Psychosocial Aspects of the Functional Gastrointestinal Disorders

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This report reviews recent research on the psychosocial aspects of the functional gastrointestinal disorders (FGIDs). A review and evaluation of existing literature was conducted by a multidisciplinary committee of experts in this field. This report is a synopsis of a chapter published in the Rome III book. The committee reached consensus in finding considerable evidence supporting the association between psychological distress, childhood trauma and recent environmental stress, and several of the FGIDs but noted that this association is not specific to FGIDs. There is also considerable evidence that psychosocial variables are important determinants of the outcomes of global well-being, health-related quality of life, and health care seeking. In line with these descriptive findings, there is now increasing evidence that a number of psychological treatments and antidepressants are helpful in reducing symptoms and other consequences of the FGIDs in children and adults. The FGIDs are a result of complex interactions between biological, psychological, and social factors, and they can only be treated satisfactorily when all these factors are considered and addressed. Therefore, knowledge about the psychosocial aspects of FGIDs is fundamental and critical to the understanding, assessment, and treatment of these disorders. More extensive physician training is needed if these aspects of treatment are to be used effectively and widely in clinical practice.

Knowledge about the psychosocial aspects of the functional gastrointestinal disorders (FGIDs) is fundamental and critical to the understanding of the FGIDs and their effective treatment. Because physicians are traditionally trained to look for pathophysiologic explanations of observed phenomena, they may feel uncertain when faced with syndromes such as the FGIDs, chronic fatigue syndrome, and fibromyalgia, which cannot be explained in this manner. The FGIDs do not fit a simple pathophysiologic model. Rather, they result from complex interactions of biological, psychological, and social factors, and this report provides an up-to-date synthesis of current research in the area.

The biopsychosocial model provides the conceptual basis of this report (Figure 1). Early life experiences, adult stressors (eg, divorce or bereavement), social support, and other social learning experiences affect both an individual's physiologic and psychological responses, including distress, psychiatric disorders, and beliefs and coping strategies. The gut responds to environmental and physiology factors, but it also interacts directly with the brain, thereby providing 2-way interactions along the "brain-gut" axis (central nervous system/enteric nervous system connections; see the neurogastroenterology report in this supplement). Genetic factors can have direct physiologic effects, and the genetic makeup of an individual can also make him or her more susceptible to environmental or social factors, thus leading to changes in physiology.

Therefore, while not specific to the FGIDs, psychological and social influences can affect the perception of symptoms, health care—seeking behaviors, and outcomes in patients with FGIDs. These psychosocial influences affect gut function, the experience of pain, health-related quality of life, work absenteeism, health care use, and medical and societal costs. This report provides recent evidence of these interactions and explores the mechanisms by which this biopsychosocial approach affects the illness experience and clinical outcome of patients with FGIDs. The report also discusses ways to apply this more integrated approach in clinical practice.

Genetics and Childhood Learning

There is substantial evidence of family aggregation of irritable bowel syndrome (IBS) and related dis-

Abbreviations used in this paper: CBT, cognitive-behavioral therapy; FGID, functional gastrointestinal disorder; GI, gastrointestinal; IBS, irritable bowel syndrome; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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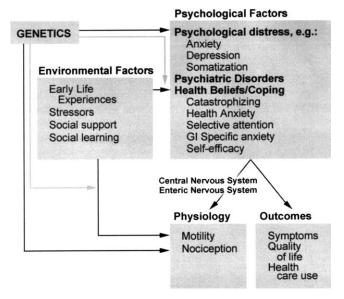


Figure 1. Conceptual model illustrating the relationships among psychological and environmental factors, physiologic variables, and outcome of FGIDs.

orders, which reflects genetic and environmental influences.¹ One study has found that a polymorphism in the serotonin reuptake transporter (*SERT*) gene that is associated with fibromyalgia^{2,3} and affective or anxiety disorders is also associated with diarrhea-predominant IBS,⁴ although negative findings regarding this relationship also have been reported.⁵ Additional association studies regarding polymorphisms in *SERT* and similar genes (eg, the enzyme catechol-O-methyltransferase⁶) may clarify the possible influence of genetic factors on the development of functional bowel disorders. In addition, children learn behaviors from their parents who have FGIDs, and this learning appears to make an even stronger contribution to the risk of developing an FGID than genetic influences.⁷

A number of social learning phenomena can influence the clinical expression of abdominal pain, including modeling (ie, where children observe and learn to display the illness behavior of their parents) and positive reinforcement. Children of adult patients with IBS make more health care visits than the children of parents without IBS, and this increased medical help seeking is not confined to gastrointestinal (GI) symptoms.8 Retrospective and prospective studies have shown that children whose mothers reinforce illness behaviors experience more severe stomachaches and miss more school than other children.^{9,10} Additional research supporting this mechanism comes from studies of children with recurrent abdominal pain (a child is considered to have recurrent abdominal pain when, in the absence of physical or laboratory findings, he or she has experienced at least 3 episodes of pain over a 3-month period that affect the child's activities¹¹). Preliminary research has shown that when parents of children with recurrent abdominal pain are taught to reduce positive or sympathetic responses to their children's reports of pain, the frequency of these complaints decreases.¹²

Environmental Stress in Childhood and Adult Life

Abuse History

High frequency rates of sexual, physical, and emotional abuse in patients with FGIDs (30%–56%) have been reported from many different referral centers in the United States and Europe, ^{13–17} especially in specialist or secondary care clinics, ^{18,19} and these figures are significantly higher than those in healthy control groups. A similar high rate of abuse history is also found in non-GI painful conditions (eg, pelvic pain, headaches, fibromyalgia).

