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ACG Releases Recommendations on the Management of Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is a common disorder characterized by abdominal discomfort and altered bowel function. It affects approximately 7 to 10 percent of persons in the world, and is more common in women, persons with lower socioeconomic status, and persons younger than 50 years. IBS is associated with impaired quality of life and reduced work productivity. Individual symptoms are of little help in diagnosis; therefore, IBS should be considered as a symptom complex. In persons who fulfill symptom-based criteria of IBS, the absence of selected alarm features (e.g., rectal bleeding; weight loss; iron deficiency anemia; nocturnal symptoms; family history of colorectal cancer, inflammatory bowel disease, or celiac disease) should confirm an IBS diagnosis.

The American College of Gastroenterology (ACG) performed a series of systematic reviews, and developed evidence-based recommendations for the management of IBS. The recommendations were classified as grade 1 (strong) or grade 2 (weak), and the strength of evidence was classified as level A (strong), level B (moderate), or level C (weak).

Recommendations

DIAGNOSTIC TESTING

Because the likelihood of diagnosing organic disease is low, routine testing with complete blood count, serum chemistries, thyroid function testing, stool ova and parasites examination, and abdominal imaging is not recommended in persons with typical IBS symptoms and no alarm features (grade 1C). Persons with diarrhea-predominant IBS (IBS-D) and mixed IBS (IBS-M) should have routine serologic screening for celiac disease (grade 1B). Lactose breath testing can be done when lactose maldigestion is a concern, despite changes in diet (grade 2B); however, there are insufficient data to recommend breath testing for small intestinal bacterial overgrowth (grade 2C). Routine colonic imaging is not recommended in persons younger than 50 years with typical IBS symptoms and no alarm features because of the low pretest probability of Crohn disease, ulcerative colitis, and colonic neoplasia (grade 1B). Colonoscopic imaging should be performed in persons who have IBS with alarm features to rule out organic disease. It should also be used in persons older than 50 years to screen for colorectal cancer (grade 1C). When performing a colonoscopy in persons with IBS-D, random biopsies should be considered to rule out microscopic colitis (grade 2C).

DIET

Evidence is lacking regarding whether food allergy testing or exclusion diets are effective in treating IBS; routine use outside of a clinical trial setting is not recommended (grade 2C). Research has shown that certain food allergies could cause IBS symptoms, and about 60 percent of persons with IBS believe that food makes their symptoms worse. A systematic review of eight trials involving 540 persons with IBS evaluated symptomatic response to exclusion diets. A positive response in 12.5 to 67 percent of T the participants was reported, but there were no control groups in the studies; therefore, it is unclear if these rates are actually just a placebo response.

DIETARY FIBER, BULKING AGENTS, AND LAXATIVES

Psyllium hydrophilic mucilloid (ispaghula husk) is moderately effective in treating IBS (grade 2C). One study found that calcium polycarbophil improved symptoms. Wheat bran or corn bran is no more effective than placebo for relieving global symptoms, and should not be routinely used (grade 2C). One study showed that polyethylene glycol (Miralax) improved stool frequency in adolescents with constipation-predominant IBS (IBS-C; grade 2C).

Most studies of dietary fiber and bulking agents had small sample sizes, short follow-up, and were conducted before the establishment of modern study design standards. Psyllium hydrophilic mucilloid improved global symptoms in four of six studies that were reviewed, with one meta-analysis showing that the number needed to treat (NNT) was 6 (95% confidence interval [CI], 3 to 50) and the relative risk of IBS symptoms not improving with psyllium was 0.78 (95% CI, 0.63 to 0.96). There

have been no placebo-controlled, randomized studies of laxatives in IBS.

ANTISPASMODICS

Although antispasmodics and some peppermint oil preparations have shown improvement in short-term IBS-associated abdominal pain or discomfort (grade 2C), evidence of long-term effectiveness is not available. Evidence of safety and tolerability is limited (grade 2C).

Evidence for effectiveness of antispasmodics and some peppermint oil preparations in the treatment of IBS exists; however, the availability of these drugs varies, and few recent data are available. Earlier trials are of poor quality; often do not differentiate between the effects on global versus individual symptoms; and vary in terms of inclusion criteria, dosing schedule, duration of treatment, and end points. The adverse effects of these drugs have not been adequately defined.

