

Delfini Group™, LLC

*Evidence-based Clinical Consults,
Medical Education Seminars, Training & Tools*

Delfini Systematic Review Summary

Study Reference: Brandt LJ, Bjorkman D, Fennerty MB et al. Systematic review on the management of irritable bowel syndrome in North America. *Am J Gastroenterol.* 2002 Nov;97(11 Suppl):S7-26).

Date: 02/12/03 Reviewer: Michael Stuart MD

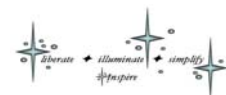
Type of study: Systematic Review

Study Purpose or Hypothesis: To identify using explicit criteria for inclusion and to grade the methodological quality and management recommendations of the relevant IBS therapy trials for the American College of Gastroenterology's evidence-based position statement on the management of irritable bowel syndrome in North America. Diagnostic and therapeutic options with evidence-graded recommendations are presented.

STUDY CHARACTERISTICS—SYSTEMATIC REVIEWS

Clearly stated questions to the literature, determined in advance: Yes

✓ **Documented comprehensive search strategy: Yes.** A search of online bibliographic databases MEDLINE and EMBASE identifying all relevant, English language articles published between 1980 and 2001. Search terms included combinations of the following terms: "antispasmodics," "antimuscarinics," "dicyclomine," "hyoscyamine," "constipation," "fiber," "polycarbophil," "bulking agents," "laxatives," "antidepressants," "tricyclic antidepressants," "tegaserod," "alosetron," "antidiarrheal agents," "loperamide," "behavioral therapy," "irritable bowel syndrome," "clinical trial," and "randomized." For epidemiology of IBS, "colonic diseases, functional" was exploded with key words "incidence," "prevalence," "prognosis," and "natural history." Similar combinations were exploded using "irritable colon." For diagnostic approach to the patient with IBS symptoms, search terms were "colonic diseases, functional (diagnosis)" or "irritable, functional, or spastic colon." These terms were then exploded with the descriptive key words "blood," "parasite," "stool analysis," "radiography," "hydrogen breath testing," "endoscopy," "barium enema," "colonoscopy or flexible sigmoidoscopy." Bibliographies from all potentially relevant articles were manually searched. Multiple pharmaceutical companies, including AstraZeneca, Pfizer, Salix, Novartis, Solvay, Merck, and GlaxoSmithKline, were contacted to identify relevant unpublished trials of IBS therapies and to obtain additional data from published trials of IBS therapies.



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✓	<p>Explicit, documented selection criteria chosen in advance for included studies: Yes. For IBS therapy trials, the selection criteria were 1) randomized controlled trial (RCT); 2) population of adult patients with IBS; 3) comparison of IBS therapy vs placebo or control therapy; 4) evaluation of relief of IBS symptoms; 5) results published in English in full manuscript form (or adequate data from investigators); and 6) therapy available in the United States. For epidemiology of IBS studies, the selection criteria were 1) studies of population-based samples of IBS patients in North America; 2) use of Manning, ROME I, or ROME II criteria to identify IBS patients; 3) population of adult patients; 4) results reported on prevalence, incidence, or natural history of IBS; and 5) results published in English and in full manuscript form. For trials about the diagnostic approach to the patient with IBS symptoms, the selection criteria were 1) use of a cohort of IBS patients explicitly diagnosed via symptom-based criteria (e.g., Manning or ROME criteria); 2) performance of a commonly applied diagnostic test with a blinded comparison to an appropriate gold standard diagnostic test for organic GI disease; and 3) quantification of the results as either normal or abnormal, in which case an additional or alternative diagnosis of organic disease was made based on the test result.</p>
✓	<p>Explicit method for determining validity: Yes. A quantitative scale of study quality was developed using the ROME committee recommendations for design of treatment trials for functional gastrointestinal disorders. Each criterion on the scale was assigned one point. A study could receive a maximum score of 14 points for quality of study methodology. For studies of diagnostic tests, a standard scale was used to evaluate the methodologic quality of studies. The quality of each diagnostic test study was determined by assessing the methodology for 1) study population; 2) verification bias; 3) blinded interpretation of test results; 4) patient selection; 5) data collection; 6) details of diagnostic tests; 7) details of reference tests; and 8) details of the study population. The total score ranged from 0 to 8.</p>
✓	<p>Explicit method for combining results: Yes. The authors assigned levels of evidence and created graded recommendations:</p> <p>Level I Evidence: RCTS (p<0.05), with adequate sample sizes and appropriate methodology</p> <p>Level II Evidence: RCTs with p>0.05 and/or inadequate sample sizes and/or inappropriate methodology</p> <p>Level III Evidence: Non-randomized trials with contemporaneous controls</p> <p>Level IV Evidence: Non-randomized trials with historical controls</p> <p>Level V Evidence: Case Studies</p> <p>Grade A Recommendations: Supported by Level I evidence</p> <p>Grade B Recommendations: Supported by Level II evidence</p> <p>Grade C Recommendations : Supported by Level III-IV evidence</p>
✓	<p>Conclusions are supported by the evidence: Yes</p>

