higher severity in women vs. men, and in IBS-C and IBS-A vs. IBS-D
Ricci (23)	IBS (Rome II)	PCP patients enrolled in clinical trial (*n*=1,426, 92% F)	Physician rating of patient's symptoms at baseline	Mild, moderate, or severe	Patients with greater severity had increased health care utilization and decreased HRQOL
Patient-perceived severity measures					
Sach (24)	IBS (Rome I)	Tertiary clinic and advertisement (*n*=256), 67% F	"How bad are your symptoms usually?"	Five-point scale: 1-none: no symptoms 2-mild: can be ignored if you do not think about it 3-moderate: cannot be ignored but does not affect your lifestyle 4-severe: affects your lifestyle 5-very severe: markedly affects your lifestyle	Discomfort and pain-predominant IBS patients have similar overall GI symptom severity ratings, psych symptoms, health care use, and HRQOL.

continued on following page

Table 1. Continued

Study	FGID	Patient population	Severity measure	Components	Findings
Hahn (25)	IBS (Rome)	Tertiary care (*n*=126), 70% F	"How bad is the discomfort usually?"	Mild: can be ignored if you do not think about it Moderate: cannot be ignored but does not affect your lifestyle Severe: affects your lifestyle Very severe: markedly affects your lifestyle	Only GI symptom which was more prevalent in severe patients was sensation of unpassed stool. Positive correlation of severity and psych symptoms in women but negative correlation in men. Greater severity was associated with decreased HRQOL
Longstreth (26)	IBS (Rome I)	HMO (*n*=2613), 71.4% F	"How much of a problem was your abdominal pain or discomfort over the last 3 months?"	Six-point Likert scale: Absent, very mild, mild, moderate, severe, and very severe	No significant health care costs association with varying degrees of severity with mild severity as a reference group
Hillila (27)	IBS (Manning 2 and 3 Rome I and II)	Community residents in Finland, random selection (*n*=5,000, 2,490 M and 2,510 F)	Pain and discomfort rating	Four-point Likert scale of abdominal pain and discomfort: mild, moderate, severe, and very severe	Did not rate overall symptoms. Severe or very severe pain was present in 27-30% Manning + and 44% of Rome +IBS. Did not report sex differences
Liu (28)	IBS (h/o intermittent abdominal pain, distension, and altered BH)	Outpatients in Taiwan (*n*=110), 44% F	Individual symptom severity rating	Four-point scale of symptoms: none, mild, moderate, severe	No assessment of overall symptom severity. Improvement of individual symptoms with peppermint oil vs. placebo
Tack (29)	IBS (Rome II)	?Tertiary clinic patients in Belgium (*n*=23), 78% F	Overall symptom severity and individual symptoms over past 2 weeks	10-cm VAS	Mean overall severity at baseline was 7/10. Crossover-design study with citalopram and placebo. Improvement of overall severity, pain, bloating and HRQOL with citalopram
Spiegel (21)	IBS (Rome I and II)	Mixed population of patients from clinic and advertisement at UCLA	Overall 0–20 scale	Single-item response rating overall severity of IBS symptoms from none (0) to 20 (most intense symptoms imaginable)	Used as an outcome variable of to determine which factors predicted patient self-report of IBS severity.

BH, bowel habit; BM, bowel movement; F, female; FAPS, functional abdominal pain syndrome; FBD, functional bowel disorder; FBDSI, Functional Bowel Disorders Severity Index; FGID, functional gastrointestinal disorder; FS, fibromyalgia syndrome; IBS, irritable bowel syndrome; ICHPPC, international classification of health problems in primary care; IBS-SSS, IBS Severity Scoring System; GI, gastrointestinal; HMO, health maintenance organization; HRQOL, health-related quality of life; M, male; PCP, primary care practice; UCLA; University of California, Los Angeles; VAS, visual analog scale.

purposes, they appear to perform equally well when assessing psychometric validity with other instruments. For example, Spiegel *et al.* recently used these measures to assess construct validity for the use of certain HRQOL measures for IBS. This has been done with the EuroQOL, a generic health utility (20), and also for a patient self-rating scale of severity using a numeric scale (21).

