Epidemiology and diagnostic criteria

FGIDs consist of a wide spectrum of syndromes, which cross over and, in some cases, overlap various anatomic areas of the luminal gut. Although irritable bowel syndrome (IBS) has traditionally been the most studied and written about, FGIDs constitute a number of unique disorders, including functional esophageal disorders (noncardiac chest pain, functional dysphagia, and globus sensation); functional dyspepsia (pain, discomfort, nausea, and other symptoms above the navel in persons who do not meet the diagnostic criteria for IBS); functional abdominal pain syndrome; functional abdominal bloating; functional diarrhea; functional disorders of the biliary tract, including Oddi sphincter; functional disorders of the anorectal area, such as pelvic floor dyssynergia; and proctalgia fugax. Functional disorders are somewhat unique in gastroenterologic practice because they are diagnosed using symptom-based criteria.

Building on the DSM model, international teams of physicians and other scientists expert in the area of FGIDs have been gathering since 1988 on a regular basis in Rome to develop symptom-based criteria for the various FGIDs. Similar to the DSM, as diagnostic criteria have been developed and field-tested, the Rome criteria have evolved over time (Table). The Rome working teams go beyond merely formulating diagnostic criteria; they also address important clinical and research issues. For instance, the Rome book includes working-team reports on pediatric FGIDs, design for treatment trials for FGIDs, and discussions of the psychosocial aspects of FGIDs. The fact that the psychosocial aspects of FGIDs receive significant recognition in the Rome process speaks to the importance of these factors in properly diagnosing and treating FGIDs.

Psychopharmacologic treatment

The earliest reported use of antidepressants for GI disease was the use of tricyclic antidepressants for the treatment of peptic ulcer disease. Tricyclics have subsequently been replaced by more effective therapy based on updated knowledge of pathophysiology. The effectiveness of tricyclic antidepressants can be influenced by their specific receptor activity. For instance, highly antihistaminic drugs, such as doxepin and imipramine, are helpful in promoting sleep. This could also influence their ability to produce analgesia. In the 1970s and 1980s the analgesic properties of antidepressants were discovered. Antidepressant agents have been successfully used for the management of a wide variety of neuropathic pain syndromes such as diabetic peripheral neuropathy, postherpetic neuralgia, migraine headache, cancer-related pain, and other painful conditions. A number of meta-analyses have supported the usefulness of antidepressants in these settings. Egbunike and Chaffee reviewed the literature on antidepressants and chronic pain and described a number of interesting findings. The first was that the analgesic effect of the drugs tended to be independent of their antidepressant effect. Second, they found that the doses of heterocyclic antidepressants used to achieve adequate analgesia seemed to be lower than those considered...
effective for the treatment of patients with mood disorders. Finally, they noticed that the onset of analgesia for neuropathic pain syndromes ranged from 1 day to 10 weeks, with unpredictable response time. This is considerably shorter than the time usually required to effectively treat patients with mood and anxiety disorders.

**GI Disorders**

The tricyclic antidepressants have also been found to play a role in treating the visceral pain associated with FGIDs. In 1987 Greenbaum and colleagues\(^5\) undertook a landmark study looking at the efficacy and mechanism of action of antidepressants in functional bowel disorders. In this study, 28 patients with IBS completed a double-blind crossover study using desipramine versus atropine versus placebo in random sequence. Atropine was used as an active because the 0.4-mg dose was able to simulate the antimuscarinic effect of desipramine. All patients underwent rectosigmoid manometry. In addition, all were administered the Hamilton depression rating scale (HAM-D) and the Brief Psychiatric Rating Scale (BPRS) to assess their psychiatric status both on entry and exit from the study. GI symptoms were also recorded.

Twenty-eight patients completed the entire protocol. Nine patients treated with desipramine complained of side effects that included anxiety, tremor, palpitations, sweating, xerostomia, and constipation. During the atropine phase of the protocol, 7 patients also had side effects, the most common being xerostomia, constipation, and palpitations. When GI symptoms were measured, there was a significant reduction in the number of stools per week in the desipramine group compared with the placebo group \(P < 0.05\).

Overall motility did not differ significantly between the 3 arms of the study, except in patients with diarrheapredominant IBS. In these patients, overall motility was decreased with desipramine compared with atropine \(P < 0.05\).

