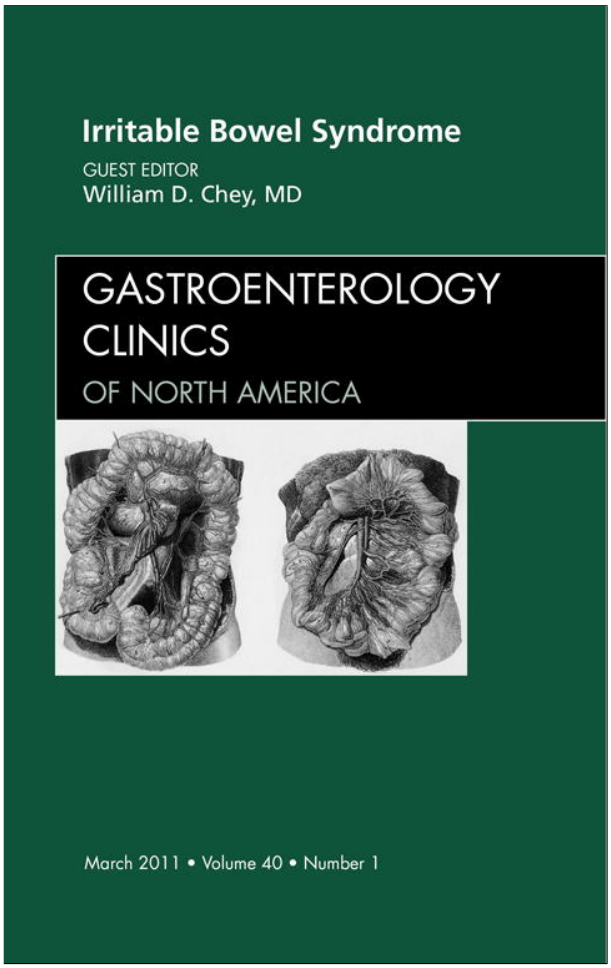

Centrally Acting Therapies for Irritable Bowel Syndrome

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KEYWORDS

• Irritable bowel syndrome • Treatment • Psychotropic agents
• Antidepressants • Behavioral treatments

A more recent expansion in our understanding of irritable bowel syndrome (IBS) is leading to important therapeutic gains. The traditional concept of abnormal motility has been insufficient to explain the symptoms and pathogenesis of IBS and other functional GI disorders (FGIDs). We now recognize that visceral hypersensitivity (enhanced perception of peripheral signals), infection/inflammation, and psychological factors that alter brain-gut axis function are all operative in understanding these disorders.[1] Modalities like brain imaging and brain-gut neurotransmitter research demonstrate a dysregulated brain-gut axis at peripheral, spinal, or supraspinal levels, all of which together contribute toward IBS and other FGID symptoms.[2,3] For example, neurotransmitters like serotonin (5 HT), norepinephrine (NE), corticotrophin-releasing factor (CRF), and opioids, among others, modify both motility and sensation in the gut. This has made centrally acting treatments (psychotropic agents and behavioral treatments) a particularly attractive treatment strategy because of their modulation of 5-HT and NE pathways causing overarching effects on the brain-gut axis in addition to their use for managing associated psychological disturbances that are commonly associated with these disorders.[4]

The use of psychotropic agents for FGIDs has grown significantly in the past 2 decades.[5] Nowadays, at least every 1 in 8 patients with IBS is offered an antidepressant.[6] A recent pharmacy database study from the United Kingdom has shown that patients prescribed ongoing therapy for presumed IBS are 2 to 4 times more likely to be prescribed central nervous system (CNS)-acting drugs than

The authors have no disclosures.

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Gastroenterol Clin N Am 40 (2011) 183–206
doi:10.1016/j.gtc.2010.12.003 gastro.theclinics.com
0889-8553/11/$ – see front matter

controls.[7] These included antidepressants, anxiolytics, antipsychotics, and hypnosedatives. In a study from Sweden, after anti-acids, antidepressants were the most commonly used drug category reported by IBS patients.[8] In a recent survey of around 2000 IBS patients, about 31% reported antidepressant use.[9] However, it still remains a challenging strategy because of insufficient understanding and the complex nature of these disorders, lack of well-designed drug studies, and variability among the treatment efficacy end points.[10]

This article describes the rationale, mechanisms, efficacy, side-effects, practical aspects involving use of psychotropics, and behavioral treatments in IBS and other FGIDs with focus on some of the more recent work in this field.

BIOPSYCHOSOCIAL CONSTRUCT OF IRRITABLE BOWEL SYNDROME AND ROLE OF PSYCHOLOGICAL FACTORS

In the biomedical model of medicine, IBS is often considered at the "functional" end of the "functional-organic" spectrum where a disorder is characterized by absence of detectable structural abnormalities using traditional diagnostic techniques, such as endoscopy or imaging. In the past 2 decades, there has been a surge in the research in the area of motility, brain imaging, and neurotransmitters, which has helped define the "brain-gut axis." As a result, pathophysiological understanding of IBS has increased, leading to organification of a "functional" disorder.[11–13] In fact, IBS can be best conceptualized with a biopsychosocial construct where an influence of central nervous system at spinal and supraspinal levels results in sensory and motor dysfunction of the GI tract. The trigger can be peripheral (eg, GI infection, abdominal surgery) or central (eg, history of abuse) but psychosocial factors often play an important role in perpetuation and clinical manifestation of this disorder through centrally mediated pathways. The influence of these factors becomes increasingly significant with increasing severity of these disorders.

