VOLUME 104 SUPPLEMENT 1 JANUARY 2009
www.amjgastro.com

SUPPLEMENT TO
AJG The American Journal of GASTROENTEROLOGY
OFFICIAL PUBLICATION OF THE AMERICAN COLLEGE OF GASTROENTEROLOGY

SUPPLEMENT

An Evidence-Based Systematic Review on the Management of Irritable Bowel Syndrome

American College of Gastroenterology Task Force on IBS

ACG INSTITUTE FOR CLINICAL RESEARCH AND EDUCATION

npg

and blurred vision, and there were no serious adverse events reported in either treatment arm in any of the trials. The relative risk of experiencing adverse events with antispasmodics compared with placebo was 1.62 (95% CI = 1.05–2.50), with statistically significant heterogeneity detected among studies ($I^2 = 38\%$, $p = 0.07$). The NNH with antispasmodic drugs was 18 (95% CI = 7–217).

A variety of preparations containing various formulations of peppermint oil are available through conventional and complementary routes and have been used for some time on a largely empiric basis for the treatment of IBS-like symptoms. Limited experimental data suggest the ability of peppermint oil to relax smooth muscle, thus its inclusion in the same category as antispasmodics. Only four studies (151–154) were identified in a systematic review (114) comparing peppermint oil with placebo in 392 patients; all but one (154) were short-term and only one reported on the type of IBS patient according to stool pattern (153).

The relative risk of IBS symptoms persisting with peppermint oil compared with placebo was 0.43 (95% CI = 0.32–0.59), with statistically significant heterogeneity detected between studies ($I^2 = 31\%$, $p = 0.23$) (114). The NNT with peppermint oil to prevent one patient with IBS remaining symptomatic was 2.5 (95% CI = 2–3) (114). Only three studies reported adverse events data (152–154), and these were few in number.

Section 2.9 Effectiveness of antidiarrheals in the management of irritable bowel syndrome

The antidiarrheal agent loperamide is not more effective than placebo at reducing abdominal pain or global symptoms of IBS, but is an effective agent for treatment of diarrhea, improving stool frequency and stool consistency (Grade 2C). RCTs with other antidiarrheal agents have not been performed. Safety and tolerability data on loperamide are lacking.

Patients with IBS who have diarrhea display faster colonic transit than healthy subjects (155,156); therefore, agents that slow colonic transit may be beneficial in reducing symptoms. Loperamide is the only antidiarrheal agent sufficiently evaluated in RCTs for the treatment of diarrhea-predominant IBS.

There have been two RCTs involving 42 patients that evaluated the effectiveness of loperamide in the treatment of IBS with diarrhea-predominant symptoms (157,158). There were no statistically significant effects of loperamide on overall symptoms compared with placebo (relative risk of IBS symptoms not improving = 0.44; 95% CI = 0.14–1.42). Both trials were double-blinded, but neither reported adequate methods of randomization nor adequate concealment of allocation. The proportion of women in each trial was unclear. Both trials used a clinical diagnosis of IBS supplemented by negative investigations to define the condition. Both trials reported that 100% of the loperamide-treated group had improved stool consistency compared with 20–45% of controls ($p = 0.006$). The pooled analysis of stool frequency suggested that the relative risk of stool frequency not improving with loperamide was 0.2. (95% CI = 0.05–0.9). There were no adverse events in one study (157), and four adverse events in each arm of the other trial (158).

Section 2.10 Effectiveness of antibiotics in the management of irritable bowel syndrome

A short-term course of a nonabsorbable antibiotic is more effective than placebo for global improvement of IBS and for bloating (Grade IB). There are no data available to support the long-term safety and effectiveness of nonabsorbable antibiotics for the management of IBS symptoms.