Most, but not all, national probability studies have shown that abuse is associated with increased risk of abdominal pain and FGIDs.²⁰⁻²² Compared with those without such a history, patients with FGIDs with abuse histories report more severe pain, greater psychological distress, greater impairment of functioning in their daily lives, and more frequent visits to the doctor. 23-26 Certain types of abuse, such as rape, repeated or multiple abuses, and life-threatening physical abuse, are more likely to produce marked symptom severity, disability, and other adverse health outcomes than other forms of abuse.²⁷ In a rare study that examined the relationship between posttraumatic stress disorder and IBS, Irwin et al found 44% of 50 consecutive patients with IBS reported a trauma history and 36% were diagnosed with posttraumatic stress disorder.28

Possible mechanisms. Possible mechanisms mediating the association between abuse history and poor outcome include (1) concurrent psychiatric disorders, moderate levels of psychological distress, and the tendency to report a large number of bodily symptoms^{29–32}; (2) altered appraisal of bodily symptoms (ie, increased hypervigilance to normal bodily sensations) and maladaptive coping styles (eg, "catastrophizing," feelings of helplessness or inability to control symptoms)^{25,33,34}; (3) impaired adult relationships (lack of social support)³⁵; (4) centrally lowered threshold for perceiving afferent GI signals; and (5) increased autonomic function and/or intestinal motility due to hyperarousal.^{23,36}

Stressful Life Events

Stressful life events are associated with symptom exacerbation among adults with IBS³⁷ and heartburn³⁸ and children with recurrent abdominal pain and are also associated with frequent health care seeking for patients with IBS.^{37,39} Chronic life stress has been found to be the main predictor of IBS symptom intensity over 16 months, even after adjusting for IBS symptom severity, anxiety, and demographic features.⁴⁰ These data indicate a direct relationship between stress and outcomes in patients with FGIDs and show that this relationship can be mediated by psychiatric disorders.

Psychological States and Traits

Patients with IBS, like many other medical patient groups, experience levels of depression and anxiety intermediate between groups of psychiatric patients and healthy controls. There is also an increased prevalence (40%–60%) of psychiatric disorders in clinic patients with some FGIDs (notably IBS) compared with healthy controls (<20%) and patients with similar abdominal symptoms that can be explained by underlying organic GI disease (<25%). The most common disorders are anxiety, depressive, panic, posttraumatic stress, and somatization disorders. These disorders frequently precede or occur simultaneously with the FGID, indicating that the psychiatric disorder cannot always be regarded as a response to the FGID.

The self-reporting of numerous bodily symptoms (somatization) is a common phenomenon among clinic patients with FGIDs and in population-based studies of FGIDs. ⁴³ Recent work suggests there is a separate dimension of somatic distress that may be partly genetically determined and that also overlaps with anxiety and depression. ⁴⁴ Although seen less commonly, some patients experience numerous bodily symptoms that have been present for many years and are associated with marked disability. This picture is recognized in the psychiatric literature as "somatization disorder" and is overrepresented in specialist clinics. ⁴⁵

Children with recurrent abdominal pain also have higher levels of anxiety and depression than healthy children, and levels of anxiety and depression are often related to the duration of symptoms in these children.⁴⁶ Depressed children with recurrent abdominal pain report numerous bodily symptoms in response to daily stressors, suggesting that stress reactivity is important in these children.³⁹

Possible Mechanisms

Psychiatric disorders are associated with alterations in the processing of visceral sensation in patients with FGIDs.⁴⁷ Patients with FGIDs who have a concom-

itant psychiatric diagnosis may also manifest alterations in gut-related autonomic nervous system function, affecting gut motility and sensation. Psychiatric disorders may directly impair health-related quality of life. 30,48

Psychophysiology: Affect and Stress Modulation of GI Function

Environmental stressors and related changes in mood alter the function of the GI tract and GI symptom perception in persons with GI diseases such as gastroesophageal reflux disease and those with FGIDs. The relationship of stressors to GI function is viewed as a direct consequence of the bidirectional modulation of GI function by the central nervous system, including motor responses, pain modulation, and even immune function. ^{49–51} These interactive relationships are important for FGIDs in that they provide the foundation for hypotheses of central nervous system dysregulation as causative in FGID symptom onset and maintenance. ^{50,52,53}

Patients with IBS may show exaggerated motility to psychological stress, balloon distention, eating, and injection of cholecystokinin.^{54–56} Such contractions are principally nonperistaltic (but can also be propulsive) contractions that could contribute to IBS symptoms by retarding (or accelerating) the movement of gas and stool or by more direct pain mechanisms. Laboratory stressors also produce increased smooth muscle tone in the rectum, which has been associated with IBS.⁵⁷ However, a critical role for motility disturbance in producing symptoms in a majority of patients with IBS has not been clearly shown.

Although the literature on autonomic nervous system function suggests that abnormalities exist among patients with FGIDs,⁵⁸ the prevalence of these abnormalities and their role in the pathophysiology of functional symptom generation or exacerbation are unclear. Most studies are of small samples with mixed symptom features and poor control of potentially confounding variables, such as menstrual cycle in women, psychological status, and comorbid conditions. Cardiovascular autonomic nervous system measures used in these studies may not be sensitive markers for GI autonomic nervous system function; pancreatic polypeptide levels (ie, abdominal vagal activation) and mucosal blood flow may provide better measures.

Possible Mechanisms

A variety of neuroendocrine pathways have been implicated in stress-induced alterations in GI function. ^{53,59} Activation of central nervous system circuits that include the emotional motor system lead to neu-

roendocrine responses such as the release of corticotrophin-releasing factor, cortisol, and norepinephrine and epinephrine. There is a positive correlation between subjective sleep disturbances and GI symptoms, but whether this is purely a secondary phenomenon is not clear.⁶⁰

Outcomes Influenced by Psychological Factors

Health-Related Quality of Life

It is well recognized that patients with IBS and other FGIDs experience considerable impairment of health-related quality of life.^{61,62} Several recent studies have shown that only some of this impairment can be accounted for by the symptoms of FGIDs; psychological factors have a major and unique negative impact on health-related quality of life that can be reversible with appropriate psychological treatment.^{30,48,63–65}

Health Care Seeking

The factors differentiating patients with IBS who seek medical help from those people in the community with IBS symptoms who do not consult (IBS nonconsulters) can be explained by the biopsychosocial model. These factors include greater pain severity, greater duration of pain, increased concern about illness, greater anxiety and depression, and seeing the disorder as unrelated to stress. 26,66-68 Some patients with FGIDs make very frequent visits to physicians for GI and non-GI symptoms and have increased hospitalizations and surgical procedures.²⁴ In a UK study comparing patients with IBS and control subjects, attendance at primary care was increased by 43%, prescriptions were increased by 85%, and gastroenterology appointments were increased by 68% in the IBS group. 61 These data are comparable to other studies,⁶⁹ but the costs are highly skewed. Half of a population-based sample of patients with IBS incur costs comparable to the general population, and 14% incur costs 5 times that of the general population⁷⁰; the latter is comparable to patients with severe IBS seen in a gastroenterology clinic.31 This high health care use is partly attributable to psychosocial factors such as depression and somatization in addition to symptoms related to the FGID itself^{48,71} and may be reduced by at least 25% following psychological treatment.⁷²

Assessment to Be Performed by Physicians

In view of the importance of physiologic, social, and psychological factors in determining outcomes of the

FGIDs, we suggest that physicians include a brief psychosocial assessment of each patient with FGID. A more in-depth psychosocial assessment, often performed by a psychologist or a psychiatrist, is particularly useful for patients with severe symptoms, previous treatment failure, poor adherence to a treatment regimen, and evidence of poor coping with illness. Standardized self-report measures are more likely to be used under these circumstances.