The two instruments differ conceptually. The FBDSI is a measure primarily of pain reporting and behavior (e.g., the intensity of pain on a visual analog scale, whether the pain is constant and the number of health-care visits), and can also be used to assess other painful functional bowel conditions such as functional abdominal pain syndrome. However, the IBS-SSS is primarily a measure of IBS symptoms including abdominal pain and distention and bowel satisfaction. Finally, the nature of the items on the two scales only permits the IBS-SSS to be used in treatment trials as a measure of treatment effect because it includes IBS symptoms that are responsive to change. In contrast, the FBDSI is more often used to identify or stratify groups based on pain severity for clinical studies.

Other physician-determined severity measures

Two other studies used non-validated physician-based assessments to rate symptom severity in IBS patients and combined assessments of GI symptoms and HRQOL (**Table 1**) (22,23). van der Horst *et al.* (22) compared IBS symptom severity in patients

in primary care practices and outpatient university clinics. Outpatient clinic patients had higher severity scores than did those seen in primary care practices. In the second study by Ricci and colleagues (23), patients perceived as having greater symptom severity were found to have increased health-care utilization and decreased HRQOL.

In summary, there are two validated measures of IBS symptom severity based on physician ratings of severity. The FBDSI is more dependent on the presence of pain and physician visits, whereas the IBS-SSS is a composite score of the intensity and frequency of various GI symptoms and impact on HRQOL.

Evaluation of patient-perceived severity

There are at least seven studies which measured patient-perceived IBS severity ratings (**Table 1**) (21,24–29), but they are limited in the value and degree of the information provided. The studies are heterogeneous and not readily comparable in population sample or method. Patient samples ranged from tertiary-care referral groups to outpatient clinics of community residents.

Overall, these studies showed that self-rated severity negatively correlates with HRQOL and positively with health-care utilization and costs (16,25,26). The committee concludes that there are insufficient data from studies of patient self-reported severity to come to meaningful conclusions to make recommendations.

Responder criteria and state-attainment criteria

The true value of valid and reliable data lies in their capacity to be interpreted. In the case of Patient-Reported Outcomes, the ability to categorize individual patients according to whether they have experienced a clinically meaningful improvement in their health or have achieved a level of symptom severity acceptable to them is paramount. The former are referred to as responder criteria and the latter as state-attainment criteria. At present, there are no internationally accepted, data-driven definitions of response or state attainment for FGIDs. The development and validation of such criteria are important, but pursuant on the availability of valid, reliable, and responsive Patient-Reported Outcomes tools, and agreement on core set measures.

Relation of symptom severity to clinical response

Although it can be assumed that symptom severity is reduced with proper treatment, in fact, few studies have adequately explored the relationship between symptom severity and clinical response to therapy. As previously noted, the IBS-SSS has been shown to be responsive specifically to behavioral but not to pharmacological treatments. In one multicenter randomized prospective trial, 431 patients with moderate-to-severe functional bowel disorder (FBD) who received cognitive-behavioral therapy vs. education, or desipramine vs. placebo, those with moderate illness severity (FBDSI) responded significantly better to either treatment than the severe group (30). A study involving 43 IBS patients who underwent brief dynamic (interpersonal) psychotherapy found the presence of constant abdominal pain to be a predictor of poorer outcome as measured by a physician global rating. However, when abdominal pain was reported as related to stressful events or was associated with symptoms of anxiety or depression and was of short duration, the outcome was better (31). Similarly, among 30 patients with severe refractory IBS undergoing hypnotherapy, those with intractable abdominal pain with little bloating or bowel habit disturbance had a poorer outcome than did patients with more 'classical' cases of IBS (32).

In 2009, the Rome Outcomes Working Team performed a large pooled analysis of existing clinical trial data and evaluated the psychometric properties of a 50% improvement in severity (33). IBS severity was measured using pain severity as there was inadequate data to assess the multiple components of the IBS-SSS. However, pain is a key symptom of IBS and drives illness severity and is a predominant symptom measured in both the IBS-SSS and the FBDSI. Although baseline severity independently predicted end-of-study 50% improvement in severity, the relationship was numerically small and not clinically significant. This end point also has strong construct validity and detected minimally clinical important differences in symptoms.