The investigators concluded that the positive effect of desipramine was independent of its antimuscarinic effect and because of the dosage used in this study, the lack of correlation with blood concentrations, and the short duration of the trial, the antidepressant effect of desipramine was not responsible for the improvement seen in the patients. Likewise, study data demonstrated a lack of correlation between patient improvement and any documentable changes in GI motility.

This study was the first to empirically designate the unique effect of antidepressants on functional bowel disorders independent of any depressant and anticholinergic effects. The lack of correlation between changes in psychiatric status and changes in GI motility also spoke to the unique property of desipramine to improve global well-being in patients with functional bowel disorders.

The literature has continued to move in a positive direction supporting the initial findings of Greenbaum and associates.\(^5\) Jackson and coauthors\(^6\) undertook a meta-analysis of published randomized controlled trials on the use of antidepressants for FGIDs. With the application of quality criteria, 11 randomized placebo-controlled trials of antidepressant therapy for FGIDs were identified in the literature. These included trials of amitriptyline, desipramine, doxepin, clomipramine, trimipramine, and mianserin (a serotonin reuptake blocker not available in the United States). The authors concluded that the odds of improvement in patients who received antidepressant therapy for functional bowel disorders was 4 to 2. They calculated that an average of 3.2 patients needed to be treated to improve 1 patient symptom. They concluded that the use of tricyclic antidepressants as functional antidepressants was effective. However, based on the literature reviewed, they could not conclude whether the effect was independent of the antidepressant effect of the drug.

In an attempt to further elucidate the role of antidepressants in functional bowel disorders, in 2002 Brandt and coworkers\(^7\) undertook a systematic review of all pharmacotherapy for IBS using evidence-based methodology. They concluded that tricyclic antidepressants are not more effective than placebo in relieving global IBS symptoms. The investigators used a subject global assessment as the methodologic gold standard to gauge effectiveness. The methodology was based on recommendations from the Rome working teams on FGIDs; however, most of the studies reviewed by Brandt and associates were performed before these recommendations existed, so the resulting negative view of tricyclic antidepressants may be unduly harsh.
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<th>Manning Criteria</th>
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<td><strong>Comparison of the diagnostic criteria for irritable bowel syndrome</strong></td>
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more frequent stools

Sensation of incomplete evacuation

Passage of mucus

Abdominal distention

Rome Criteria
Continuous or recurrent symptoms of:

- Abdominal pain, relieved with defecation or
- associated with change in frequency or
- consistency of stool;
and/or

Disturbed defecation (2 or more of):

- Altered stool frequency

- Altered stool form (hard
or loose/watery)

Altered stool passage

(straining or urgency, feeling of incomplete evacuation),

Passage of mucus
Usually with

Bloating or feeling of

abdominal distention
preceding 12 months of

abdominal discomfort or

pain that has 2 out of 3

features:

Relieved with defecation;

and/or
Onset associated with a change in frequency of stool; and/or

Onset associated with a
change in form

(apppearance) of stool.

Symptoms that cumulatively support the
diagnosis of irritable bowel syndrome

bowel syndrome
- Abnormal stool frequency (for research purposes)

"abnormal" may be defined as greater than 3 bowel
movements per

day and less than

3 bowel

movements per

week;

- Abnormal stool
form (lumpy/hard or loose/watery stool);

- Abnormal stool passage (straining, urgency, or
At least 12 weeks or more, which need not be consecutive. In the absence of symptoms, patients may have a feeling of incomplete evacuation.