ANTIDIARRHEALS

Loperamide (Imodium) is effective for the treatment of diarrhea, reduction of stool frequency, and improvement of stool consistency, but it is no more effective than placebo for the relief of pain, bloating, or global IBS symptoms (grade 2C). There are no randomized controlled trials (RCTs) comparing loperamide with other antidiarrheals, and data on safety and tolerability are lacking.

Loperamide is the only antidiarrheal that has been adequately assessed in RCTs for IBS-D. Two trials evaluating effectiveness found that loperamide had no notable effects compared with placebo for treating symptoms of IBS-D, including bloating, abdominal discomfort, and global IBS symptoms. Loperamide appeared to improve stool frequency and consistency, but the overall impact on symptoms was not statistically significant. There were inadequate data on adverse effects.

ANTIBIOTICS

Compared with placebo, short-term nonabsorbable antibiotics are more effective for the treatment of bloating and global improvement of IBS (grade 1B). No evidence exists on the long-term safety and effectiveness of nonabsorbable antibiotics for the management of IBS symptoms.

Three RCTs of 545 persons with IBS found statistically significant improvements in global IBS symptoms, bloating, or both with rifaximin (Xifaxan) compared with placebo. Although not approved by the U.S. Food and Drug Administration (FDA) for the treatment of IBS, rifaximin is approved for the treatment of traveler's diarrhea. Neomycin, metronidazole (Flagyl), and clarithromycin (Biaxin) have also been studied for the treatment of IBS. In one RCT of 111 persons, those treated with neomycin were more likely to have a 50 percent improvement in global symptoms compared with those treated with placebo (43 versus 23 percent; $P < .05$). Another RCT showed that clarithromycin was not markedly better than placebo for IBS therapy. In a third trial, metronidazole provided notable improvement compared with placebo, but the data were not presented in an extractable form.

PROBIOTICS

Lactobacilli do not appear to be effective for the treatment of IBS; however, *Bifidobacteria* and some combinations of probiotics do appear to be effective (grade 2C). Available literature on the use of probiotics in IBS is difficult to interpret because the probiotics used in the studies varied in terms of species, strains, preparations, and doses. The studies also had limitations in their design and conflicting data. Dichotomous data suggest that all probiotics trend toward being effective for the treatment of IBS; however, continuous data show that *Lactobacilli* do not affect symptoms, that *Bifidobacteria* trend toward improving symptoms, and that probiotic combinations improve symptoms. Most of the studies were short-term; long-term data are lacking.

5-HT_3 RECEPTOR ANTAGONISTS

Compared with placebo, alosetron (Lotronex) is more effective for relieving global IBS symptoms in persons with IBS-D. Possible adverse effects include constipation T and colon ischemia, which occur more often in persons taking alosetron versus placebo (grade 2A). A balance of benefits and harms is most favorable in women with severe IBS-D who have not responded to conventional therapy (grade 1B). The quality of evidence for the effectiveness of 5-hydroxytryptamine (5-HT) receptor 3 antagonists in IBS is high.

Alosetron is the only 5-HT_3 receptor antagonist approved in the United States for the treatment of severe IBS-D in women. Alosetron has been shown to be superior to placebo for the treatment of abdominal pain, urgency, global symptoms, and diarrhea-related symptoms in eight well-designed clinical trials. Using the primary end point of “adequate relief ” of abdominal pain and discomfort or urgency, the relative risk of IBS continuing despite treatment was 0.79 (95% CI, 0.69 to 0.91), with an NNT of 8 (95% CI, 5 to 17). One placebo-controlled trial found that alosetron provided sustained relief of abdominal pain, discomfort, and urgency in persons with IBS-D for up to 48 weeks. Another randomized placebo-controlled trial demonstrated that alosetron was more effective than placebo for abdominal pain and discomfort in men with IBS-D.

A systematic review of seven studies in which patients were randomized to treatment with alosetron or placebo reported that those taking alosetron were more likely to report an adverse event compared with those taking placebo (relative risk of adverse event = 1.18; 95% CI, 1.08 to 1.29). The number needed to harm with alosetron was 10 (95% CI, 7 to 16). Dose-dependent constipation was the most common adverse event. Another systematic review of clinical and postmarketing surveillance data from persons with IBS and the general population also found a greater incidence of severe complicated constipation and ischemic colitis with alosetron therapy, but the incidence was low, with a rate of 1.1 cases of ischemic colitis and 0.66 cases of constipation per 1,000 patient-years of alosetron use.