Psychosocial factors can play a vital role at any and all stages in the natural history of IBS, being responsible for predisposition, precipitation, and perpetuation of symptoms and illness behavior. In one series, up to three-fourths of patients with FGID seeking care at a tertiary care referral center meet diagnostic criteria for a psychiatric disorder, most commonly anxiety and depression,[14] although in general the prevalence is much lower for patients seen in primary care or even general gastroenterology practice.[15] A history of major stressful life events, such as sexual abuse, separation, and personal losses are common in IBS, particularly for patients with more severe symptoms who perpetuate the severity via maladaptive illness behavior (catastrophizing).[16,17] Abuse, life stress, and poor or maladaptive coping can directly influence symptom severity, health-related quality of life (HRQOL), and response to treatment.[18] Feelings of distress in response to the GI condition can have adverse effects on psychological state or health status independent of presence of a preexisting psychiatric diagnosis. Furthermore, a negative workup, incomplete understanding, and an unsatisfactory explanation from the physician lead to constant worry, fear, and anxiety and often perpetuates the symptom severity.[19] Postinfectious (PI)-IBS provides an ideal example of psychological factors on IBS disease process.[20] Psychosocial distress at the time of infection has been shown to be an independent predictor of later development of PI-IBS. Stress has been proposed to act by overarching effects on inflammation and the brain-gut axis in PI-IBS.

In addition, a subgroup of patients with IBS, particularly with more severe and refractory symptoms, report many non-GI symptoms, and some have hypothesized the existence of broader neurophysiological processes (eg, so called "somatization")

in up to 15% to 45% of patients with IBS.[21] In effect, these patients have central dysregulation of pain regulatory pathways[22] and often have comorbid problems such as fibromyalgia, chronic fatigue, or chronic generalized pain. This understanding has important implications on using centrally acting treatments, alone or in combination, to target this broader polysymptomatic process with FGIDs and even predicting response to these agents. These individuals may set lower thresholds for symptom reporting and often turn out to be "nonresponders" to a variety of different, especially peripherally based, pharmacologic interventions.[23]

RATIONALE FOR THE USE OF PSYCHOTROPIC AGENTS AND BEHAVIORAL THERAPIES

Most widely used psychotropic agents in IBS and other FGIDs are antidepressants, especially tricyclic antidepressants (TCAs). The rationale for the use of these agents in IBS is highlighted in **Box 1**. In spite of significant heterogeneity in study designs and treatment end points, several reviews and meta-analyses have shown both pain reduction and global improvement as potential benefits of antidepressants in IBS and other FGIDs.[24,25] A recent American College of Gastroenterology–funded meta-analysis showed significantly decreased relative risk of persistent IBS symptoms with antidepressant treatment.[24] Others have estimated an overall improvement in IBS with an odds ratio of 2.6 to 4.2.[26] On average, 3 to 4 patients needed to be treated with an antidepressant to improve 1 patient's symptom.[24,26] Up to 80% of patients with IBS appear to have moderate to greater physician-rated benefits in an open-label clinical practice, and adherence to antidepressants is higher than for other treatments.[6,27] The peripheral effects of these agents on the gut may be of secondary importance considering that most patients treated with antidepressants have failed treatment with conventional gut-acting agents. In addition, studies on therapeutic effects of antidepressants on visceral hypersensitivity are mixed.[28,29] Also, treatment satisfaction with TCAs[30] or selective serotonin reuptake inhibitors (SSRIs)[31,32] has not been consistently correlated with reduction in the pain ratings. Overall, the benefit with these agents, especially SSRIs seems to correlate more with improvement in global measures of well-being rather than improvements in pain ratings. This improvement in global distress is still therapeutic, as morbidity associated with FGIDs is linked to

Box 1
Potential benefits for use of psychopharmacological agents in FGIDs

Central effects:

1. Alters central pain perception: analgesia or antihyperalgesia.
2. Therapeutic effects on mood: to manage general anxiety, hypervigilance, symptom-related anxiety, agoraphobia, and increased stress responsiveness.
3. Treatment of associated psychiatric disorders: depression, posttraumatic stress disorder, somatization.
4. Treatment of associated sleep disturbances.

Peripheral effects:

1. Peripheral analgesic effects: alters visceral afferent signaling.
2. Effect in GI physiology (motility and secretion) via effects on cholinergic, noradrenergic, and serotonergic pathways.
3. Smooth muscle effects on viscera, eg, gastric fundic relaxation.

global distress in the form of social impairment, work absenteeism, and other functional limitations.

The concept of neuroplasticity with loss of cortical neurons in psychiatric trauma, and neurogenesis (ie, regrowth of neurons) with clinical treatment, also provides rationalization for the use of central treatments. Functional MRI studies have shown reduced neuron density in cortical brain regions involved in emotional and pain regulation in patients with pain disorder[33] and with IBS.[34] Notably, recent data suggest that antidepressant (and possibly psychological) treatments may restore lost neurons. Levels of brain-derived neurotrophic factor, a precursor of neurogenesis, increase with antidepressant treatment and correlate with longer periods of treatment and with the degree of recovery from depression.[35] Furthermore, the longer patients are treated with antidepressants, the lower is the frequency of relapse or recurrence of the depression.[36] These findings provide insight into neuronal growth regulation in key areas of the central pain matrix and provide new and important opportunities for research and patient care using antidepressants for treatment of IBS.[37]

PSYCHOTROPIC AGENTS

Four major classes of psychotropic agents of interest and investigation in IBS are tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antipsychotics. Among these, TCAs and SSRIs have been most widely studied. However, other agents, especially SNRIs, are gaining popularity for treatment for other chronic pain conditions such as fibromyalgia and are likely to be further explored in IBS and other FGIDs.