Rifaximin, a nonabsorbable antibiotic, has demonstrated efficacy in three RCTs evaluating 545 IBS patients (159–162). All of these RCTs were well designed, meeting all criteria for appropriately designed RCTs (i.e., truly randomized studies with concealment of treatment allocation, implementation of masking, completeness of follow-up and intention-to-treat analysis) and meeting most criteria of the Rome committee for design of treatment trials of functional GI disorders (e.g., patients met Rome criteria for IBS, no placebo run-in, baseline observation of patients to assess IBS symptoms, and primary study outcome is improvement in global IBS symptoms) (163). All of these RCTs demonstrated statistically significant improvement in symptoms with rifaximin, and rifaximin-treated patients were 8–23% more likely to experience global improvement in IBS symptoms, bloating symptoms, or both compared with placebo-treated patients. Rifaximin is not FDA-approved for treatment of IBS, although it is FDA-approved for treatment of traveler's diarrhea at the dose of 200 mg twice daily for three days. However, IBS trials utilized higher doses of rifaximin for longer periods: 400 mg three times daily for 10 days (162,164), 400 mg twice daily for 10 days (161), and 550 mg twice daily for 14 days (159,160). The largest RCT ($n = 388$ patients) only examined IBS-D patients, and in this trial, rifaximin-treated patients demonstrated significant improvement in their diarrhea compared with placebo-treated patients (164). Based on these results, rifaximin is most likely to be efficacious in IBS-D patients or IBS patients with a predominant symptom of bloating and the appropriate dosage is approximately 1,100–1,200 mg/day for 10–14 days.

In the largest trial, 388 IBS-D patients were randomized to rifaximin 550 mg twice daily for two weeks followed by placebo for another two weeks or, alternatively, they took placebo for four weeks. In this trial, patients had to experience adequate relief of IBS symptoms in two of the three final weeks to be defined as a responder. Rifaximin-treated patients were significantly more likely to be responders (52.4 vs. 44.2%, $p = 0.03$). Notably, most of the improvement was not noted until after completion of the course of treatment. In a well-publicized RCT (162,164), 87 IBS patients were randomized to rifaximin 400 mg three times daily for 10 days or placebo with a 10-week follow-up period. In this study, severity of global IBS symptoms was based on a composite symptom score, and patients had to experience a 50% improvement in global IBS symptoms from baseline to one week after completion of antibiotics to be defined as a responder

(37.2 vs. 15.9%, $p < 0.05$). Based on assessment of the entire 10-week follow-up period, rifaximin-treated patients were significantly more likely than placebo-treated patients to experience 50% improvement in bloating (49.2 vs. 22.6%), diarrhea (50.6 vs. 35.3%), abdominal pain (39.7 vs. 28.9%), and constipation (35.1 vs. 28.1%) (164), although a separate mixed-model statistical analysis of the same data did not demonstrate significant improvement for the individual symptoms of diarrhea, abdominal pain, or constipation (162). Finally, another RCT examined 103 patients with a primary complaint of bloating, 70 of whom met Rome II criteria for IBS. Among IBS patients, rifaximin-treated patients were significantly more likely than placebo-treated patients to state that "symptoms have improved since starting the drug" after completion of study treatment (41 vs. 18%), but the percentage of patients who continued to state that "symptoms have improved since starting the drug" decreased 10 days after completion of study treatment in both groups (27 vs. 9%). This finding suggests that relief of IBS symptoms may not be durable after completion of antibiotics, although other RCTs (162,164) have demonstrated that IBS symptom improvement lasts for at least 10 weeks. Furthermore, an Italian study (165) examined 61 consecutive patients with positive lactulose hydrogen breath tests, who were treated with rifaximin 400 mg three times daily for seven days. These patients had repeat breath tests at three, six and nine months. Breath tests gradually became positive in a substantial proportion of patients at three months (13%), six months (28%), and nine months (46%), and recurrences of positive breath tests were associated with increases in abdominal pain, bloating, flatulence, and diarrhea, based on mean visual analog scale scores. Based on one open-label retrospective study, IBS patients with recurrent symptoms respond to repeated courses of rifaximin (166).