Studies using serotonin reuptake inhibitors

In the last few years, an increasing number of studies on the effect of selective serotonin reuptake inhibitors (SSRIs) on FGIDs have been published. Using a double-blind randomized design, Kuiken and coauthors studied 40 patients with IBS who had no evidence of major depressive disorder. All patients underwent rectal sensitivity testing using balloon distention before and after a 6-week course of treatment with either fluoxetine 20 mg/d or placebo. In addition, the investigators recorded abdominal pain scores, individual GI symptoms, subject’s global self-assessment, and psychological symptoms using the Symptom Check List (SCL)-90-R on entry and exit from the study. They found that at study entry, IBS patients were more likely to show hypersensitivity to rectal distention. They noted that fluoxetine did not significantly alter the threshold for discomfort/pain relative to placebo either in hypersensitive patients or in patients who did not show hypersensitivity to balloon distention on entry. They also found no significant improvement in abdominal pain scores between the fluoxetine and placebo groups after 12 weeks of treatment. In the patients who were hypersensitive to balloon distention, fluoxetine significantly reduced the number of patients reporting significant abdominal pain ($P = .04$). Other GI symptoms, such as bloating, flatulence, urgency, incomplete evacuation, and global symptom relief were not significantly altered by fluoxetine compared with placebo. There was also no significant difference in psychological distress scores as measured by the SCL-90-R in the fluoxetine versus the placebo group. They concluded that fluoxetine did not reduce overall symptoms in patients with IBS.

Tabas and associates studied patients with IBS who were assessed regarding fiber intake. Group 1 consisted of 98 patients who were consuming less than 25 g/d of fiber. Group 2 consisted of 12 patients who were consuming a high-fiber diet (greater than 25 g/d). All patients were evaluated using the IBS Quality-Of-Life questionnaire and the Beck Depression Inventory. Bowel symptoms were recorded on study entry and exit. Group 1 was randomized to a high-fiber diet and group 2 was randomized to a double-blind placebo-controlled trial of paroxetine versus placebo. At the end of 12 weeks, patients in group 1 either self-reported improvement ($n = 25$) or failed to improve ($n = 69$) and were then allocated to paroxetine. The subjects, therefore, consisted of those that did not improve on fiber, as well as those who did improve on fiber. This was done to specifically study the impact of paroxetine on both populations who received fiber supplementation. This created a total
study sample of 81 patients for the paroxetine portion of the trial. Of this group, 30 were randomized to paroxetine 20 mg/d and 36 received placebo.

In group 1, overall well-being improved in 26% of patients and all pain and bloating decreased in 22% and 26%, respectively, with the use of a highfiber diet alone. In group 2, overall well-being improved more with paroxetine than placebo ($P = .01$) but abdominal pain, bloating, and social functioning did not. Paroxetine significantly reduced food avoidance ($P = .03$). Work functioning was marginally better in the paroxetine group ($P = .08$). Interestingly, before unblinding, more paroxetine patients than placebo patients wanted to continue with their study medication (84% vs 37%; $P = .01$). This study is interesting for a number of reasons. It demonstrated the clinical utility of using an SSRI for the treatment of IBS, and it showed that even in patients who had improved with higher fiber consumption, an antidepressant offered further advantage.

**More recent studies**

Building on the past, a number of new studies with SSRIs and tricyclic antidepressants have been conducted using contemporary methodology for the design of functional bowel treatment trials. Employing the more rigorous methodology derived from the recommendations of the Rome working teams has improved the quality of the results.

In a recent study, Creed and colleagues\(^{10}\) evaluated the cost effectiveness of psychotherapy versus paroxetine for the treatment of IBS. Patients in the National Health Service of the United Kingdom who were felt to have severe refractory IBS ($n = 257$) were randomized to either ongoing standard medical treatment, paroxetine 20 mg/d, or 8 hours of interpersonal psychodynamic psychotherapy.

In this study, all patients in the standard medical treatment group completed the trial, while 31% of the psychotherapy group and 49% of the paroxetine group dropped out. Neither psychotherapy nor paroxetine were superior to standard medical treatment in reducing pain but both were significantly better in improving the physical aspects of health-related quality of life. There was no significant difference in the psychological component of health-related quality of life in either of the 3 treatment arms. None of the subjects showed any significant difference when compared to their pretreatment state. At the 1-year follow-up, the psychotherapy group had a significant reduction in overall health care costs compared with standard medical treatment, but the paroxetine group did not. These data suggest that for patients with severe IBS, both psychotherapy and paroxetine improve health-related quality of life. However, antidepressant treatment seems to be not as effective as psychotherapy for overall improvement in IBS symptoms and ability to reduce health care costs compared with standard medical treatment.