Tricyclic Antidepressants

The tricyclic antidepressants (TCAs) are the most rigorously studied class of psychotropic agents used in IBS. The results of some of the recent randomized controlled trials (RCTs) are summarized in **Table 1**. The reason for marginal intention-to-treat effects in our large study was because one-fourth of the patients dropped out from the treatment arm, primarily because of side effects. However, a per protocol post hoc analysis showed a 20% effect size margin.[30] Clouse and colleagues[27] reported managing 138 patients with IBS with antidepressants in whom TCAs were used 130 times, newer agents 39 times, and anxiolytics 47 times. Improvement occurred in 89% and complete remission in 61% of patients. For the most part, despite methodological problems in designing good studies with antidepressants, there is evidence of treatment benefit with TCAs, providing patients are able to stay on medication.

TCAs reduce pain sensitivity in chronic neuropathic animal models, more effectively than SSRIs.[44] In animal studies, they reduce the frequency of nerve impulses evoked by noxious distension in the colon.[44,45] The analgesic properties are also likely contributed by alpha-adrenergic, sodium channel blockade, and N-methyl D-aspartate (NMDA) antagonistlike action.[46] Their effect on visceral perception has been mixed.[47] A recent study showed that TCAs do not have significant effects on gastric motor function or satiation post nutrient challenge in healthy individuals.[48] In another recent proof on concept study, amitriptyline appeared to decrease stress-induced rectal hypersensitivity in patients with IBS, thus providing mechanistic insights of potential disease-modifying actions of TCAs.[49]

The lack of substantive data on peripheral analgesic properties of TCAs in humans suggests that the more pronounced effects are on central pain modulation. In functional MRI studies, the mid cingulate cortex (MCC) is activated during painful rectal

Table 1
Recent studies on use of TCAs in IBS

Citation	Drug	Sample	Study Design	Outcome
Drossman et al,[30] 2003	Desipramine	Women; moderate to severe IBS (n = 431)	12 weeks Multicenter, comparator-controlled RCT	Per-protocol analysis: desipramine superior to placebo; intention-to-treat analysis: not significant. With dosages up to 150 mg, there is no relationship between total dose or plasma level and the clinical response.[38]
Otaka et al,[39] 2005	Amitriptyline	Refractory Functional Dyspepsia (n = 14)	4 weeks Double-blind RCT	Amitriptyline showed 66.7% efficacy in famotidine-failed group and 75.0% efficacy in the mosapride-failed group.
Morgan et al,[40] 2005	Amitriptyline	Women with severe IBS (n = 19)	4 weeks RCT	During stress, amitriptyline reduced pain-related cerebral activations in the perigenual ACC and the left posterior parietal cortex.
Vahedi et al,[41] 2008	Amitriptyline	IBS-D (n = 50)	8 weeks Double-blind RCT	Lower incidence of loose stool and feeling of incomplete defecation. Increased report of "loss of all symptoms" compared with placebo (68% vs 28%).
Bahar et al,[42] 2008	Amitriptyline	Adolescent IBS (n = 33)	13 weeks Double-blind RCT	Improved overall quality of life. Reduction in IBS diarrhea. Improved abdominal pain.
Abdul-Baki et al,[43] 2009	Imipramine	IBS (n = 107)	12 weeks RCT	Higher global symptom relief. Improvements in SF-36 scales.

Abbreviations: ACC, anterior cingulate cortex; IBS, irritable bowel syndrome; RCT, randomized controlled trial; TCA, tricyclic antidepressant.

distensions in patients with IBS. This activation is associated with poor clinical status in severe IBS and there is reduced activation with clinical improvement.[50] Those with IBS and abuse report more pain, greater MCC activation, and reduced activity of anterior cingulate cortex (ACC), which is implicated in pain inhibition and arousal.[51] Furthermore, amitriptyline reduced brain activation during pain in the perigenual (limbic) ACC and parietal association cortex during stress.[40]

Side effects depend on the class of TCAs but for the most part include sedation, anticholinergic (constipation, tachycardia, urinary retention, and xerostomia), and CNS side effects (insomnia, agitation, nightmares). TCAs can slow both small bowel and colonic transit.[52] However, the side-effect profiles vary because of differences in the postsynaptic receptor affinities. In general, secondary amine TCAs (eg, desipramine, nortriptyline) are better tolerated than tertiary amine TCAs (eg, amitriptyline, imipramine) because of their lower antihistaminic and anticholinergic properties.[5]

Selective Serotonin Reuptake Inhibitors

The main action of selective serotonin reuptake inhibitors (SSRIs) is to selectively inhibit the re-uptake of 5HT and block the 5HT transporter protein at the level of presynaptic nerve endings, increasing synaptic concentration of 5HT. These agents have effects on animal somatic pain models, although weaker than the TCAs.[44] Activation of opioid descending spinal pathways is another proposed mechanism of action. Data on visceral pain perception with SSRIs is mixed and central nociceptive effects of SSRIs have not been studied. **Table 2** summarizes some of the recent RCTs on use of SSRIs in FGIDs.