Among other antibiotics, a single RCT (167) of 111 patients demonstrated that neomycin-treated patients were more likely to experience 50% improvement in global IBS symptoms compared with placebo-treated patients (43 vs. 23%, $p < 0.05$). One trial of clarithromycin (168) did not assess efficacy of antibiotics for IBS as a primary outcome. In this trial, a cohort of 40- to 49-year-old individuals was screened for *Helicobacter pylori*. If an individual was positive for *H. pylori*, then he/she received clarithromycin, omeprazole and tinidazole, or placebos for one week. As part of this study, patients also completed gastrointestinal symptom questionnaires at baseline, six months and two years, and IBS was defined as presence of three or more Manning criteria. Among 274 participants with IBS at baseline, 42% of the antibiotic group and 42% of the placebo group had IBS two years after their one-week course of treatment. Finally, one trial (169) reported that metronidazole was more effective than placebo at improving global IBS symptoms, but this study did not present data that were extractable.

No study reported on overall adverse events, but all stated that antibiotics were well tolerated with no severe adverse events. Two trials assessing rifaximin (159,160,162,164) provided data on individual adverse events, and no significant differences in individual adverse events were noted between rifaximin-treated and placebo-treated patients.

Overall, rifaximin consistently demonstrates improvement in global IBS symptoms and bloating in well-designed trials. The majority of patients in rifaximin trials had IBS-D. Therefore, rifaximin is most likely to be beneficial in IBS-D patients or IBS patients with bloating as their primary symptom. The most appropriate dose of rifaximin for IBS is unclear. Based on currently available data, 400 mg three times a day for 10–14 days is efficacious. IBS symptom relief appears to last for 10–12 weeks, but symptoms may recur over three to nine months. Neomycin also demonstrated efficacy in a single, small RCT of IBS patients. Adverse events were not more common in antibiotic-treated than placebo-treated patients. However, given the often chronic and recurrent nature of IBS symptoms and the theoretical risks related to long-term treatment with any antibiotic, a recommendation regarding continuous or intermittent use of this agent in IBS must await further, long-term studies. It must also be stressed that available data on rifaximin is based on phase II studies; phase III studies have yet to be reported.

Section 2.11 Effectiveness of probiotics in the management of irritable bowel syndrome

In single organism studies, lactobacilli do not appear effective; bifidobacteria and certain combinations of probiotics demonstrate some efficacy (Grade 2C).

Probiotics have been used on an empiric basis for many years in the treatment of IBS, although recent interest in the science of the intestinal flora (microbiota) and probiotics, and our increasing awareness of putative factors in IBS pathophysiology, such as exposure to enteric pathogens, qualitative and quantitative changes in the enteric flora, and subtle levels of colonic inflammation or immune activation, have stimulated more extensive studies of the use of these preparation in IBS.

Our systematic review (170) identified 19 studies (171–189) including a total of 1,668 participants that were deemed eligible. The quality of studies was reasonable with nine (173,174,178, 180,181,183,187–189) reporting an adequate method of randomization and six (173,174,181,183,187,189) describing appropriate methods of concealment of allocation. All but three (175,176,184) recruited patients according to Rome or Manning criteria.

Eleven trials (173,175–177,180–182,186–189) evaluated 936 participants and reported IBS symptoms as a dichotomous outcome. Taken as a group, probiotics had a statistically significant effect to reduce IBS symptoms (RR symptoms persisting in probiotic group = 0.71; 95% CI = 0.57–0.87) with an NNT of four (95% CI = 3–12.5). These data probably overestimate the effects of probiotics, however, as there was heterogeneity and evidence of funnel asymmetry, suggesting there may be publication bias with an overrepresentation of small positive studies in the published literature. Furthermore, higher quality studies reported a more modest treatment effect compared with lower quality trials. There was no difference among the different types of