Whether brief or in depth, the assessment should include the following areas (suggested screening instruments are included for each): (1) depression and anxiety (including potential red flags, see Figure 2) (Hospital Anxiety and Depression Scale⁷³), (2) somatization (the general tendency to report numerous bodily symptoms) (Patient Health Questionnaire⁷⁴), (3) health beliefs and coping (Cognitive Strategies Questionnaire-Catastophizing or Visceral Sensitivity Index), 75,76 (4) illness impact and health-related quality of life (IBS-Quality of Life),⁷⁷ and (5) exploration of the chronological "coincidences" between psychosocial factors and periods of worsening or improvement of symptoms. For screening purposes, the Hospital Anxiety and Depression Scale for mood and Patient Health Questionnaire 15 to assess somatization would probably be satisfactory. Assessment of psychosocial factors is facilitated if the physician interviews the patient in a confidential venue, explains the routine nature of the questions, and is prepared to discuss the findings, including their clinical relevance.

Success in treating patients with FGIDs does not only involve assessing the patient's psychological and social status; an effective physician-patient relationship should be developed in which questions arise and information is passed from the physician to the patient and vice versa. The physician should adopt an active listening approach and an enthusiastic, positive, and encouraging attitude with regard to treatment. The most successful approach is likely to be a patient-centered one, in which the physician elicits and addresses the patient's concerns such as fears of cancer.

The physician may find it helpful to predict negative results to investigations, when this seems likely, as a first step away from regarding organic disease as the cause of the symptoms. The physician should be prepared to address psychosocial issues directly. This may involve prescription of an antidepressant or similar drug and possibly referring the patient to a mental health professional. This approach should help the patient to adopt an appropriate way of coping with the symptoms rather than expecting a complete cure from medication.

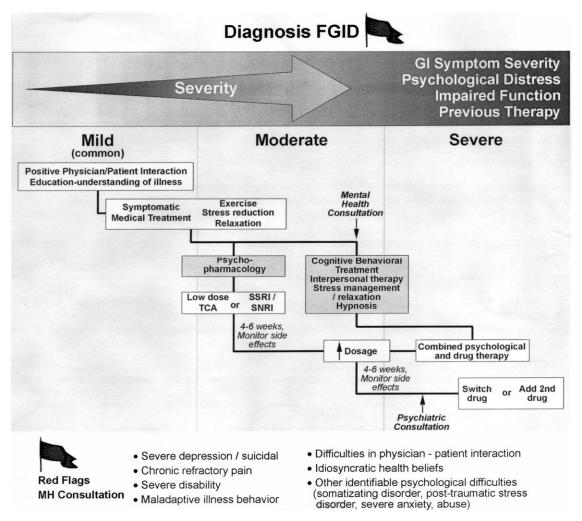


Figure 2. Treatment algorithm for patients with FGIDs. "Red Flags" are indications for consideration of early referral to a mental health professional. TCA, tricyclic antidepressant.

Overview of Psychological Treatment Approaches

Psychological treatments are often appropriate for patients with FGIDs because of the psychosocial factors listed in the previous sections (see Lackner for meta-analytic review).⁷⁸ In clinical practice, 2 or more forms of psychological therapy may be used concurrently.

Cognitive-Behavioral Therapy

The theoretical basis of cognitive-behavioral therapy (CBT) lies in social learning, which includes the concept that behavior is shaped by its consequences. CBT recognizes that social consequences produced in the environment may influence cognitions, motor behavior, and physiologic responses; in turn, how individuals respond may influence the reaction they get from their environment. Thus, CBT interventions address the thoughts, behaviors, and responses that result from patients' daily interactions. Because patients with IBS have

been shown to often have distortions about their symptoms,⁷⁹ CBT may be particularly valuable for these patients because it may help patients recognize how particular beliefs about symptoms may help perpetuate pain and pain-related activities. Relaxation/stress management is often incorporated into CBT packages because of its effect in reducing autonomic arousal and anxiety in IBS.80 One recent study has shown CBT to be more effective than an educational intervention in terms of satisfaction, overall symptom relief, and global wellbeing after 3 months, but there was little or no difference in pain scores.⁸¹ Often patients reported that "the pain is still there but I'm managing it better," indicating improved coping. Such improvement may be associated with less time off work and less treatment seeking.⁷² CBT was effective regardless of the severity of the IBS and whether an abuse history or current depression was present.81 Similar approaches in children with recurrent abdominal pain lead to significantly more pain-free days

compared with standard medical care or symptom monitoring.⁸²

Relaxation Training

Relaxation or arousal reduction techniques (including progressive muscle relaxation, biofeedback, autogenic training, and meditation) teach patients to counteract the physiologic sequelae of stress or anxiety and may lead to a significant reduction in GI symptoms.⁸³

Combined Psychotherapies

Nine studies have combined progressive muscle relaxation training with CBT, and all of them reported this treatment combination to be superior to a waiting list control group or conventional medical therapy.⁸⁴ Results are less clear in the studies that used an active placebo control.^{78,85} Multicomponent behavioral therapy, including progressive muscle relaxation, training in illness-related knowledge, and cognitive coping strategies, problem solving, and assertiveness training, showed significantly greater IBS symptom reduction than standardized medical treatment with a gastroenterologist.⁸⁶

Dynamic Psychotherapy

This form of therapy (similar to brief interpersonal psychotherapy) requires a close relationship between the patient and the therapist, in which the patient can learn how he or she responds in such a relationship. A recent, large study showed that brief psychodynamic therapy can be used in routine clinical practice for patients with severe IBS and that this treatment is cost-effective. The Like a selective serotonin reuptake inhibitor (SSRI) antidepressant (paroxetine), psychodynamic interpersonal therapy led to a marked improvement in health-related quality of life in the long-term compared with treatment as usual. This result could not be explained by improvement in pain or improved psychological status. Recent reviews conflict in their support for these therapies in IBS. The Research of the service of

Hypnotherapy

Controlled trials of hypnotherapy in IBS and functional dyspepsia have shown that this can be an effective treatment, with benefits that persist over time. 89-91 However, little is known about the applicability of the technique in a wide range of patients, because most studies have been performed on patients seeking this type of treatment at selected centers. Some uncontrolled studies support the efficacy of both individual and group hypnotherapy at other locations. 92

We would like to add a caveat to the interpretation of many of the studies described previously. Careful reviews of these psychological treatment studies found that very few trials were methodologically strong. 78,85 Many used waiting list or "treatment as usual" as control conditions (thus not controlling for potentially confounding and powerful effects of attention and support), studies often included very small numbers, and participants were recruited by advertisement from the general population (raising questions of their generalizability to clinic populations). Both reviews, however, indicated superiority of psychological treatments over control conditions in terms of abdominal pain, bowel dysfunction, depression, and anxiety. Furthermore, more methodologically rigorous recent trials discussed previously do permit greater confidence in their conclusions, and we expect that further information will become available as additional methodologically strong studies are conducted.