The recommended starting dosage of alosetron is 0.5 mg twice daily. After four weeks, if symptoms are not sufficiently controlled, the dosage can be escalated to 1 mg twice daily. Patients should discontinue alosetron if they develop signs or symptoms of severe constipation or ischemic colitis, or if they do not respond to the 1-mg twice-daily dosage after four weeks.

5-HT_4 RECEPTOR AGONISTS

There are no 5-HT_4 receptor agonists currently available for use in North America. The FDA had approved tegaserod for use in women with IBS-C; however, it was removed from the market in 2007 because of a small number of cardiovascular events in treated patients. Tegaserod was evaluated in multiple well-designed RCTs that showed that a dosage of 6 mg daily was superior to placebo for global symptoms.

C-2 CHLORIDE CHANNEL ACTIVATORS

Compared with placebo, lubiprostone (Amitiza) in a dosage of 8 mcg twice daily is more effective for the relief of global IBS symptoms in women with IBS-C (grade 1B).

Lubiprostone is approved by the FDA for use in women with IBS-C. Two large, well-designed clinical trials showed that lubiprostone improved global symptoms in twice as many persons as placebo (18 versus 10 percent; $P < .001$). It also improved abdominal discomfort and pain, stool constancy, straining, and constipation severity. Adverse effects of lubiprostone include nausea, diarrhea, and abdominal pain. It should not be used in persons with mechanical bowel obstruction or preexisting diarrhea. Women of childbearing age should have a documented negative pregnancy test before starting therapy. Studies in men need to be done before lubiprostone can be recommended for this population.

ANTIDEPRESSANTS

Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) are more effective than placebo for relief of global IBS symptoms. They also appear to help with abdominal pain. There are limited data on the safety and tolerability of these agents in patients with IBS (grade 1B).

Nine trials have evaluated tricyclic antidepressants for the treatment of IBS. The antidepressants were superior to placebo (NNT = 4; 95% CI, 3 to 6), and there was no evidence that the dose has to be in the antidepressant range. Two trials showed notable benefit with antidepressants for abdominal pain. Five trials evaluated SSRIs and found a benefit over placebo (NNT = 3.5). Theoretically, SSRIs should have the most benefit in persons with IBS-C, and antidepressants should have the most benefit in patients with IBS-D because of their differential effects on intestinal transit time; however, data are lacking. The safety of antidepressants for IBS is poorly documented, but data do suggest that SSRIs are better tolerated than tricyclic antidepressants.

PSYCHOLOGICAL THERAPY

Psychological therapies (not including relaxation therapy) are more effective than usual care in the relief of global IBS symptoms (grade 1B).

Persons with IBS will typically also have anxiety, depression, or features of somatization. Because psychological disorders tend to overlap with IBS, studies have assessed psychological therapy, including T cognitive behavior therapy, dynamic psychotherapy, hypnotherapy, and relaxation therapy, in the treatment of IBS. Twenty RCTs found that, compared with usual care, there was some benefit with cognitive behavior therapy, dynamic psychotherapy, and hypnotherapy, but not with relaxation therapy. Cognitive behavior therapy is the most studied approach, with one large, high-quality trial showing benefit.

HERBAL THERAPY AND ACUPUNCTURE

Chinese herbal mixtures have shown some benefit in RCTs; however, these studies cannot be combined into a meaningful meta-analysis, and any benefit of Chinese herbal therapy in IBS can be confounded by the variability in components used and their purity. There also are concerns about toxicity. A systematic review of acupuncture trials was inconclusive because of heterogeneous outcomes. More studies on acupuncture and herbal therapy are needed before any recommendations can be made.

EMERGING THERAPY

A variety of therapeutic agents for IBS have been identified. Agents are also being developed for IBS with predominantly peripheral effects, and some with peripheral and central effects. Classes of drugs with peripheral effects include agents that affect chloride secretion, calcium channel blockers, opioid receptor ligands, and motilin receptor ligands. Classes of drugs with peripheral and central effects include novel serotonergic agents, corticotropin-releasing hormone antagonists, and autonomic modulators.

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