In summary, most previous studies published to date of the IBS-SSS have not fully evaluated the effectiveness of therapy for the severity of IBS. The few that have suggest that patients with severe symptoms of chronic and refractory pain do more poorly in response to treatments. The recent comprehensive pooled analysis by the Rome Outcomes Working Team confirms that reduction of IBS severity measured by the surrogate measure of pain severity can detect clinically meaningful improvements in symptoms (33). Nevertheless, the committee concludes that existing patient-reported severity instruments have not been developed following the FDA's Patient-Reported Outcomes guidance (34). The absence of criteria for categorizing response and state attainment limits the capacity to adjudicate treatment responses at the level of individual patients.

Some studies have assessed how some other factors relate to severity in IBS (6):

Gender: Women may report more severe symptoms than men, although there is some heterogeneity in the results. In one study (35), the severity of IBS symptoms and the intensity of abdominal discomfort and pain were similar between men and women, but women more frequently reported bloating, distention, nausea, incomplete evacuation, and non-GI symptoms (e.g., urinary urgency and muscle aches). Another study found women with IBS to have more severe abdominal pain and bloating than men. In a third study (22) from primary care and internal medicine outpatient clinics, a summed severity score was developed (rated 0–3) based on symptoms of: (i) frequency of abdominal complaints, (ii) the interference with daily activities, and (iii) avoidance of activities resulting from these complaints. Women attending the internal medicine outpatient clinics had a higher severity score than did men attending the same clinics, but women and men attending the primary care clinics had the same severity.

Age: A study of 826 primary care and gastroenterology patients with FBD at a health maintenance organization (HMO) (36) using the IBS-SSS found that severity and impairment in HRQOL was less among older (post-menopausal) female IBS patients compared with younger female IBS patients. In addition, women under the

age of 50 years had significantly higher IBS severity scores than did same-age men, but these differences disappeared in older age groups when the severity scores in women were reduced. Similar differences were not seen in male IBS patients.

Visceral hypersensitivity: Although it might be presumed that greater illness severity would be associated with lower visceral sensation thresholds, in fact, IBS severity (FBDSI moderate vs. severe) was shown to only weakly correlate with visceral hypersensitivity using rectal balloon distention (7). In another study, IBS severity did not predict the development of rectal hypersensitivity to repetitive sigmoid distention (37). This observation as previously noted may reflect the fact that greater degrees of severity is explained more by central dysregulation rather than by peripheral factors like visceral hypersensitivity, as was shown in at least one study (38).

Psychosocial: Three studies have explored the relationship between IBS severity and psychosocial factors. In one large study of >200 patients (7) with IBS and other FBDs, those with severe FBD had greater pain scores and psychological distress than did patients with moderate FBD as measured by the Beck Depression Inventory, the Overall Scale of the Sickness Impact Profile, and most subscales of the Sickness Impact Profile, and they also exhibited more of a maladaptive catastrophizing coping style and less perceived ability to decrease or control their symptoms. In a smaller IBS study (25), patient-rated severity was not related to physical or psychological symptoms (SCL-90) or health-care utilization (physician visits), but was related to health status impairment (SF-36). However, this study may be confounded by the fact that severity was defined by the degree of lifestyle impairment. Thus, in research and clinical care, when patients have more severe IBS, it is important to consider comorbid psychosocial factors.

At the Rome Foundation's Endpoints and Outcomes Conference in 2009 (39), the Psychosocial and Co-morbidities subcommittee came to the consensus that psychosocial factors should serve more as secondary end points rather than as a primary end point. In addition, the presence of psychiatric comorbidity does not have to be an exclusion criterion in FGID clinical trials unless it limits full participation in the study. It is important to measure psychological symptoms to determine whether they affect treatment outcome.

SYNTHESIS OF NEW KNOWLEDGE

Taken together, although there are signals in the existing literature for an association between severity and the several factors reviewed, the conflicting study results, variability in the definition of severity, and study design limitations make it difficult for the Rome Working Team to meet its aims to develop a consensus understanding of IBS or to make recommendations to help direct diagnostic and treatment approaches. Therefore, the committee suspended its activity for 2 years to help direct or await the results from newer studies by its committee members that were directed toward gaining additional knowledge in this area. What follows is a summary of three Rome Foundation-endorsed studies assessing patient-perceived severity in different clinical settings: a patient focus group, survey of a tertiary-care clinic population, and an Internet survey. Each study provides additional and overlapping new information to guide our understanding of severity from the patient's perspective.