Pharmacologic Treatment

In addition to the effect on anxiety and depression described previously, antidepressants have direct analgesic effects that are useful in treating patients with FGIDs.

Antidepressants

In a meta-analysis of 11 randomized placebocontrolled trials of acceptable quality, the summary odds ratio for improvement of FGIDs using antidepressants compared with placebo was 4.2 (95% confidence interval, 2.3-7.9).93 In this study, the antidepressants amitriptyline, clomipramine, desipramine, doxepin, trimipramine, and mianserin were studied. All these studies were randomized controlled trials and yielded positive results. The main outcome measure was pain. Another systematic review included 6 randomized control trials of antidepressant therapy in FGIDs.⁹⁴ Although the trials were of low quality, the investigators concluded that tricyclic antidepressants were ineffective in relieving global IBS symptoms but did lead to improved abdominal pain. Neither review could draw any clear conclusions regarding the utility of SSRIs in the treatment of IBS or distinguish clearly between the analgesic and antidepressant effects of the drugs.

The more recent antidepressant treatment trials for functional bowel disorders with satisfactory trial design have shown that both desipramine and paroxetine have significant general beneficial effects, at least in those patients who complied fully with the treatment to which they were randomized^{72,81}; dropouts were numerous in both studies. In patients with IBS who had not responded to a high-fiber diet, paroxetine has shown superiority over placebo in terms of overall well-being,

quality-of-life scores, fewer problems with stool passage, and IBS-related anxiety but not in abdominal pain.⁹⁵

The published studies provide reasonable evidence that tricyclic antidepressants produce benefit for patients with moderate to severe IBS, provided the patients adhere to the prescribed medications. They are currently the favored antidepressant for treating patients with IBS based on the available literature. The evidence for SSRIs is more equivocal; possibly without the noradrenergic effect of the tricyclic antidepressants there is theoretically less benefit for pain, although the effect in reducing central anxiety may have secondary effects on global well-being.64 Similarly, in one study,96 the SSRI fluoxetine did not change rectal sensitivity but did lower pain perception. The serotonin-norepinephrine reuptake inhibitors (SNRIs) are a relatively new class of antidepressants that have substantial serotonergic and noradrenergic effects (unlike the SSRIs) to reduce pain but without the antihistaminic and anticholinergic effects of the tricyclic antidepressants that lead to most of the side effects. Venlafaxine, an SNRI, reduced sensation during colonic distention in healthy humans⁹⁷ but has limited usefulness in the FGIDs due to its tendency to produce GI distress, particularly nausea and vomiting. Duloxetine, a more recently marketed SNRI, has been studied for the treatment of major depressive disorder associated with pain and has an indication for the pain of peripheral neuropathy and proven efficacy for fibromyalgia.98 Thus, it may find a role for treatment of patients with FGIDs, although the main side effect is nausea.

In clinical practice, side effects of antidepressants can limit their usefulness unless clinicians warn patients about these and emphasize that these reduce with time as the beneficial effect becomes more prominent. If a patient cannot tolerate one antidepressant, it is reasonable to change to another drug in the same class or switch to another class of agents. This has been shown to be effective in psychopharmacology practice. ⁹⁹ Continued failure to improve suggests that a referral to a psychiatrist may be appropriate. A psychiatrist can be particularly helpful in determining further drug or dosage changes.

Anxiolytics

Anxiolytic agents can be used in patients with FGIDs, especially when there are comorbid generalized anxiety and panic disorders. However, the risk of addiction with the benzodiazepines and their tendency to produce mild transient cognitive dysfunction means that they have very limited use in the GI setting. A newer class of antianxiety agents, the azapirones (eg, buspirone), which act by serotonin agonist activity at presyn-

aptic 5-HT_{1A} receptors, may be more useful because they potentiate the action of antidepressants, are well tolerated, and have no addictive potential.

Algorithm for Treatment of Psychological Aspects of the FGIDs

In clinical practice, the use of psychological and antidepressant therapies depends on the severity of the FGID and any associated psychosocial factors. We recommend a "stepped care" approach (Figure 2).

- 1. In the initial assessment, the physician has 3 tasks: develop a satisfactory physician-patient relationship, make a positive diagnosis of the FGID, and identify any "red flag" indications that indicate a psychological management strategy (see Figure 2).
- 2. Facilitate the patient's understanding of the disorder.
- 3. Recommend symptomatic medical therapies and/or simple behavioral/lifestyle changes. Medical therapies refer to strategies such as dietary manipulation, prokinetics, H₂ blockers or proton pump inhibitors, laxatives, bulking agents, antidiarrheals, and antispasmodics. Preferred behavioral/lifestyle changes may be determined by assessing situations in which the patient's symptoms deteriorate or improve. In general, if stress is a likely factor, several forms of relaxation training (eg, yoga, relaxation classes, meditation, and so on) may be available.
- 4. Select psychopharmacologic medication or more specific psychological management. This selection may be determined in part by patient preferences, time or cost constraints (of medications and testing), health insurance, referral physician assumptions, and the opportunity for referral to a psychologist or other professional who is trained to treat patients with FGIDs, among other factors. If the psychological route is chosen, a detailed psychosocial assessment is performed by the psychologist or other mental health professional. If the psychopharmacologic route is chosen, the physician should be knowledgeable about appropriate psychopharmacologic agents for this population and be prepared to monitor the patient's progress.
- 5. Consider adding the second form of treatment (psychopharmacologic or lifestyle/behavioral) to the first. There is evidence in favor of such combined treatment in several disorders. 100–103 There are also good theoretical grounds for combined treatment in patients with FGIDs, because antidepressants have some direct action on pain, anxiety, and depression and can increase the patient's motivation to engage in therapy. Psychological treatments are effective in modifying

health anxiety, selective attention, catastrophizing, and aspects of poor coping and can also increase adherence to psychopharmacologic treatments.

