



TREATMENTS OF IBS

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INTRODUCTION

In recent years, there has been increased interest by physicians and the pharmaceutical industry regarding newer treatments for IBS. Before discussing these new treatments, it is important to consider the overall management strategy in IBS. This is necessary because patients with IBS exhibit a wide spectrum of symptoms of varying frequencies and degrees of severity. There is no one ideal treatment for IBS, and the newer medications may work best for only a subset of patients having this disorder. Therefore, the clinician must first apply certain general management approaches and, following this, treatment choices will depend on the nature (i.e., predominant diarrhea, constipation, or bloating, etc.) and severity (mild, moderate, severe) of the symptoms. The symptoms of IBS may have any of several underlying causes. These can include: (a) abnormal motility (uncoordinated or excessive contractions that can lead to diarrhea, constipation, bloating) (b) visceral hypersensitivity (lower pain threshold of the nerves that can produce abdominal discomfort or pain) resulting from the abnormal motility, stress or infection (c) dysfunction of the brain's ability to regulate these visceral (intestinal) activities. Treatments will vary depending on which of these possibilities are occurring. In general, milder symptoms relate primarily to abnormal motility, often in response to food, activity or stress, and/or visceral hypersensitivity. They are commonly treated symptomatically with pharmacological agents directed at the gut. However, more severe symptoms often relate to dysfunction of the brain-gut regulatory system with associated psychosocial effects, and psychological or behavioral treatments and antidepressants are frequently helpful.

In addition to identifying treatments for the specific symptoms of IBS, therapeutic options also depend on the severity of the symptoms reported, particularly when abdominal pain is prominent.

The most frequently seen group of IBS patients has mild symptoms. They are seen in primary care practices, usually maintain normal daily activities, have little or no psychosocial difficulties (although they may have a flare of symptoms with stress), and do not over utilize health care services. Treatment involves education, reassurance and dietary/lifestyle changes, and prescription medications or psychological treatments are not necessarily needed.

A smaller proportion of patients have moderate symptoms that are usually intermittent, although at times are disabling. Symptoms may produce emotional distress and greater physiological gut reactivity (e.g., worse with eating, relieved by defecation). Treatments involve gut-acting

pharmacological agents (e.g., anticholinergics, antidiarrheals, newer GI treatments etc.) and, if more persistent, possibly low dose tricyclic antidepressants (TCA) and/or psychological treatments. Finally, a very small proportion of patients have severe symptoms. They are mostly seen in referral center, and frequently have severe, often constant pain, psychological distress (e.g., depression, anxiety) and other psychosocial difficulties (e.g., a history of sexual/physical abuse, or maladaptive coping styles), with high health care use rates. In these cases, antidepressant medication and possibly mental health or pain center referral are needed, along with an ongoing relationship with the primary care physician to provide psychosocial support through brief, regular visits.

Table 1

Spectrum of Clinical Features among Patients with IBS⁽⁴⁸⁾

Clinical Feature	Mild	Moderate	Severe
Estimated Prevalence	70%	25%	5%
Practice Type	Primary	Specialty	Referral
Correlation with Gut Physiology	+++	++	+
Symptoms Constant	0	+	+++
Psychosocial Difficulties	0	+	+++
Health Care Use	+	++	+++
Illness Behavior	0	+	+++
Psychiatric Diagnoses	0	+	+++

*0 = Generally Absent; + = Mild; ++ = Moderate; +++ = Marked

Gonsalkorale WM, Houghton LA, Whorwell PJ. Hypnotherapy in irritable bowel syndrome: a large-scale audit of a clinical service with examination of factors influencing responsiveness. *Am J Gastroenterol.* 2002 Apr;97(4):954-61.

Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable-bowel syndrome. *Lancet.* 1984 Dec 1;2(8414):1232-4.

GENERAL MANAGEMENT APPROACHES

Physician-Patient Relationship: An effective physician-patient relationship is the cornerstone of treatment. This relationship builds from a partnership. It involves an interactive process where the physician and patient engage in a dialogue, with the goal of enhancing the patient's knowledge of the illness and treatment options. Similarly, the physician needs to understand more about the patient's illness experience, health concerns and treatment preferences in order to make optimal treatment recommendations. The process for the clinician involves:

- (1) active listening to determine the patient's understanding of the illness and his or her concerns
- (2) thoroughly explaining the specifics of the medical disorder
- (3) identifying and responding to the patient's concerns and expectations
- (4) helping to set realistic and consistent limits
- (5) involving the patient in the treatment strategy
- (6) establishing a long-term relationship (with a gastroenterologist or primary care provider).

In turn, the patient has a responsibility to:

- (1) actively engage in this dialogue with the physician
- (2) take responsibility for asking questions and seeking clarifications as needed
- (3) share in the decision-making on treatment options presented.