SSRIs can be used to augment the overall benefit of TCAs through their effect on anxiety, or in sufficient dosages in treating psychiatric comorbidities. Although they are reported to show analgesic effect in neuropathic pain, back pain, and migraines, the studies do not show an independent effect of SSRIs on GI pain.[58]

In summary, SSRIs may help in treating FGIDs because (1) they improve global well-being and some GI-specific symptoms (independent of the effects on depression); (2) they have anxiolytic properties and can target social phobia, agoraphobia, and symptom-related anxiety; (3) they may augment the analgesic effects of other agents (TCAs); and (4) they treat psychiatric comorbidities. In contrast to the dose ranging needed with TCAs, SSRIs do not require much dose readjustment because of selective receptor affinity for 5HT. Thus, diarrhea may be a side effect, and SSRIs may benefit patients with constipation. Within the SSRI class, paroxetine has more muscarinic effect and may be useful for those with predominant diarrhea. Fluoxetine has a longer half-life and fewer withdrawal effects and may be selected if poor compliance is an issue. Side effects include agitation, hostility, and suicidality.

Serotonin-Norepinephrine Reuptake Inhibitors

The serotonin-norepinephrine reuptake inhibitors (SNRIs), including venlafaxine, duloxetine, and desvenlafaxine, may potentially be as effective as the TCAs, owing to their dual blockade of reuptake of NE and 5HT receptors. Currently these agents are gaining increased use for other somatic painful conditions such as fibromyalgia.

Duloxetine

This is the only SNRI agent that has been studied for the treatment of IBS. In a 12-week open-label study of 15 nondepressed patients with IBS, duloxetine (60 mg daily dosage) appeared to be effective for pain, severity of illness, quality of life, loose stool, work and family disability, and anxiety. Seven patients withdrew from the study reporting adverse effects, most notably constipation.[59] It lacks activity at muscarinic,

histamine, and adrenergic sites, thus avoids side effects seen with TCAs. Most common side effects are nausea, dry mouth, and constipation. It can also rarely cause nonspecific elevation of liver enzymes.

Venlafaxine

This agent inhibits both 5HT and NE reuptake and can increases stimulated pain threshold.[60] However, higher dosages are needed to achieve pain benefit. It is also a mild inhibitor of dopamine reuptake. It can improve postprandial accommodation of the proximal stomach and may be used for treating functional dyspepsia.[61] However, a recent multicenter RCT did not identify any benefit in functional dyspepsia.[62] It has also been shown to decrease the sensitivity of colon to rectal distension.[63] Nausea is a side effect to consider. Venlafaxine can be started at 37.5 mg or 75 mg and titrated up to achieve maximum effect.

Desvenlafaxine

Desvenlafaxine is related to venlafaxine in molecular structure and has recently been released for treatment of depression. Its benefit for painful GI conditions has not yet been studied.

Milnacipran

Milnacipran also belongs to the SNRI class and is currently used in the treatment of fibromyalgia. This agent can also potentially be used in pain-related chronic GI conditions such as IBS.

Atypical Antipsychotics

Atypical antipsychotics have gained wide acceptance for treatment of bipolar disorder and schizophrenia because of their efficacy and low toxicity. They can also be beneficial in lower dosages for patients with FGIDs because of their analgesic properties (alone or in synergism with antidepressants[64]) and their sedative and anxiolytic effects. They can enhance a more normal sleep architecture.[65] Recently, we have used a low-dose atypical antipsychotic agent (eg, quetiapine 25–100 mg) with dopaminergic actions for augmenting treatment in our patients with FGIDs. Preliminary data from our clinic show that about 50% of patients with severe IBS and functional abdominal pain syndrome, who previously failed antidepressants and who are prescribed quetiapine with an antidepressant, stay on it, and most of those who do stay on it achieve some benefit.[66] Olanzapine, another drug of this class, has shown promise for treating nausea and vomiting in patients with cancer.[67]

BEHAVIORAL THERAPIES

The forms of behavioral therapies studied in IBS include cognitive behavior therapy (CBT), relaxation training, psychodynamic interpersonal therapy (PIT), hypnotherapy, mindfulness meditation, and multicomponent psychotherapies. The rationale for their use is summarized in **Box 2**.

Cognitive Behavior Therapy

Cognitive behavior therapy (CBT) is based on social learning theory, which recognizes that behavior is shaped as a result of its social consequences. It focuses on ways to increase or decrease thoughts and behaviors. With treatment of the IBS, it typically consists of 3 components: cognitive change where patients learn to recognize the relationship between their beliefs and symptoms, addressing thoughts, behaviors, and responses that result from their experiences, and changing behavior by teaching

Table 2
Recent studies on the use of SSRIs in IBS

Citation	Drug	Sample	Study Design	Outcome
Creed et al,[31] 2003	Paroxetine	Severe IBS (n = 257)	3 months Multicenter Parallel RCT	Improved physical component of SF-36 (QOL) scale. Decreased health care costs at 1-year follow-up. Decreased severity and number of days in pain.
Kuiken et al,[28] 2003	Fluoxetine	IBS (n = 40)	6 weeks Double-blind placebo-controlled RCT	Improved abdominal pain score (53% vs 26%) showing trends toward significance. Patients on fluoxetine were more likely to continue with the drug (84% vs 37%). Significant reduction in abdominal pain in patients with gut hypersensitivity.
Tabas et al,[32] 2004	Paroxetine	IBS (n = 110)	12 weeks Double-blind placebo-controlled RCT	Improved overall well-being. Increased desire to continue medication. Less IBS-related anxiety. Decreased food avoidance. Benefit seen in nondepressed.
Vahedi et al,[53] 2005	Fluoxetine	IBS-C (n = 44)	12 weeks Double-blind RCT	Decreased abdominal discomfort and bloating. Increased frequency of bowel movements and decreased stool consistency. Insignificant reduction in the mean number of symptoms per patient.