Recommended Training Curriculum of Psychosocial Aspects of FGIDs for Gastroenterologists and Primary Care Physicians

To optimize care for patients with FGIDs along the principles of the biopsychosocial model, physicians may need additional training in the following areas so they can follow adequately the recommendations for assessment and treatment proposed in this report:

- Interviewing skills: establishing rapport and empathy, providing education and reassurance, facilitating patient disclosure of psychosocial information, facilitating patient involvement in care, and eliciting patient disclosure of thoughts and feelings
- Application of biopsychosocial principles in assessment and treatment
- Ability to screen for anxiety, depression, and somatization within a clinical interview
- Ability to use appropriate psychotropic medications in clinical practice
- Skills in working within a multidisciplinary team, including knowledge and skills concerning when and how to refer to mental health professionals and providing continuity of care
- Awareness of physician's personal reactions and appropriate response to difficulties in physician-patient relationship.

Recommendations for Future Research

This review suggests a number of questions that need to be addressed in future research.

Health Services Research Questions

- How we can best integrate our knowledge of psychosocial factors into routine clinical practice? The problem is not confined to gastroenterological practice; the problem of underdetection and treatment of depression and anxiety is also well recognized in primary care.¹⁰⁴
- 2. Is screening for the psychosocial factors effective, and which forms of physician education make a difference, especially the evaluation of clinical guidelines and treatment algorithms?

3. How cost-effective are the different interventions in real-life clinical settings?

Clinical Questions

- 1. Which treatments are effective for which subgroups of patients (characteristics, cultural groups, and so on), and are differential responses based on severity of pain, presence of marked anxiety, depression, or somatization?
- 2. What is the relative efficacy of tricyclic, SSRI, and SNRI antidepressants in treating patients with FGIDs?
- 3. Is it possible to identify preventative strategies for development of FGIDs in high-risk populations?
- 4. Because treatments for patients with posttraumatic stress disorder (eg, exposure-type therapies) address only whether symptoms of posttraumatic stress disorder improve, we need to determine whether FGIDs (and other associated health problems) are also helped by this treatment.

Transcultural, Ethnicity, and Gender Questions

Where current knowledge is limited to Western cultures and specific gender or ethnic groups, would similar findings be obtained in different cultures and groups regarding treatment effectiveness and the relationships between psychosocial factors and the FGIDs? See the report in this supplement on gender, age, society, culture, and the patient's perspective for further information about current knowledge on culture and FGIDs.

Mechanism Questions

- 1. How is childhood trauma (in all its forms) related to the development and course of FGIDs?
- 2. What are the mechanisms linking psychosocial factors to symptom expression and outcomes in FGIDs?
- 3. How do positive factors, such as social support and coping mechanisms, protect from the development of FGIDs?
- 4. Are the mechanisms of treatment response from psychological and pharmacologic interventions similar or different? If the latter, what is the effect of combined treatment?
- 5. To what extent can the physiologic abnormalities observed in FGIDs be explained by psychological distress and psychiatric disorders?
- 6. What are the mechanisms involved in the pain experience? In line with the biopsychosocial model, neurobiological and psychosocial factors need to be studied simultaneously, not separately.

Conclusions

Considerable research has shown the interrelationships among biological, psychological, and social factors and the development and maintenance of the FGIDs. Several promising lines of research have also been investigating possible mechanisms for these relationships. Many treatment strategies have also been shown to be effective, including behavioral/lifestyle recommendations and psychological and psychopharmacologic treatments. Although many unanswered questions remain, our ability to have confidence in our recommendations of critical areas of assessment and treatment has grown considerably in recent years. We expect this trend to continue as research in this area evolves and physicians and other health and mental health care workers receive more training in the biopsychosocial aspects of these disorders. We also want to particularly encourage training in psychosocial assessment as part of GI fellowship training and perhaps even recertification. We believe this report has shown that the ability to take and utilize a psychosocial history and assessment is as important to practice as most GI procedures commonly taught in training programs.

References

- Locke GR III, Zinsmeister A, Talley NJ, Fett SL, Melton J. Familial association in adults with functional gastrointestinal disorders. Mayo Clin Proc 2000;75:907–912.
- Offenbaecher M, Bondy B, de Jonge S, Glatzeder K, Kruger M, Schoeps P, Ackenheil M. Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. Arthritis Rheum 1999;42:2482–2488.
- Cohen H, Buskila D, Neumann L, Ebstein RP. Confirmation of an association between fibromyalgia and serotonin transporter promoter region (5-HTTLPR) polymorphism, and relationship to anxiety-related personality traits. Arthritis Rheum 2002;46: 845– 847
- 4. Yeo A, Boyd P, Lumsden S, Saunders T, Handley A, Stubbins M, Knaggs A, Asquith S, Taylor I, Bahari B, Crocker N, Rallan R, Varsani S, Montgomery D, Alpers DH, Dukes GE, Purvis I, Hicks GA. Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. Gut 2004;53:1452–1458.
- 5. Camilleri M. Is there a SERT-ain association with IBS? Gut 2004:53:1396-1399.
- Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, Goldman D, Xu K, Shabalina SA, Shagin D, Max MB, Makarov SS, Maixner W. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 2005;14:135–143.
- Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. Gastroenterology 2001;121:799– 804.
- Levy RL, Whitehead WE, Von Korff MR, Saunders KW, Feld AD. Intergenerational transmission of gastrointestinal illness behavior. Am J Gastroenterol 2000;95:451–456.
- Levy RL, Whitehead WE, Walker LS, Von Korff M, Feld AD, Garner M, Christie D. Increased somatic complaints and health-care utilization in children: effects of parent IBS status and parent