This type of approach is associated with reduced health care visit and improved patient satisfaction and, when diagnostic and prognostic information is provided, there is also a reduction in symptoms.

Dietary Modifications: It is often assumed that specific foods create the symptoms of IBS and that specific diets are important in treatment. Surprisingly, specific diets are not as important as with other GI disorders (e.g., avoiding gluten in celiac sprue, or nuts and seeds in diverticular disease). Rather, symptoms of IBS may occur more as a generalized response to eating, and this is why some patients find the need to reduce the amount they eat or avoid eating in the daytime to reduce the pain and diarrhea that may occur 15-30 minutes later. In general, eating small meals more frequently places less stress on the GI tract and can help reduce post-prandial (i.e., after meal) symptoms. However there are some dietary substances that may aggravate IBS symptoms. This includes fatty foods (which delay stomach emptying but also stimulate the lower bowels leading to bloating and discomfort and diarrhea), beans and gas producing foods (which can produce bloating and diarrhea), as well as alcohol, caffeine and lactose in individuals with lactose intolerance. In some cases, even excess fiber can produce bloating or gaseousness, because the bacteria in the intestines can metabolize the cellulose to produce gas. In general, care should be taken to avoid an unnecessarily restrictive diet, and it is best to consult with a physician to identify the best dietary plan.

Symptom monitoring: It is frequently helpful to use a diary for 2-3 weeks to monitor the timing and severity of symptoms, the presence of possible aggravating factors, and the emotional impact of the symptoms. The diary may also identify dietary indiscretions or specific stressors not previously considered, and may also give the patient a greater level of participation in the planning of care. Finally, it provides a basis to review the findings and consider dietary, lifestyle or behavioral modifications. Maladaptive coping styles (e.g., profound pessimism or feelings of ineffectiveness) may be identified, which can lead to reappraisal and modification, or referral for psychological treatments like cognitivebehavioral therapy.

TRADITIONAL TREATMENTS FOR IBS

For pain and bloating, antispasmodics (e.g., anticholinergics) are smooth muscle relaxing medications that may be helpful, particularly when symptoms are worsened after meals.

Available studies primarily in Europe suggest that many antispasmodics can be effective, although the trials may have been inadequate by modern standards. Furthermore, most of these medications (e.g., cimetropium bromide, trimebutine, octyloinium bromide, mebeverine, pinaverium bromide, are not even available in the US, because they did not undergo sufficient testing to be approved by the Food and Drug Administration (FDA).

Within the US, the commonly prescribed dicyclomine (Bentylâ) and hyosyamine (Levsinâ) have shown varying successes in clinical trials and seem to work best with milder symptoms. Peppermint oil, commonly used as a medication in Europe and as over the counter medications and teas, have also had varying success, but at a minimum are not harmful. In clinical practice, anticholinergic agents are best used on an as-needed basis up to three times per day for acute attacks of pain or before meals. They are taken as needed and become less effective with chronic use. Side effects are similar to antihistamines -- dry mouth, blurring of vision and dizziness, particularly when arising. Low dose tricyclic antidepressants may be considered when the pain is more constant and/or disabling (see below).

For constipation, increased dietary fiber (25 gm/day) is recommended for simple constipation, although its effectiveness, based on several studies, in reducing pain in constipation-predominant IBS is mixed. If fiber is not helpful, osmotic laxatives such as milk of magnesia, sorbitol, or polyethylene glycol (Miralax, PEG solution) may be used.

For diarrhea, loperamide (Imodium) taken in 2-to-4 mg. doses up to four times a day or diphenoxylate (lomotil) which consists of 2.5 mg. diphenoxylate with .025 mg. atropine can be taken up to 3 or 4 times a day. It can reduce loose stools, urgency and fecal soiling {Read, 1982 7205 /id}. Cholestyramine (Questran) may be considered for a subgroup of patients with cholecystectomy or who may have bile acid malabsorption.