Tack et al,[54] 2006	Citalopram	IBS patients (n = 23)	6 weeks Double-blind placebo-controlled RCT	Improved abdominal pain and bloating. Less impact of symptoms on daily life and improved overall well-being. Effects independent of psychologic and colonic sensory-motor function.
Talley et al,[55] 2008	Imipramine and Citalopram	IBS patients (n = 51)	12 week Multicenter double-blind parallel-group RCT	Imipramine improved bowel symptom severity rating for interference and distress. Imipramine improved depression and SF-36 (mental component) score. Neither imipramine nor citalopram significantly improved Rome III global IBS end point (adequate relief).
Masand et al,[56] 2009	Paroxetine (controlled release)	IBS patients (n = 72)	12 week Double-blind RCT	No significant differences in composite pain scores (primary outcomes). Higher proportion of responders in treatment group per clinical global improvement scale (secondary outcome).
Ladabaum et al,[57] 2010	Citalopram	Nondepressed IBS patients (n = 54)	4 weeks Double-blind RCT	Not superior to placebo in achieving global relief, specific symptom, or QOL improvement.

Abbreviations: IBS, irritable bowel syndrome; QOL, quality of life; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor.

Box 2
Targets for behavioral treatments in FGIDs

1. To establish a rational model of illness: reframe maladaptive beliefs
2. To reduce overresponsiveness to stress, eg, stress and autonomic reactivity
3. To reduce or modify maladaptive psychological responses: catastrophizing, symptom-specific anxiety, shame/guilt
4. To reduce or modify maladaptive behaviors, eg, agoraphobia, seeking diagnostic studies

relaxation and stress-management strategies. The specific content of the therapy is based on a biopsychosocial assessment of the patient's background and current difficulties. For example, if a history of sexual abuse interferes with adaptation to the disorder, factors related to the abuse will be discussed. Several studies have looked at CBT for IBS (**Table 3**), but with significant heterogeneity. Various ways to implement CBT (group, individual, therapist based, Internet based) have been assessed. In 2 recent separate analyses, early response (4 weeks) and maladaptive coping have been shown to be predictive of sustained response.[78,79] It has been shown that CBT has a direct effect on global IBS symptom improvement, independent of its effects on distress, and symptom improvements are not moderated by variables reflecting the mental well-being of patients with IBS.[80] Symptom benefit with CBT may be mediated through changes in neural activity of cortical-limbic regions that subserve hypervigilance and emotion regulation.[81]

Relaxation Training

Relaxation techniques are to train patients to counteract physiologic sequelae of stress or anxiety. Five recent studies have assessed efficacy of relaxation therapy in IBS (**Table 4**). Although there has been significant heterogeneity in the study designs, relaxation alone or in combination with CBT and other therapies can be beneficial for IBS symptoms.

Psychodynamic Interpersonal Therapy

Psychodynamic interpersonal therapy (PIT) focuses on the impact of GI symptoms on a person's feelings and relationships. Unlike CBT, the emphasis is on addressing the person's feelings and inner mood states as they relate to flare-ups of symptoms rather than modifying thoughts or cognitions. Bowel disorders have an impact on relationships and family life in a way that can become counterproductive and even damaging for the person with bowel problems and his or her family. PIT looks at the whole marital/relationship system or family system where appropriate, and it can help address and manage issues related to previous sexual/physical abuse. Problems or difficulties with emotions or relationships are brought alive in the sessions, and possible solutions tried and tested out with the therapist, before transference to real-life situations. At the end of the therapy, the patient is provided with a detailed personal letter outlining the key points of therapy, plans for the future, and ways to cope with bowel symptoms should they recur.[87] The key to success is the development of a trusting and supportive relationship with the treating therapist. Interpersonal psychotherapy has been used with success in the treatment of refractory IBS by Guthrie and colleagues,[88] where improvement in symptoms and lesser disability and health care use were reported.[89] Creed and colleagues,[31] when comparing usual medical treatment to paroxetine to PIT, found that paroxetine and PIT significantly

reduced pain scores and improved HRQOL compared with usual medical treatment. However, only the psychotherapy group had a reduction in health care cost in the 1-year follow-up period. A recent study by Hyphantis and colleagues[90] has suggested that improvement in interpersonal problems is associated with improved psychosocial distress and improved health status following psychotherapy in patients with IBS.

Hypnotherapy

The essence of hypnotherapy is to create a relaxing, calming environment that allows the patient to refocus away from uncomfortable symptoms and toward a more pleasant perception of his or her current state. It capitalizes on the use of heightened suggestibility, where the patient becomes receptive to viewing his or her symptoms in a more refocused and positive way. Hypnotherapy has been shown to be effective for the treatment of IBS[91] and a recent review concluded that hypnosis has a favorable impact on refractory IBS symptoms.[92] One approach directs the patient away from experiencing uncomfortable sensations such as pain toward more positive interpretations of the sensations such as a gentle "flowing" of their bowels. Its long-term efficacy in IBS[93] and functional dyspepsia[94] has been shown. Thus, hypnotherapy is becoming increasingly recognized as a viable treatment modality for IBS.[93,95] The mechanism is unclear, although there is some evidence that it reduces gut contractility and normalizes pain thresholds after balloon rectal distension,[96] although this has not been confirmed by others.[97] Some have demonstrated changes similar to that after CBT[98] with reduction in anxiety and somatization scores[97] without physiologic changes in the gut. The median response rate to hypnosis treatment is 87%, bowel symptoms can generally be expected to improve by about half, psychological symptoms and life functioning improve after treatment, and therapeutic gains are likely long lasting.[92]

Mindfulness Meditation

As compared with relaxation, which is a passive state of mind, mindfulness meditation is an active, yet relaxed state of consciousness. A recent, open, 10-week pilot study showed significant reduction in symptoms, which were sustained at follow-up.[99] Another recent study has demonstrated feasibility to undertake a rigorous RCT of mindfulness training for people with IBS, using a standardized protocol adapted for those experiencing IBS.[100] More investigations are expected exploring mindfulness meditation in IBS in the future.