Focus group assessment of IBS patient perspectives on severity

In a collaboration between the Rome Foundation and the International Foundation for Functional GI Disorders (IFFGD), a patient focus group was conducted in Milwaukee, Wisconsin, to obtain a general assessment of the symptoms experienced with IBS, its impact, and the factors associated with self-perceived severity (40). A total of 16 men and women with IBS ranging from mild to severe were seen in 3 focus groups based on predominant stool habit (IBS with mixed pattern (IBS-M), IBS-D, and IBS with constipation and IBS-M). Standard qualitative research methods were used to identify common themes. With regard to self-perceived severity, the following was reported: (i) severity is closely linked to, but is not fully explained by impaired HRQOL; (ii) severity is strongly influenced by abdominal pain and other symptoms (such as diarrhea, constipation, bloating, nausea and non-GI symptoms such as fatigue) but did not relate specifically to stool subtype, however; and (iii) severity is multicomponent in nature and also relates to: (i) feelings of unpredictability and uncertainty with the condition, (ii) imposed activity limitations (food restriction, inability to work), (iii) concomitant thoughts and feelings (e.g., associated anxiety, stress, impaired memory, and concentration), and certain symptom modifiers (e.g., the frequency and clustering of attacks, and intensity and constancy of symptoms). This qualitative information can be used to help shape more quantitative studies in the future as occurred with the other two studies below.

University-based tertiary-care survey

Given this knowledge that IBS severity is not based solely on symptoms but rather represents a multi-component framework, a study of 755 tertiary-care IBS patients from the UCLA (University of California, Los Angeles) database evaluated a broad range of clinical predictors, including individual GI, extraintestinal, and psychological symptoms and disease-specific HRQOL measures, which predicted patient-perceived overall IBS severity (21). As noted previously, the main outcome was the patient-assessed "overall severity of GI symptoms," as measured on a 0–20 numeric rating scale (20 = most severe). Additional construct validition of this patient self-report scale was done that confirmed its strong significant association with severity (FBDSI and IBS-SSS) and the generic HRQOL. In the predictive analysis, severity was highly related to symptoms of visceral hypersensitivity (e.g., abdominal pain $P<0.001$; bloating $P=0.05$), extraintestinal somatic symptoms (e.g., myalgias $P=0.02$), outlet symptoms (e.g., straining $P<0.001$), urgency with defecation ($P=0.03$), and disease-related concerns (e.g., belief that "something is seriously wrong" $P<0.001$). The findings held after adjusting for patient demographics, disease chronicity, and health care-seeking behaviors. This study again confirmed that patient-derived severity in IBS is related to, yet distinct from, HRQOL, and that pain is a dominant feature and the full understanding of severity relates to biopsychosocial determinants having multiple components. Although these

Table 2. Relationship of health status measures with IBS severity (FBDSI) from Internet IBS population (41)

Variable	Mild: <36 (*N*=617)	Moderate: 36–110 (*N*=949)	Severe: ≥111 (*N*=400)
% Out of work from IBS	5.3%	10.3%	30.3%
# Days activity restriction	44±80	63±86	139±118
# Times seen MD past 6 months	1.0+1.5	2.3+1.8	6.6+8.2
IBSQOL (higher=better QOL)	59.8+21.8	51.0+20.1	38.1+19.7
% Clinical anxiety (HADS)	35.2	48.8	61.3
% Clinical depression (HADS)	10.2	10.6	26.5
Abdominal pain (VAS 0–100)	13.0±13.7	44.2±21.6	59.2±26.0
# Providers consulted in life	3.4±3.0	4.4±5.9	6.6±9.7

FBDSI, Functional Bowel Disorders Severity Index; HADS, Hospital Anxiety/Depression Scale; IBS, irritable bowel syndrome; QOL, quality of life.

findings may assist in future efforts to define and measure severity in IBS, prospective studies evaluating additional components that may predict IBS severity are required.