NEWER MEDICAL TREATMENTS

Newer treatment of the diarrhea and pain/discomfort of IBS are based on certain new drugs that block the 5-HT₃ receptors. 5-HT₃ receptors are found on the intestinal (enteric nerves) and on higher nerve locations, such as the vomiting center. Blocking these receptors reduces visceral (i.e., GI) pain, colonic transit, and small intestinal secretion {Kozlowski, 2000 7239 /id}. Alosetron hydrochloride (Lotronex), a selective 5-HT₃ antagonist, is effective in relieving pain and normalizing bowel frequency as well as reducing urgency in diarrhea-predominant, female patients with IBS(19). It is more effective than placebo in inducing adequate relief of pain and discomfort, and improvement in bowel frequency, consistency and urgency(20-22) in women with diarrhea-predominant IBS. The most common adverse event is constipation, affecting up to 28% in clinical trials, but with only 10% withdrawing from these studies for this symptom. A significant adverse event with unclear relationship to Alosetron is acute ischemic colitis, estimated to occur in 0.1 to 1%. The drug was withdrawn from the market in November 2000 because of these side effects, but after further evaluation was re-approved by FDA in Spring 2002, under restrictive guidelines that require the physician and patient to sign a release form and the patient to be monitored by the company for possible side effects. There is no clear evidence that this medication is effective in men, but this may be because only a small proportion of men, relative to women, have been evaluated with this medication. The starting dose is 1 mg./day, which can be increased to 1 mg. twice a day in a month, if there are no side effects.

Another 5-HT₃ antagonist, cilansetron (Calmactin), has demonstrated similar benefit to that of Alosetron in early (i.e., Phase II) clinical trials(23), and was effective in male patients (possibly due to a larger number of male patients studied). This drug has completed Phase III trials and is under review by the FDA. If approved, this medication will be released later this year.

For constipation-predominant IBS, the partial 5-HT₄ agonists Tegaserod (Zelnorm) can be considered. This medication resulted in global relief of IBS symptoms and constipation in females(24). The effective dose of Tegaserod is 12 mg per day in two divided doses (6 mg b.i.d.). Tegaserod appears safe with no serious adverse events for females with constipation predominant IBS. The drug is also being used clinically and trials are underway for other indications, including constipation, esophageal reflux, dyspepsia, gastroparesis, and pseudo-obstruction.

Other new approaches being explored in early (Phase II) studies include: newer type 3 antimuscarinic agents, NK1 and NK3 receptor antagonists, cholecystokinin antagonists, the alpha2 adrenergic

agonists, clonidine(25), a 5-HT₁ agonist, buspirone(26), and an SSRI, citalopram(27,28). The value of these experimental treatments needs to be determined based on their clinical efficacy, safety and cost.

COMPLEMENTARY AND ALTERNATIVE TREATMENTS

Over the past several years, the use of complementary and alternative treatments has gained popularity(29-32). But, their efficacy has not been established in controlled trials(33).

One exception is a placebo-controlled 16-week trial of Chinese herbal medicines that showed improved bowel symptom scores, global symptoms, and reduced IBS related interference with life relative to placebo(34). Because many herbs were used, it is not possible to make specific recommendations.

PSYCHOLOGICAL TREATMENTS

Psychological treatment is recommended when IBS symptoms are moderate to severe, there has been failure to respond to medical treatments, or when there is evidence that stress or psychological factors are contributing to the intensity of the GI symptom. It is important for the patient to understand the rationale for psychological treatments, since motivation to engage in the treatment is critical to success. There are four major types of psychological or behavioral treatments used in IBS:

(1) Cognitive-Behavioral Treatment (CBT), where patients use diaries and do exercises with the therapist to modify "maladaptive" thoughts as a means to increase or regain control over the symptoms (2) "Psychodynamic" or interpersonal psychotherapy, commonly used in England, where patients identify and address difficulties in interpersonal relationships that may lead to worsening GI symptoms (3) Hypnosis, commonly done in England and at UNC where hypnotic suggestion is used to relax the bowel and reduce symptoms (4) Stress Management/Relaxation Training, which can be a component of the other psychological treatments, where imaging and relaxation methods are used to reduce autonomic (blood pressure, pulse) activity and muscle tension.

Psychological treatment trials may have methodological limitations, because it is difficult to blind patients or the investigators as to the type of treatment, and it is difficult to find a credible placebo. In fact, not all studies have been controlled, or had sufficient numbers of patients to be certain of their efficacy(35,36). Recently, two well-designed studies involving large numbers of patients have provided new information. In one study(37), using psychodynamic psychotherapy compared to paroxetine, an antidepressant and usual medical care, it was found that both psychotherapy and paroxetine were superior to usual care in improving health related quality of life. Furthermore, one year later, the psychological treatment showed reductions in health care costs when compared to the other treatments. In a Phase III multicenter trial done by our group at UNC and the University of Toronto(12), we found that CBT was significantly better than an educational comparison group over 12 weeks of treatments. CBT was even effective for patients with more severe symptoms or with a history of abuse, but was not as effective if the patients had severe depression. This suggests for patients with severe depression, CBT may need to be done either for a longer period of time or in conjunction with an antidepressant. Also, it has been proposed that patients who exhibit maladaptive coping styles or cognitions (e.g., "catastrophizing") relative to their symptoms, or perceive an inability to decrease them, may be particularly responsive to CBT.