Multicomponent Psychotherapies

Three studies have compared multicomponent psychological therapy to control therapy or physicians' "usual management."[101–103] IBS symptoms persisted in 55 (51.9%) of 106 of those assigned to multicomponent psychological therapy compared with 80 (76.2%) of 105 of those allocated to control therapy or physicians' "usual management." These results suggest a potential role for multicomponent psychotherapy in the treatment of IBS.

PRACTICAL STRATEGIES ON WHEN AND HOW TO USE CENTRALLY ACTING TREATMENTS

Fig. 1 conceptualizes a stepwise algorithm for treatment of IBS across the severity of symptoms. For most patients with mild to moderate symptoms, there are environmental- and gut-related factors (eg, dietary, infection, bowel injury, hormonal factors) that "turn up" afferent excitation system. For milder symptoms, lifestyle and dietary changes may be sufficient. For more moderate symptoms, medications that act on

Table 3
Recent studies on the use of CBT in IBS

Citation	Therapy	Sample	Study Design	Outcome
Greene et al,[68] 1994	CBT	IBS patients (n = 20)	8 weeks RCT	Significant symptom reduction (80% vs 10% of the monitoring group). Results sustained at 3-month follow-up.
Payne and Blanchard,[69] 1995	CBT	IBS patients (n = 34)	8 weeks Triple arm RCT	Significantly greater reductions in individual GI symptoms and composite GI symptom index change compared with wait list or support group. Results maintained at 3-month follow-up.
Vollmer et al,[70] 1998	CBT	IBS patients (n = 32)	8 weeks Triple-arm RCT	Significantly greater GI composite symptom score reduction as compared with monitoring. No differences in group and individual cognitive treatment groups.
Drossman et al,[30] 2003	CBT	Women; moderate to severe IBS (n = 431)	12 weeks Multicenter RCT	On intention-to-treat analysis, CBT significantly more effective than education alone. Number needed to treat was 3.
Tkachuk et al,[71] 2003	CBT (group therapy)	Refractory IBS (n = 28)	9 weeks	Significant improvement with CBT than weekly telephone contact on posttreatment global measures and daily diary pain scores at 3-month follow-up. Significant improvement in psychological distress and health-related quality of life.
Kennedy et al,[72] 2006	CBT (nurse delivered)	Moderate or severe IBS (resistant to the antispasmodic mebeverine) (n = 149)	6 weeks RCT	Benefit on symptom severity compared with mebeverine alone (persisting at 3 and 6 months after therapy but not later). Persistent (12-month) significant benefit on the work and social adjustment scale.

Blanchard et al,[73] 2007	CBT (group based)	At least moderately severe IBS (n = 202)	8 weeks RCT with active control	Both group CBT and psychoeducational support (active control) were superior to intensive symptom monitoring in long and short term but none was superior to another.
Sanders et al,[74] 2007	CBT (self-administered)	IBS (n = 28)	10 weeks Crossover RCT	Self-help CBT group significantly decreased composite GI symptom scores in comparison with the wait list, but not in QOL scales.
Lackner et al,[75] 2008	CBT (10-session, therapist-administered vs 4-session, patient-administered)	Moderate or severe IBS (n = 71)	10 weeks RCT	At week 12, both CBT versions were significantly superior to wait list in the percentage of participants reporting adequate relief and improvement of symptoms. CBT-treated patients reported significantly improved QOL and IBS symptom severity but not psychological distress relative to wait list.
Hunt et al,[76] 2009	Internet-based brief CBT	IBS (n = 54)		Treatment completers experienced statistically and clinically significant declines in IBS symptoms and improvements in QOL.
Moss-Morris et al,[77] 2010	CBT-based self-management program	IBS (n = 64)	8 weeks RCT	At 2-, 3-, and 6-month follow-up, significantly more reported symptom relief in the self-management group compared with usual treatment; 83% showed significant change in IBS severity scales compared with 49% in the control group at 8 months.

Abbreviations: CBT, cognitive behavior therapy; IBS, irritable bowel syndrome; QOL, quality of life; RCT, randomized controlled trial.