Internet survey of IBS patients

A collaborative study was undertaken using the websites of the University of North Carolina (UNC) Center for Functional GI and Motility Disorders and the IFFGD to evaluate among IBS patients accessing these sites the symptoms, health status, and factors associated with severity (41). A total of 1,966 IBS patients meeting Rome III criteria were evaluated (83% female, mean age 49 years, 60% married/co-habiting, 91% White, 78% United States/Canada, mean of 6.6 years of illness). It was noted that the health status and quality of life was poor: 77%% self-reported moderate-to-severe (42% moderate, 36% severe) symptoms with on average 20% of days restricting activities each year, and 13% were out of work because of health. A comparison between the patient's self-report of severe symptoms (36%) with the physician-based measures indicated a lower score (20.4%) for the FBDSI and a higher score (55.4%) for the IBS-SSS; by all measures, this is considerably higher than the original estimates of 5% (4). There was a clear and highly significant association of severity (using FBDSI) with other health status measures (see **Table 2**). For example, 30% with severe symptoms reported being out of work because of health problems compared with 10% for moderate and 5% for severe symptoms.

When given a check list to identify up to 14 items previously identified to be associated with severity, multiple factors were selected, averaging 7 (<3% reported only 1 item) again confirming that severity is a heterogeneous concept with multiple components. The four most frequently endorsed items were pain (80%), bowel difficulties (74%), bloating (69%), and limitations on diet and eating (69%). These items clustered together suggesting a high degree of homology for these symptoms to define severity for patients with IBS: >90% reported at least 2 of the 4 items, 2/3 reporting 3 of the 4, and over 1/3 reported all 4 of these items. The authors concluded that this clustering of four symptoms could be used as an outcome measure for treatment ("How would you rate your IBS when considering all factors contributing to it (may include pain, bowel difficulties, bloating and the need to restrict or change your diet")). Additional items reported by more than ½ included limitations in social activities (62%), and the inability to leave home (54%). This study needs to be considered in the light of possible sampling bias and may not be generalizable to the total population of IBS patients. Patients who used the Internet in this study are self-selected with more severe symptoms. In addition, further study is required to understand the nature of the population not using the Internet. Given this caveat, the data supported the validity of severity measures based on their association with health status, and provided additional insights into understanding which factors are likely to be associated with self-reports of severity.

COMMITTEE SUMMARY AND RECOMMENDATIONS

On the basis of review of the previous literature, the results from the three Rome Foundation-endorsed studies on patient-based assessment of severity and the consensus of the committee, several conclusions can be made:

First, severity in IBS is not understood just as the intensity of pain or other symptoms. Rather, we define it as a "biopsychosocial composite of patient reported gastrointestinal and extra-intestinal symptoms, degree of disability, and illness related perceptions and behaviors." Second the physiological factors contributing to severity have both visceral and central nervous system contributions. As severity increases, the role the central nervous system provides a greater contribution and this is manifest by its co-association with psychosocial distress and comorbidities increased symptom reporting and maladaptive coping. Third, severity is related to and influences HRQOL and guides diagnostic and therapeutic clinical decision making; future studies are required to understand the relative influence of the various biopsychosocial factors contributing to severity, and the nature of severity in various populations and clinical subgroups. Finally, severity can be understood not only on a continuum, and used as a measure of clinical responsiveness, but can also be subcategorized into clinically meaningful subgroups as mild (~40%), moderate (~35%), and severe (~25%); the prevalence of each category and their distinguishing features will require further study.

In **Table 3**, we provide a working model of factors that can differentiate severity empirically for use in clinical practice. This categorization can serve as a template in future studies to help achieve validation of a composite severity measure. Such a measure can be used in a standard manner for clinical research, and help to characterize severity in various demographic groups and clinical populations, as well as cross-culturally. This measure will also permit more accurate physiological and psychosocial assessments and clinical trials.

Table 3. Proposed clinical profile for patient-rated severity in IBS[a]

Clinical feature	Mild	Moderate	Severe
Estimated prevalence	40%	35%	25%
Psychometric correlate	FBDSI: <36 IBS-SSS: 75–175	FBDSI: 36–109 IBS-SSS: 175–300	FBDSI: >110 IBS-SSS: >300
Physiological factors	Primarily bowel dysfunction	Bowel dysfunction and CNS pain dysregulation	Primarily CNS pain dysregulation
Psychosocial difficulties	None or mild psych distress	Moderate psych distress	Severe—high psych distress, catastrophizing, abuse history
Gender	Men=women	Women>men	Women>>men
Age	Older>younger	Older=younger	Younger>older
Abdominal pain	Mild/intermittent	Moderate, frequent	Severe/very frequent or constant
# Other symptoms	Low (1–3)	Medium (4–6)	High (≥7)
Health-related quality of life	Good	Fair	Poor
Health-care utilization	0–1/Year	2–4/Year	≥5/Year
Activity restriction	Occasional (0–15 days)	More often (15–50 days)	Frequent/ constant (>50)
Work disability	<5%	6–10%	≥11%

CNS, central nervous system; FBDSI, Functional Bowel Disorders Severity Index; IBS, irritable bowel syndrome; IBS-SSS, IBS Severity Scoring System.
[a]This is based on existing data on severity in IBS and needs to be further tested and validated.