- response to gastrointestinal symptoms. Am J Gastroenterol 2004;99:2442–2451.
- Whitehead WE, Crowell MD, Heller BR, Robinson JC, Schuster MM, Horn S. Modeling and reinforcement of the sick role during childhood predicts adult illness behavior. Psychosom Med 1994;6:541–550.
- 11. Apley J, Naish N. Recurrent abdominal pains: a field survey of 1000 children. Arch Dis Child 1958;33:165–170.
- Levy RL, Garner MD, Christie DL, Whitsett SF, Whitehead WE, Walker LS, Feld A. Changes in childhood recurrent abdominal pain and parental responses with cognitive behavior therapy (abstr). Gastroenterology 2003;124(Suppl 1):A-530.
- Talley NJ, Fett SL, Zinsmeister AR. Self-reported abuse and gastrointestinal disease in outpatients: association with irritable bowel-type symptoms. Am J Gastroenterol 1995;90:366– 371.
- Delvaux M, Denis P, Allemand H, French Club of Digestive Motility. Sexual and physical abuses are more frequently reported by IBS patients than by patients with organic digestive diseases or controls. Results of a multicenter inquiry. Eur J Gastroenterol Hepatol 1997;9:345–352.
- Scarinci IC, McDonald-Haile JM, Bradley LA, Richter JE. Altered pain perception and psychosocial features among women with gastrointestinal disorders and history of abuse: a preliminary model. Am J Med 1994;97:108–118.
- Heitkemper M, Jarrett M, Walker E, Landenburger K, Bond EF. Effect of sexual and physical abuse on symptom experiences in women with irritable bowel syndrome. Nurs Res 2001;50:1–9.
- Ali A, Toner BB, Stuckless N, Gallop R, Diamant NE, Gould M, Vidins E. Emotional abuse, self-blame and self-silencing in women with irritable bowel syndrome. Psychosom Med 2000; 62:76–82.
- Longstreth GF, Wolde-Tsadik G. Irritable bowel-type symptoms in HMO examinees. Prevalence, demographics, and clinical correlates. Dig Dis Sci 1993;38:1581–1589.
- Drossman DA, Leserman J, Nachman G, Li Z, Gluck H, Toomey TC, Mitchell CM. Sexual and physical abuse in women with functional or organic gastrointestinal disorders. Ann Intern Med 1990;113:828–833.
- McCauley J, Kern DE, Kolodner K, Dill L, Schroeder AF, DeChant HK, Ryden J, Derogatis LR, Bass EB. Clinical characteristics of women with a history of childhood abuse: unhealed wounds. JAMA 1997;277:1362–1368.
- Talley NJ, Fett SL, Zinsmeister AR, Melton LJ. Gastrointestinal tract symptoms and self-reported abuse: a population-based study. Gastroenterology 1994;107:1040–1049.
- Walker EA, Gelfand A, Katon WJ, Koss MP, Von Korff M, Bernstein D, Russo J. Adult health status of women with histories of childhood abuse and neglect. Am J Med 1999;107:332–339.
- Drossman DA, Talley NJ, Olden KW, Leserman J, Barreiro MA. Sexual and physical abuse and gastrointestinal illness: review and recommendations. Ann Intern Med 1995;123:782–794.
- Drossman DA, Li Z, Leserman J, Toomey TC, Hu Y. Health status by gastrointestinal diagnosis and abuse history. Gastroenterology 1996;110:999–1007.
- Drossman DA, Li Z, Leserman J, Keefe FJ, Hu YJ, Toomey TC. Effects of coping on health outcome among female patients with gastrointestinal disorders. Psychosom Med 2000;62: 309–317.
- 26. Koloski NA, Talley NJ, Boyce PM. Predictors of health care seeking for irritable bowel syndrome and nonulcer dyspepsia: a critical review of the literature on symptom and psychosocial factors. Am J Gastroenterol 2001;96:1340–1349.
- Leserman J, Li Z, Hu YJB, Drossman DA. How multiple types of stressors impact on health. Psychosom Med 1998;60:175– 181.

- 28. Irwin C, Falsetti SA, Lydiard RB, Ballenger JC, Brock CD, Brener W. Comorbidity of posttraumatic stress disorder and irritable bowel syndrome. J Clin Psychiatry 1996;57:576–578.
- Talley NJ, Boyce PM, Jones M. Is the association between irritable bowel syndrome and abuse explained by neuroticism? A population based study. Gut 1998;42:47–53.
- Naliboff BD, Balice G, Mayer EA. Psychosocial moderators of quality of life in irritable bowel syndrome. Eur J Surg Suppl 1998;57–59.
- Creed FH, Ratcliffe J, Fernandes L, Palmer S, Rigby C, Tomenson B, Guthrie E, Read N, Thompson DG. Outcome in severe irritable bowel syndrome with and without depressive, panic and neurasthenic disorders. Br J Psychiatry 2005;186:507–515.
- Hobbis IC, Turpin G, Read NW. A re-examination of the relationship between abuse experience and functional bowel disorders. Scand J Gastroenterol 2002;37:423–430.
- Drossman DA, Hu Y, Jia H, Toner BB, Whitehead WE, Diamant NE, Ringel Y, Dalton C, Bangdiwala SI. The influence of psychosocial factors on health care utilization in patients with functional bowel disorders (FBD). Gastroenterology 2000;118(Suppl 2):A842.
- 34. Salmon P, Skaife K, Rhodes J. Abuse, dissociation, and somatization in irritable bowel syndrome: towards an explanatory model. J Behav Med 2003;26:1–18.
- Biggs AM, Aziz Q, Tomenson B, Creed F. Effect of childhood adversity on health related quality of life in patients with upper abdominal or chest pain. Gut 2004;53:180–186.
- Jarrett ME, Burr RL, Cain KC, Hertig V, Weisman P, Heitkemper MM. Anxiety and depression are related to autonomic nervous system function in women with irritable bowel syndrome. Dig Dis Sci 2003;48:386–394.
- 37. Whitehead WE, Crowell MD, Robinson JC, Heller BR, Schuster MM. Effects of stressful life events on bowel symptoms: subjects with irritable bowel syndrome compared to subjects without bowel dysfunction. Gut 1992;33:825–830.
- 38. Naliboff BD, Mayer M, Fass R, FitzGerald LZ, Chang L, Bolus R, Mayer EA. The effect of life stress on symptoms of heartburn. Psychosom Med 2004;66:426–434.
- Walker LS, Garber J, Smith CA, Van Slyke DA, Claar RL. The relation of daily stressors to somatic and emotional symptoms in children with and without recurrent abdominal pain. J Consult Clin Psychol 2001;69:85–91.
- Bennett EJ, Tennant CC, Piesse C, Badcock CA, Kellow JE. Level of chronic life stress predicts clinical outcome in irritable bowel syndrome. Gut 1998;43:256–261.
- 41. Drossman DA. Do psychosocial factors define symptom severity and patient status? Am J Med 1999;107:41S–50S.
- Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. Gastroenterology 2002;123:2108–2131.
- Locke GR III, Weaver AL, Melton LJ III, Talley NJ. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. Am J Gastroenterol 2004;99:350–357.
- Gillespie NA, Zhu G, Heath AC, Hickie IB, Martin NG. The genetic aetiology of somatic distress. Psychol Med 2000;30:1051– 1061.
- North CS, Downs D, Clouse RE, Alrakawi A, Dokucu ME, Cox J, Spitznagel EL, Alpers DH. The presentation of irritable bowel syndrome in the context of somatization disorder. Clin Gastroenterol Hepatol 2004;2:787–795.
- 46. Walker LS, Heflinger CA. Quality of life predictors in paediatric abdominal pain patients: findings at initial assessment and five year follow-up. In: Drotar DD, ed. Measuring health-related quality of life in children and adolescents: implications for research and practice. Mahwah, NJ: Lawrence Erlbaum, 1998:237–252.