Table 4
Recent studies on the use of relaxation training or therapy in IBS

Citation	Therapy	Sample	Study Design	Outcome
Blanchard et al,[82] 1993	Progressive muscle relaxation	IBS patients (n = 16)	8 weeks RCT	Significant (≥50%) reduction in baselines symptom score compared with symptom monitoring.
Keefer et al,[83] 2001	Relaxation response meditation	IBS patients (n = 16)	6 weeks Controlled treatment study	Significant (≥50%) improvement in IBS composite primary reduction scores compared with symptom monitoring. Improved flatulence, belching, bloating, and diarrhea. Effects persisted at 3-month follow-up.
Boyce et al,[84] 2003	CBT and relaxation therapy	IBS patients (n = 105)	8 weeks Triple-arm RCT	Cognitive behavior and relaxation therapy not to be superior to standard care alone.
Van der Veek et al,[85] 2007	Relaxation training	IBS patients (n = 98)	3 months RCT	IBS symptom severity significantly reduced in relaxation training group compared with standard medical care at 3, 6, and 12 months, Improved QOL. Reduced frequency of doctor visits.
Lahmann et al,[86] 2010	Functional relaxation	IBS patients (n = 80)	5 weeks RCT	Impairment in impairment-severity score (IS). Effects remained stable at 3-month follow-up.

Abbreviations: CBT, cognitive behavior therapy; IBS, irritable bowel syndrome; QOL, quality of life; RCT, randomized controlled trial.

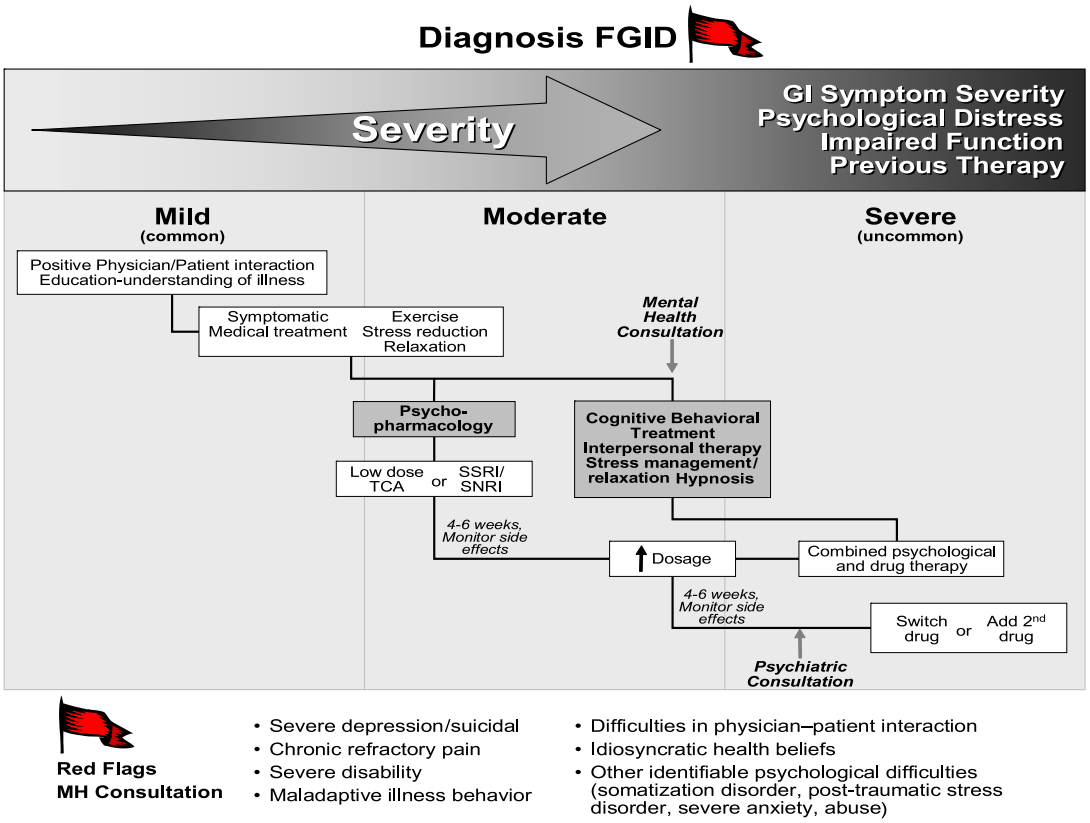

Fig. 1. Treatment algorithm for patients with FGIDs. "Red flags" are indications for considering early referral to a mental health professional. There is a range of intensity of psychological approaches to treatment and intensity of treatment is matched with the severity of FGID. (*From* Grover M, Drossman DA. Psychopharmacologic and behavioral treatments for functional gastrointestinal disorders. Gastrointest Endosc Clin N Am 2009;19(1):151–70, vii–viii; with permission.)

the gut (eg, anticholinergics, peripheral 5HT agents) can be considered. On the opposite end are the 20% of patients who suffer from severe IBS characterized by increased levels of pain, poorer HRQOL, higher levels of health care use, more psychosocial difficulties, and a higher frequency of psychiatric comorbidities. Because these patients are usually refractory to first- and second-line therapies,[18] they require behavioral (eg, CBT, PIT, hypnosis, stress-management/relaxation) or psychotropic agents or a combination of these two. **Fig. 1** also lists some of the red flags that warrant referral to and comanagement with a mental health person, such as a psychotherapist. Notably, many of these treatments can be used in addition to gut-acting agents.