The committee proposes several recommendations. We believe that the outcome of these recommendations will be of value to clinical investigators to help direct future research and to clinicians and patients in planning care.

1. Develop and validate a multi-component rating scale:
   a. that includes GI symptoms and other clinical domains (e.g., psychosocial factors, physiological dysfunction, disability) and which can be reduced to a single linear score or verbal description (e.g., mild, moderate, severe)
   b. which is anchored to a patient self-rated scale of severity to establish clinical meaningfulness and
   c. aligns with the FDA Patient-Reported Outcomes Guidance document.
2. Using this multi-component rating measure, validate and/or modify the proposed clinical profiles (**Table 3**) that attempt from existing data to characterize severity in a dimensional manner and categorically as mild, moderate, and severe.
3. Perform multi-national prospective epidemiological studies to assess the degree of variability and fluctuation of severity, and identify factors predictive of change in severity. Determine the degree to which the severity measure developed is responsive to change, as in clinical trials.
4. Determine whether differences in severity exist in other subgroups (e.g., based on gender, age, psychosocial difficulties, or symptoms such as stool subtype or diarrhea).
5. Conduct research studies in other clinical settings (primary care, tertiary care) to further characterize severity.
6. Identify through multi-national studies whether cross-cultural differences exist in severity and responsiveness to treatments.
7. Incorporate an assessment of severity in clinical trials as a measure of response to treatment and outcome.
8. Establish guidelines for severity assessment in clinical practice and research based on the newly acquired data.
9. Establish for clinicians a short version of a severity measure, as well as algorithms for diagnosis and treatment based on severity.
10. Develop responder and state-attainment criteria for clinical research and practice applications.
11. Consider the use of a multi-axial classification scheme that includes severity along with other parameters (diagnostic criteria, psychosocial distress, physiological dysfunction, disability/overall severity) for Rome IV. A Rome Foundation committee is being created to address this recommendation.

CONFLICT OF INTEREST

Guarantor of the article: Douglas A. Drossman, MD.

Specific author contributions: All authors are responsible for study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript. Drossman is responsible for technical support and supervision, study supervision, and for obtaining funding. Drossman and Chang are responsible for drafting of the manuscript.

Financial support: Drossman receives grant support from Astra Zeneca, Ironwood, and Takeda Pharmaceuticals and has served as a consultant for Astra Zeneca, Ironwood, Lexicon, Prometheus, Sucampo, and Takeda Pharmaceuticals. Chang receives grant support from Rose Pharma, Shire, and Takeda Pharmaceuticals and has served as a consultant for GlaxoSmithKline, Ironwood, Forest, Movetis/Shire, Novo Nordisk, Salix, Takeda Pharmaceuticals, Ocera, Movetis, and Prometheus. Lembo has served as a consultant for Astra Zeneca, GSK, Ironwood, Prometheus, and Salix, Pharmaceuticals and Aryx therapeutics. Mearin has served as a consultant for Almirall, Astra Zeneca, Menarin, and Solvay Pharmaceuticals. Ms Norton has served as a consultant for Degge Group Ltd and American Medical Systems. Whorwell is an advisory board member or has received research funding from Novartis Pharma, GSK, Rotta Research, Procter & Gamble, Danone Research, Astellas Pharma, Ironwood Pharmaceuticals, Sucampo Pharmaceuticals, Movetis UK, Almirall.

Potential competing interests: Bellamy has no disclosures to make. This Rome Committee paper on IBS severity was edited by Hugo E Gallo-Torres in his private capacity. No official support or endorsement by the FDA is intended or should be inferred. Gallo-Torres' views were that of his own as an expert is drug study design and was not speaking for the FDA. He is currently retired from the FDA.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The concept of severity in irritable bowel syndrome (IBS) is important for clinical decision making with regard to treatment.
- ✓ Little is known about the components that comprise severity in IBS.
- ✓ Although severity is assumed to be related to symptom intensity, clinical judgment suggests other possibilities.