- 47. Guthrie E, Barlow J, Fernandes L, Ratcliffe J, Read N, Thompson DG, Tomenson B, Creed F, North of England IBS Research Group. Changes in tolerance to rectal distension correlate with changes in psychological state in patients with severe irritable bowel syndrome. Psychosom Med 2004;66:578–582.
- 48. Creed F, Ratcliffe J, Fernandez L, Tomenson B, Palmer S, Rigby C, Guthrie E, Read N, Thompson D. Health-related quality of life and health care costs in severe, refractory irritable bowel syndrome. Ann Intern Med 2001;134:860–868.
- 49. Mulak A, Bonaz B. Irritable bowel syndrome: a model of the brain-gut interactions. Med Sci Monit 2004;10:RA55–RA62.
- Mayer EA, Naliboff BD, Chang L, Coutinho SV. Stress and the gastrointestinal tract v. stress and irritable bowel syndrome.
 Am J Physiol Gastrointest Liver Physiol 2001;280:G519–G524.
- Mayer EA. The neurobiology of stress and gastrointestinal disease. Gut 2000;47:861–869.
- 52. Monnikes H, Tebbe JJ, Hildebrandt M, Arck P, Osmanoglou E, Rose M, Klapp B, Wiedenmann B, Heymann-Monnikes I. Role of stress in functional gastrointestinal disorders. Evidence for stress-induced alterations in gastrointestinal motility and sensitivity. Dig Dis 2001;19:201–211.
- Tache Y, Martinez V, Million M, Wang L. Stress and the gastrointestinal tract: III. Stress-related alterations of gut motor function: role of brain-corticotropin-releasing factor receptors. Am J Physiol Gastrointest Liver Physiol 2001;280:G173–G177.
- 54. Harvey RF, Read AE. Effect of cholecystokinin on colon motility and symptoms in patients with the irritable bowel syndrome. Lancet 1973;1:1–3.
- Simren M, Castedal M, Svedlund J, Abrahamsson H, Bjornsson E. Abnormal propagation pattern of duodenal pressure waves in the irritable bowel syndrome (IBD). Dig Dis Sci 2000;45:2151– 2161.
- Ford MJ, Camilleri M, Zinsmeister AR, Hanson RB. Psychosensory modulation of colonic sensation in the human transverse and sigmoid colon. Gastroenterology 1995;109:1772–1780.
- 57. Whitehead WE, Crowell MD, Davidoff AL, Palsson OS, Schuster MM. Pain from rectal distension in women with irritable bowel syndrome: relationship to sexual abuse. Dig Dis Sci 1997;42: 796–804.
- 58. Tougas G. The autonomic nervous system in functional bowel disorders. Gut 2000;47(Suppl 4):iv78–iv80.
- Heitkemper M, Jarrett M, Cain K, Shaver J, Bond E, Woods NF, Walker E. Increased urine catecholamines and cortisol in women with irritable bowel syndrome. Am J Gastroenterol 1996; 91:906–913.
- Jarrett M, Heitkemper M, Cain KC, Burr RL, Hertig V. Sleep disturbance influences gastrointestinal symptoms in women with irritable bowel syndrome. Dig Dis Sci 2000;45:952–959.
- 61. El-Serag HB, Olden K, Bjorkman D. Health-related quality of life among persons with irritable bowel syndrome: a systematic review. Aliment Pharmacol Ther 2002;16:1171–1185.
- 62. Akehurst RL, Brazier JE, Mathers N, O'Keefe C, Kaltenthaler E, Morgan A, Platts M, Walters SJ. Health-related quality of life and cost impact of irritable bowel syndrome in a UK primary care setting. Pharmacoeconomics 2002;20:455–462.
- Creed FH, Ratcliffe J, Fernandes L, Palmer S, Rigby C, Tomenson B, Guthrie E, Read N, Thompson DG. Outcome in severe irritable bowel syndrome with and without accompanying depressive, panic and neurasthenic disorders. Br J Psychiatry 2005;186:507–515.
- Spiegel BM, Gralnek IM, Bolus R, Chang L, Dulai GS, Mayer EA, Naliboff B. Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. Arch Intern Med 2004; 164:1773–1780.
- 65. Halder SL, Locle GR III, Talley NJ, Fett SL, Zinmaster AR, Melton LJ III. Impact of functional gastrointestinal disorder on health-