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Reported Results –

Table 1: Summary of Graded Recommendations for IBS Patients

Epidemiology, Diagnosis	Grade of Recommendation
Definition of IBS: abdominal discomfort associated with altered bowel habits	Grade C
Quality of Life Statement: IBS significantly diminishes quality of life (QOL)	Grade C
Treatment is indicated with patient and physician believe QOL is diminished	Grade C
IBS therapies should improve global IBS symptoms (abdominal discomfort, bloating, altered bowel habits)	Grade C
Female/male ratio is 2:1	Grade C
IBS patients without alarm symptoms do not require routine diagnostic testing (flex sig, barium enema, colonoscopy, fecal occult blood tests, stool for culture or ova and parasites, thyroid function testing)	Grade C
Among IBS with diarrhea, testing for celiac sprue may be considered	Grade C
Alarm symptoms include but are not limited to: hematochezia, weight loss greater than 10 lbs, FH of colon cancer, fever, anemia, chronic severe diarrhea	Grade C

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Table 2: Summary of Graded Recommendations for IBS Patients

Treatment	Grade of Recommendation
Bulking agents: not more effective than placebo in relieving global symptoms of IBS	Grade B
Loperamide: not more effective than placebo in relieving global symptoms of IBS	Grade B
Tricyclic antidepressants: improve abdominal pain	Grade B
Tegaserod (serotonin receptor agonist): more effective than placebo at relieving global IBS symptoms in women with constipation	Grade A
Alosetron (serotonin receptor antagonist): more effective than placebo at relieving global IBS symptoms in women with diarrhea	Grade A
Behavioral therapy: more effective than placebo at relieving individual IBS symptoms	Grade B

Authors' Conclusions:

- Prevalence of IBS: The prevalence of IBS in North America is approximately 10–15%, equally divided among IBS with constipation, IBS with diarrhea, and IBS alternating between diarrhea and constipation.
- Antispasmodics: There are insufficient data to make a recommendation about the effectiveness of the antispasmodic agents (smooth muscle relaxants, anticholinergics or antimuscarinics (e.g., dicyclomine, hyoscyamine) available in the United States.
- Bulking Agents: IBS patients with constipation exhibit delayed intestinal transit. Therefore, bulking agents that accelerate intestinal transit may be beneficial for these patients.
- Antidiarrheal Agents: IBS patients with diarrhea demonstrate accelerated intestinal transit. Therefore, antidiarrheal agents that delay intestinal transit may be beneficial for these patients. Loperamide is the only antidiarrheal agent appropriately evaluated for treatment of IBS. Among patients with pain who alternate between constipation and diarrhea, loperamide-using patients improve significantly more than placebo-using patients with regard to stool frequency and stool consistency. Adverse event data are sparse.
- TCAs: improve abdominal pain in IBS patients. Adverse event data with TCAs indicate that these agents may cause constipation and should be used with caution in IBS patients with constipation.
- Tegaserod (serotonin receptor agonist) for constipation: Tegaserod is more effective than placebo at relieving global IBS symptoms in women with constipation. Diarrhea is the most common adverse event associated with tegaserod use and was reported as an adverse event in 9–10% of tegaserod-using patients vs 4–5% of placebo-using patients. Approximately 1–2% of tegaserod- using patients discontinued medication because of diarrhea. It may be prudent to advise patients to temporarily discontinue tegaserod if significant diarrhea occurs. When prescribing tegaserod, physicians should remember that

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the FDA-approved indication for tegaserod is “for the short-term treatment of women with IBS whose primary bowel symptom is constipation.”

- Alosetron (a 5HT₃ (serotonin) receptor antagonist) is the only FDA-approved agent for the treatment of IBS patients with diarrhea. Alosetron is more effective than placebo at relieving global IBS symptoms in female IBS patients with diarrhea. Alosetron slows colonic transit and decreases discomfort during distension of the colon. In November 2000, distribution of alosetron was halted because of concerns about ischemic colitis and serious complications of constipation. In June 2002, the FDA approved restricted marketing of alosetron for “the treatment of women with severe, diarrhea-predominant IBS who have failed to respond to conventional IBS therapy.” Physicians should educate patients about the potential risks of alosetron and instruct patients to discontinue alosetron if constipation occurs.
- Behavioral therapy is more effective than placebo at relieving individual IBS symptoms.

Reviewer’s Conclusions: There are no lethal threats to validity in this systematic review.

Clinical Implications: Patients should be made aware of this evidence and a shared decision-making process between clinician and patient should be utilized in determining which therapeutic interventions are to be employed in managing their symptoms of IBS.