WHAT IS NEW HERE

- ✓ Severity in IBS is defined as a biopsychosocial composite of patient-reported gastrointestinal and extraintestinal symptoms, degree of disability, and illness-related perceptions and behaviors.
- ✓ Both visceral and central nervous system (CNS) physiological factors affect severity; as severity increases, the CNS provides a greater contribution.

REFERENCES

1. Longstreth GF, Thompson WG, Chey WD *et al.* Functional Bowel Disorders. In Drossman DA, Corazziari E, Delvaux M *et al.* (eds). Rome III: The Functional Gastrointestinal Disorders, 3rd edn. Degnon Associates: McLean, VA, 2006 pp. 487–555.
2. Drossman DA, Camilleri M, Mayer EA *et al.* AGA Technical Review on Irritable Bowel Syndrome. Gastroenterology 2002;123:2108–31.
3. DeVaul RA, Faillace LA. Persistent pain and illness insistence—a medical profile of proneness to surgery. Am J Surg 1978;135:828–33.
4. Drossman DA, Thompson WG. The irritable bowel syndrome: review and a graduated, multicomponent treatment approach. Ann Intern Med 1992;116:1009–16.
5. Drossman DA, Li Z, Andruzzi E *et al.* U.S. householder survey of functional gastrointestinal disorders: prevalence, sociodemography and health impact. Dig Dis Sci 1993;38:1569–80.
6. Lembo A, Ameen V, Drossman DA. Irritable bowel syndrome: toward an understanding of severity. Clin Gastroenterol Hepatol 2005;3:717–25.
7. Drossman DA, Whitehead WE, Toner BB *et al.* What determines severity among patients with painful functional bowel disorders? Am J Gastroenterol 2000;95:974–80.
8. Drossman DA, Li Z, Leserman J *et al.* Effects of coping on health outcome among female patients with gastrointestinal disorders. Psychosom Med 2000;62:309–17.
9. Creed F, Levy R, Bradley L *et al.* Psychosocial Aspects of Functional Gastrointestinal Disorders. In Drossman DA, Corazziari E, Delvaux M *et al.* (eds). Rome III: The Functional Gastrointestinal Disorders, 3rd edn. Degnon Associates: McLean, VA, 2006 pp. 295–368.
10. Sperber AD, Morris CB, Greemberg L *et al.* Development of abdominal pain and IBS following gynecological surgery: a prospective, controlled study. Gastroenterology 2008;134:75–84.
11. Drossman DA, Li Z, Leserman J *et al.* Health status by gastrointestinal diagnosis and abuse history. Gastroenterology 1996;110:999–1007.
12. Mayeux R, Drossman DA, Basham KK *et al.* The stress response. Gulf War and Health: Physiologic, Psychologic, and Psychosocial Effects of Deployment-Related Stress, Volume 6 edn. The National Academies Press: Washington, DC, 2008 pp. 49–74.
13. Drossman DA, Li Z, Toner BB *et al.* Functional bowel disorders: a multicenter comparison of health status, and development of illness severity index. Dig Dis Sci 1995;40:986–95.
14. Sperber AD, Carmel S, Atzmon Y *et al.* Use of the Functional Bowel Disorder Severity Index (FBDSI) in a study of patients with the Irritable bowel syndrome and fibromyalgia. Am J Gastroenterol 2000;95:995–8.
15. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997;11:395–402.
16. Coffin B, Dapoigny M, Cloarec D *et al.* Relationship between severity of symptoms and quality of life in 858 patients with irritable bowel syndrome. Gastroenterol Clin Biol 2004;28:11–5.
17. Kennedy T, Jones R, Darnley S *et al.* Cognitive behaviour therapy in addition to antispasmodic treatment for irritable bowel syndrome in primary care: randomised controlled trial. BMJ 2005;331:435.
18. Carruthers HR, Miller V, Morris J *et al.* Using art to help understand the imagery of irritable bowel syndrome and its response to hypnotherapy. Int J Clin Exp Hypn 2009;57:162–73.
19. Lembo AJ, Conboy L, Kelley JM *et al.* A treatment trial of acupuncture in IBS patients. Am J Gastroenterol 2009;104:1489–97.
20. Spiegel B, Harris L, Lucak S *et al.* Developing valid and reliable health utilities in irritable bowel syndrome: results from the IBS PROOF cohort. Am J Gastroenterol 2009;104:1984–91.