- related quality of life: a population-based case-control study. Aliment Pharmacol Ther 2004;19:233–242.
- Drossman DA, McKee DC, Sandler RS, Mitchell CM, Cramer EM, Lowman BC, Burger AL. Psychosocial factors in the irritable bowel syndrome. A multivariate study of patients and nonpatients with irritable bowel syndrome. Gastroenterology 1988; 95:701–708.
- 67. Talley NJ, Boyce PM, Jones M. Predictors of health care seeking for irritable bowel syndrome: a population based study. Gut 1997;41:394–398.
- Kettell J, Jones R, Lydeard S. Reasons for consultation in irritable bowel syndrome: symptoms and patient characteristics.
 Br J Gen Pract 1992;42:459–461.
- Camilleri M, Williams DE. Economic burden of irritable bowel syndrome reappraised with strategies to control expenditures. Pharmacoeconomics 2000;17:331–338.
- Le Pen C, Ruszniewski P, Gaudin AF, Amouretti M, Bommelaer G, Frexinos J, Poynard T, Maurel F, Priol G, Bertin C. The burden cost of French patients suffering from irritable bowel syndrome. Scand J Gastroenterol 2004;39:336–343.
- Levy RL, Von Korff M, Whitehead WE, Stang P, Saunders K, Jhingran P, Barghout V, Feld AD. Costs of care for irritable bowel syndrome patients in a health maintenance organization. Am J Gastroenterol 2001;96:3122–3129.
- Creed F, Fernandes L, Guthrie E, Palmer S, Ratcliffe J, Read N, Rigby C, Thompson D, Tomenson B. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. Gastroenterology 2003;124:303–317.
- Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002;52:69–77.
- Spitzer RL, Williams JB, Kroenke K, Linzer M, deGruy FV III, Hahn SR, Brody D, Johnson JG. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. JAMA 1994;272:1749–1756.
- 75. Keefe FJ, Brown GK, Wallston KA, Caldwell DS. Coping with rheumatoid arthritis pain: catastrophizing as a maladaptive strategy. Pain 1989;37:51–56.
- Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, Metzger LJ, Lasko NB, Orr SP, Pitman RK. A positron emission tomographic study of symptom provocation in PTSD. Ann N Y Acad Sci 1997;821:521–523.
- Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development of a new measure. Dig Dis Sci 1998;43:400–411.
- Lackner JM. Psychological treatments for irritable bowel syndrome: a systematic review and meta-analysis. J Consult Clin Psychol 2004;72:1100–1113.
- Toner BB, Stuckless N, Ali A, Downie FP, Emmott SD, Akman DE. The development of a cognitive scale for functional bowel disorders. Psychosom Med 1998;60:492–497.
- Payne A, Blanchard EB. A controlled comparison of cognitive therapy and self-help support groups in the treatment of irritable bowel syndrome. J Consult Clin Psychol 1995;63:779–786.
- 81. Drossman DA, Toner BB, Whitehead WE, Diamant NE, Dalton CB, Duncan S, Emmott S, Proffitt V, Akman D, Frusciante K, Le T, Meyer K, Bradshaw B, Mikula K, Morris CB, Blackman CJ, Hu Y, Jia H, Li JZ, Koch GG, Bangdiwala SI. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology 2003;125:19–31.
- 82. Weydert JA, Ball TM, Davis MF. Systematic review of treatments for recurrent abdominal pain. Pediatrics. 2003;111:e1-e11.
- 83. Blanchard EB, Greene B, Scharff L, Schwarz-McMorris SP. Relaxation training as a treatment for irritable bowel syndrome. Biofeedback Self Regul 1993;18:125–132.

- 84. Drossman DA, Creed FH, Olden KW, Svedlund J, Toner BB, Whitehead WE. Psychosocial aspects of the functional gastro-intestinal disorders. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. Rome II. The functional gastrointestinal disorders: diagnosis, pathophysiology and treatment; a multinational consensus. 2nd ed. McLean, VA: Degnon and Associates; 2000:157–245.
- Spanier JA, Howden CW, Jones MP. A systematic review of alternative therapies in the irritable bowel syndrome. Arch Intern Med 2003;163:265–274.
- 86. Heymann-Mönnikes I, Arnold R, Florin I, Herda C, Melfsen S, Mönnikes H. The combination of medical treatment plus multi-component behavioral therapy is superior to medical treatment alone in the therapy of irritable bowel syndrome. Am J Gastroenterol 2000;95:981–994.
- 87. Spanier JA, Howden CW, Jones MP. A systematic review of alternative therapies in the irritable bowel syndrome. Arch Intern Med 2003;163:265–274.
- 88. Talley NJ, Owen BK, Boyce P, Paterson K. Psychological treatments for irritable bowel syndrome: a critique of controlled treatment trials. Am J Gastroenterol 1996;91:277–286.
- 89. Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable bowel syndrome. Lancet 1984;2:1232–1233.
- Gonsalkorale WM, Miller V, Afzal A, Whorwell PJ. Long term benefits of hypnotherapy for irritable bowel syndrome. Gut 2003;52:1623–1629.
- 91. Calvert EL, Houghton LA, Cooper P, Morris J, Whorwell PJ. Long-term improvement in functional dyspepsia using hypnotherapy. Gastroenterology 2002;123:1778–1785.
- Harvey RF, Hinton RA, Gunary RM, Barry RE. Individual and group hypnotherapy in treatment of refractory irritable bowel syndrome. Lancet 1989;1:424–425.
- Jackson JL, O'Malley PG, Tomkins G, Balden E, Santoro J, Kroenke K. Treatment of functional gastrointestinal disorders with antidepressant medications: a meta-analysis. Am J Med 2000;108:65–72.
- 94. Brandt LJ, Bjorkman D, Fennerty MB, Locke GR, Olden K, Peterson W, Quigley E, Schoenfeld P, Schuster M, Talley N. Systematic review on the management of irritable bowel syndrome in North America. Am J Gastroenterol 2002;97:S7–S26.
- 95. Tabas G, Beaves M, Wang J, Friday P, Mardini H, Arnold G. Paroxetine to treat irritable bowel syndrome not responding to high-fiber diet: a double-blind, placebo-controlled trial. Am J Gastroenterol 2004;99:914–920.
- 96. Kuiken SD, Tytgat GN, Boeckxstaens GE. The selective serotonin reuptake inhibitor fluoxetine does not change rectal sensitivity and symptoms in patients with irritable bowel syndrome: a double blind, randomized, placebo-controlled study. Clin Gastroenterol Hepatol 2003;1:219–228.
- Chial HJ, Camilleri M, Burton D, Thomforde G, Olden KW, Stephens D. Selective effects of serotonergic psychoactive agents on gastrointestinal functions in health. Am J Physiol Gastrointest Liver Physiol 2003;284:G130–G137.
- Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, Goldstein DJ. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 2004;50: 2974–2984.
- 99. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? J Clin Psychiatry 1995;56:30–34.
- 100. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, Markowitz JC, Nemeroff CB, Russell JM, Thase ME, Trivedi MH, Zajecka J. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and

- their combination for the treatment of chronic depression. N Engl J Med 2000;342:1462–1470.
- Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. JAMA 2000;283:2529– 2536.
- 102. Perlis RH, Nierenberg AA, Alpert JE, Pava J, Matthews JD, Buchin J, Sickinger AH, Fava M. Effects of adding cognitive therapy to fluoxetine dose increase on risk of relapse and residual depressive symptoms in continuation treatment of major depressive disorder. J Clin Psychopharmacol 2002;22:474–480.
- 103. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J, Treatment for
- Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA 2004;292:807–820.
- 104. Gelenberg A. Depression is still underrecognized and undertreated. Arch Intern Med 1999;159:1657–1658.

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