An early placebo-controlled trial of hypnosis showed this treatment to be more effective for reducing abdominal pain and altered bowel habits compared to placebo tablets plus discussion of the role of emotion in symptoms. These results have been replicated by other investigators and are well-maintained at 5 years follow-up. A recent study published in *Gastroenterology* shows that hypnosis is also effective for functional dyspepsia and that it results in decreased health care utilization and decreased use of prescribed medication.

Currently, there is no evidence that one psychological treatment is superior to another.

Favorable responses occur when patients have:

- (1) awareness that stress worsens their bowel symptoms
- (2) some psychological distress associated with the symptoms
- (3) abdominal pain or diarrhea and not just constipation
- (4) abdominal pain that comes and goes in response to eating, defecation, or stress rather than being constant pain
- (5) symptoms are of relatively short duration.

ANTIDEPRESSANTS

Medical physicians commonly prescribe antidepressants for painful medical disorders, including migraine headache, fibromyalgia and moderate-to-severe IBS. Two classes of antidepressants are most commonly used: tricyclic antidepressants/TCA's (e.g., amitriptyline/Elavil, imipramine/Tofranil, desipramine/Norpramin, nortriptyline/Pamelor, doxepin/Sinequan), and selective serotonin reuptake inhibitor/SSRIs (e.g., fluoxetine/Prozac, sertraline/Zoloft, paroxetine/Paxil, citalopram/Celexa, escitalopram/Lexapro). Less frequently, novel antidepressants not belonging to these two classes (such as, venlafaxine/Effexor, mirtazapine/Remeron) are prescribed. The rationale for antidepressant use relates to:

treatment of accompanying psychiatric diagnoses (e.g., major depression, anxiety disorders) associated with IBS (usually higher dosages are required) their effects directly on the GI system to modify visceral sensitivity, motility and secretion most importantly, reduction of central pain perception arising from the intestines. There is also some evidence that antidepressants may enhance the effects of psychological treatments. Several randomized controlled trials of TCA medications in IBS have been published, and were evaluated in a meta-analysis. Improvement in global GI symptoms against placebo was highly significant, and there was also improvement in pain score. Notably, the TCA dosages were lower than that used to treat major depression, suggesting that the benefit was unrelated to the TCA's antidepressant effects. But, these studies had limitations due to small sample sizes, short study lengths, variable study design quality, and other difficulties, making it difficult to draw firm conclusions.

More recently, our multi-center NIH-sponsored Phase III study found that the benefit of Desipramine, averaging 100 mg./day, was equivalent to our CBT treatment. However, it was not significantly greater than the placebo when all patients, including those who dropped out, were studied. The medication did produce side effects in about 30-40% of the patients taking the medications, and the 30% who dropped out of the study were due primarily to side effects. Thus, when the study was analyzed to evaluate those who completed the 12 weeks of treatment (*per protocol*)

analysis), there was significant benefit over placebo. These data indicate that the medication is helpful for treating IBS, but only if the patient is able to stay on a full course of treatment. Thus, the physician and patient need to work together to find the proper dosage that allows the patient to stay on the medication long enough for it to work.

Antidepressants are generally used for patients with frequent or moderate-to-severe symptoms of pain and diarrhea, and must be given on a continuous rather than an "as needed" basis. Low doses of TCA's (e.g., 10-50 mg/day) are recommended because they produce fewer side effects, while still showing benefit. However, full dosages might be considered if the benefit is incomplete and there are no or few side effects. The side effects are similar to anticholinergic drugs and include dry mouth, blurry vision, sexual difficulties, and dizziness. In general, the side effects tend to diminish after 1-2 weeks, while the benefit increases over several weeks.

There is only one published controlled study on the use of SSRI's or novel antidepressants for IBS. This study showed the effect of Paroxetine to be equivalent to psychodynamic psychotherapy in terms of improved quality of life. A few other studies suggest clinical benefit particularly if there is associated anxiety, panic or phobic symptoms (e.g., fear of eating because of pain or of leaving home because of inaccessibility of rest rooms, etc.). In contrast to the TCA's, because SSRI's increase intestinal motility, they can be used for patients with more diarrhea-type symptoms. They also have fewer side effects, which can include dizziness, anxiety at the beginning of treatment, and sleep and sexual disturbances.

CONCLUSION

There are a variety of treatments that can be used for treating patients with IBS. A general approach includes an effective physician-patient relationship, proper education, and dietary or lifestyle modifications necessary for any treatment plan. In addition, the options for treatment are based on the nature of the symptoms as well as their severity and frequency.

The newer receptor active medications have added considerably to the treatment options that can be considered and they focus primarily on the functioning of the GI system. In addition, psychological treatments and antidepressants are of particular value to patients with more moderate to severe symptoms. Both physician and patient can work together to define the clinical needs for treatment and then choose the best treatment strategy.