Drossman and associates\(^{11}\) conducted a recent landmark study on the use of antidepressant therapy for functional bowel disorders. They compared 431 patients randomized to 2 experimental arms. The first received either cognitive-behavioral therapy or an educational module. The second received desipramine 50 to 150 mg/d or placebo. In an intent-to-treat (ITT) analysis, behavior therapy was significantly better than the educational intervention, with responder rates of 70% versus 37%, respectively. Here the number needed to treat (NNT) was 3.1 for cognitive behavioral therapy. Desipramine was not superior to placebo in an ITT analysis. However, in a per-protocol analysis, analyzing individuals who had completed 12 weeks of desipramine treatment and not analyzing dropouts, desipramine was superior to placebo, with responder rates of 73% versus 49%, respectively (NNT = 5.2). Similar to the results found by Creed and associates,\(^{10}\) psychotherapy was superior to antidepressant therapy, which, was superior to placebo treatment.

These 2 studies are helpful for a number of reasons. The first is that they demonstrate a role for both SSRIs and tricyclic antidepressants in the treatment of functional bowel disorders. In addition, they demonstrate that the major issue confronting the use of antidepressants in functional bowel disorders is not one of effectiveness but an issue of side effects and patient tolerance. The high dropout rates in the antidepressant arms in the studies by Creed and associates\(^{10}\) and Drossman and coworkers\(^{11}\) (49% and 28%, respectively) demonstrate the need for the clinician to be alert to side effects reported by patients and to deal with them aggressively, either by adjusting the dose of the medication or by changing to another antidepressant. Caution is suggested in using tricyclics in patients who have IBS with constipation because they may exacerbate the patient's constipation symptoms.

**Role of the psychiatrist**

Psychiatrists should be comfortable and competent as primary clinicians for patients being treated for FGIDs with antidepressants, as well as acting as consultants to nonpsychiatric colleagues. Primary care physicians and gastroenterologists are not as skilled at understanding the pharmacology of various antidepressant agents. Anticholinergic, antihistaminic, and noradrenergic effects of the various antidepressants can be prescribed advantageously to individual patients. The
psychiatrist clearly is in a unique role to provide this type of guidance. Likewise, the adverse events associated with various antidepressant agents--such as sexual dysfunction associated with SSRIs, as well as rare but dangerous side effects such as serotonin syndrome--make it clear that the involvement of a psychiatrist, who would be familiar with these effects, would be beneficial. Finally, the psychiatrist has the ability to diagnose comorbid psychiatric disorders in the patient who presents with FGIDs. The high prevalence of anxiety and mood disorders in patients with FGIDs make the psychiatrist a vital contributor to patient care. Collaborative care, where the psychiatrist and the nonpsychiatric physician care for patients with FGIDs has been demonstrated to be quite effective. For psychiatrists to be effective participants in the care of patients with FGIDs, they need to understand the basic nature of these disorders and their attendant comorbidities, as well as the role of psychopharmacologic and behavioral treatment.

In addition to psychopharmacologic approaches, psychotherapy has also been shown to be individually effective when treating patients with functional bowel disorders. A number of studies have shown a significant improvement in functional bowel symptoms in patients exposed to a variety of psychotherapeutic approaches, including cognitive behavioral therapy and interpersonal therapy, as well as hypnosis directed toward bowel symptoms. It is important for physicians to recognize that behavioral tools at their disposal can also be highly effective in treating these patients.

Conclusions
The usefulness of antidepressants for the treatment of functional bowel disorders has been reasonably well established. The recent meta-analyses by Jackson and associates and others, show that antidepressants are safe and effective for the management of functional bowel disorders. In addition to IBS, investigators over the last 15 years have shown the benefit of antidepressants therapy for noncardiac chest pain, functional vomiting, and functional dyspepsia. The more contemporary studies using high quality methodology further demonstrate the usefulness of both SSRIs and tricyclic antidepressants in this setting. Clearly, trials of newer antidepressants such as duloxetine and mirtazapine should be considered for patients with FGIDs. A trial of escitalopram is under way for the treatment of IBS. Side-effect profiles in patients with FGIDs also need to be more intensely studied to help optimize patient-drug matching. The use of pharmacogenomics and better definitions of functional bowel disorders will clearly help in doing this.

Dr Olden is a professor of medicine and psychiatry at the University of South Alabama in Mobile. He has indicated that he is a consultant for Novartis, Sucampo Pharmaceuticals, Takeda Pharmaceuticals, and Axcan Pharma Inc; he is also a recipient of grant support from Novartis.

References:

cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome.


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