Box 3 summarizes a general approach for prescribing psychotropic agents in IBS. An effective physician-patient relationship is crucial in the management of IBS with psychotropic agents. A positive physician-patient interaction has been related to reduced use of ambulatory health services by patients with IBS.[104] The choice of the agent depends on specific symptoms targeted, side-effect profile, and past experience with antidepressants. The therapeutic benefit may take 4 to 6 weeks to achieve; however, side effects may be reported within 1 to 2 weeks.[105] Starting at a low dose and a closer follow-up, especially in the first week, may increase compliance. It is important to "set the stage" by summarizing the long-term treatment plan and expectations before starting these agents. Global outcomes such as daily function, coping, QOL, and emotional well-being should be emphasized rather than specific GI symptoms. It is important to explain the use of these agents in the context of GI health

Box 3
Approach toward management of IBS with psychopharmacological agents

1. Choice of the agent:
   - Specific symptom treated
   - Side-effect profile
   - Cost of the drug
   - Previous experiences and preferences with psychotropic agents
   - Coexisting psychiatric conditions targeted
2. Initiating treatment:
   - Negotiate treatment plan
   - Consider previous drugs that worked
   - Start with a low dosage (eg, 25 mg/d of TCA)
3. Continuing treatment:
   - Escalate dose by 25% to 50% every 1 to 2 weeks to receive therapeutic effect with least possible dose.
   - Watch for side effects. Counsel that most of them disappear in 1 to 2 weeks. If not, try to continue same or lower dose from same class before switching to a different class.
   - Follow-up within first week and then within 2 to 3 weeks to ensure adherence.
   - Gauge treatment benefit with improvement in coping, daily function, QOL, and emotional state.
   - If a poor initial response:

     Re-address patient concerns

     Switch to a different class

     Combination therapies (eg, SSRI+TCA, pharmacologic and psychological treatment)

     If needed, psychiatry consultation for pharmacotherapy.
   - Increase dosages up to full psychiatric dosages if patient can tolerate before discontinuing.
   - If there is no benefit in 6 to 8 weeks on higher dosages, alternate strategies (eg, adding psychological treatment or referral) should be sought.
   - Depending on the response and side effects, another agent with different mechanism of action can be added to augment treatment efficacy and minimize side effects.
4. Stopping treatment: Continue treatment at minimum effective dosages for 6 to 12 months. Long-term therapy may be warranted for some patients. Gradual taper to prevent withdrawal symptoms.

From Grover M, Drossman DA. Psychopharmacologic and behavioral treatments for functional gastrointestinal disorders. Gastrointest Endosc Clin N Am 2009;19(1):151–70, vii–viii; with permission.

and share your willingness to continue to work on the patients as they undergo these treatments. Some of the issues with prescribing these agents are a suboptimal dose or failure to escalate dose if the response is poor, there is nonadherence, or if there is a delayed response.[5] Depending on the response and side effects, another agent with different mechanism of action can be added to augment treatment efficacy and minimize side effects. **Table 5** summarizes the class effect of various

Table 5
Class effects of psychotropic agents

	TCAs	SSRIs	SNRIs
Agents	Amitriptyline Imipramine Doxepin Desipramine Nortriptyline	Fluoxetine Sertraline Paroxetine Citalopram Escitalopram	Duloxetine Venlafaxine
Dose range	10–50 mg 10–200 mg (Desipramine)	10–40 mg 25–100 mg (Sertraline)	30–90 mg (Duloxetine) 75–225 (Venlafaxine)
Potential benefits			
Peripheral pain modulation	++	?	++
Central anti-nociception	+++	+	+++
Anxiolysis			
Motility			
Visceral pain	+	+++	+
Sleep	++	+	?
Psychiatric comorbidities	+++ ++ ++ (high doses)	? — +++	? ? +++
Adverse effects	Sedation Constipation Dry mouth/eyes Weight gain Hypotension Sexual dysfunction	Insomnia Diarrhea Night sweats Weight loss Agitation Sexual dysfunction	Nausea Agitation Dizziness Fatigue Liver dysfunction
Time to action	Few days–2 weeks (low doses) 2–6 weeks (high doses)	4–6 weeks	4–6 weeks
Efficacy	Good	Moderate	Not well studied
Dose adjustments	Required	Usually Not	Required

Abbreviations: SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonic reuptake inhibitor; TCA, Tricyclic antidepressant; +, weak effect; ++, moderate effect, +++, strong effect.

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psychotropic agents. Patients with high degrees of somatization tolerate medication side effects poorly, and the overall effectiveness of the medication regimen is impaired. Some investigators have suggested starting with even a lower dose (10 mg of TCA) and escalating slowly in these individuals.[5] Patients with a good response can be successfully maintained on antidepressant medications for months to years and tapering the dosage before withdrawing minimizes the likelihood of withdrawal syndromes.

Failure to maintain treatment occurs in nearly a quarter of outpatients given antidepressants for FGIDs.[106] Somatization features[21] and presence of depression[30] or anxiety most significantly interfered with treatment by predicting side effects, poor

treatment response, and premature antidepressant discontinuation. Patients less likely to have a good outcome with antidepressant therapy are those with constipation-predominant IBS, patients with objective indicators of gastrointestinal motility delay, patients with medical comorbidities exacerbated by antidepressant medications, and patients with somatization disorder.[5,30] Management algorithms should include specific strategies targeted at patients with these risk factors and poor treatment adherence.[107]

SUMMARY

As we expand our understanding of etiopathogenesis and clinical manifestations of IBS, the use of centrally acting psychopharmacological and behavioral treatments is expected to grow. Psychosocial factors play a key role in the natural history of IBS, especially at the moderate to severe end of the spectrum. Although better designed treatment trials are needed and in spite of significant heterogeneity among available studies, the evidence favors the use of both psychopharmacological and behavioral therapies. To enhance the therapeutic effect and improve adherence to treatment, an effective physician-patient relationship is essential and guidelines for this can be found elsewhere.[108] Future work in the management of IBS will lead to the evaluation of multicomponent treatments (eg, the common combination of psychotherapy and pharmacotherapy) and physician treatment behaviors.

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