21. Spiegel B, Strickland A, Naliboff BD *et al.* Predictors of patient-assessed illness severity in irritable bowel syndrome. Am J Gastroenterol 2008;103:2536–43.
22. van der Horst HE, Van Dulmen AM, Schellevis FG *et al.* Do patients with irritable bowel syndrome in primary care really differ from outpatients with irritable bowel syndrome? Gut 1997;41:669–74.
23. Ricci JF, Jhingran P, Harris W *et al.* Impact of differences in severity of irritable bowel syndrome (IBS) on patients' well being and resource use. Gastroenterology 2001;120:A406.
24. Sach J, Bolus R, FitzGerald L *et al.* Is there a difference between abdominal pain and discomfort in moderate to severe IBS patients? Am J Gastroenterol 2002;97:3131–8.
25. Hahn BA, Kirchdoerfer LJ, Fullerton S *et al.* Patient-perceived severity of irritable bowel syndrome in relation to symptoms, health resource utilization and quality of life. Aliment Pharmacol Ther 1997;11:553–9.
26. Longstreth GF, Wilson A, Knight K *et al.* Irritable bowel syndrome, health care use, and costs: a U.S. managed care perspective. Am J Gastroenterol 2003;98:600–7.
27. Hillila MT, Farkkila MA. Prevalence of irritable bowel syndrome according to different diagnostic criteria in a non-selected adult population. Aliment Pharmacol Ther 2004;20:339–45.
28. Liu JH, Chen GH, Yeh HZ *et al.* Enteric-coated peppermint-oil capsules in the treatment of irritable bowel syndrome: a prospective, randomized trial. J Gastroenterol 1997;32:765–8.
29. Tack J, Broekaert D, Fischler B *et al.* A controlled cross-over study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. Gut 2006;55:1095–103.
30. Drossman DA, Toner BB, Whitehead WE *et al.* Cognitive-behavioral therapy verses education and desipramine verses placebo for moderate to severe functional bowel disorders. Gastroenterology 2003;125:19–31.
31. Guthrie E, Creed F, Dawson D *et al.* A controlled trial of psychological treatment for the irritable bowel syndrome. Gastroenterology 1991;100:450–7.
32. Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable bowel syndrome. Lancet 1984;2:1232–3.
33. Spiegel B, Camilleri M, Bolus R *et al.* Psychometric evaluation of enpoints in IBS randomized controlled trials: a Rome Foundation Working Group Report. Gastroenterology 2009;137:1944–53.
34. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH). Guidance for industry patient-reported outcome measures: Use in medical product development to support labeling claims. Health Qual Life Outcomes 2006;4:1–32.
35. Lee OY, Mayer EA, Schmulson M *et al.* Gender-related differences in IBS symptoms. Am J Gastroenterol 2001;96:2184–93.
36. Palsson OS, Whitehead WE, Barghout V *et al.* IBS severity and health-related quality of life improve with age in women but not in men. Am J Gastroenterol 2003;98:S272.
37. Lembo T, Naliboff B, Munakata J *et al.* Symptoms and visceral perception in patients with pain-predominant irritable bowel syndrome. Am J Gastroenterol 1999;94:1320–6.
38. Dorn SD, Palsson OS, Thiwan SM *et al.* Increased colonic pain sensitivity in irritable bowel syndrome is the result of an increased tendency to report pain rather than increased neurosensory sensitivity. Gut 2007;56:1202–9.
39. Chang L, Drossman DA. Rome Foundation Endpoints and Outcomes Conference 2009: Optimizing Clinical Trials in FGIDs. Am J Gastroenterol 2010;105:722–30.
40. Drossman DA, Chang L, Schneck S *et al.* A focus group assessment of patient perspectives on irritable bowel syndrome and illness severity. Dig Dis Sci 2009;54:1532–41.
41. Drossman DA, Morris C, Schneck S *et al.* International survey of patients with IBS: symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. J Clin Gastroenterol 2009;43:541–50.