Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized controlled trials

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Authors' objectives
To evaluate the efficacy of pharmacological agents for the irritable bowel syndrome.

Searching
Articles published in the English language were identified in the following: MEDLINE from 1966 to 1999; EMBASE from 1980 to 1999; PsycINFO from 1967 to 1999; the Cochrane Trials Register; and bibliographies from all retrieved publications. The MeSH term was 'colonic diseases, functional' and a keyword search for 'irritable', 'functional' or 'spastic' adjacent to 'bowel' or 'colon' was performed. The search was supplemented by various combinations of truncated keywords that described the type of publication such as 'random', 'double-blind', 'random allocation', 'placebo', 'clinical trials' and 'comparative study'. Abstracts, studies not published in full, dissertations and book chapters were excluded.

Study selection
Study designs of evaluations included in the review
Randomised, double-blind, placebo controlled trials of either parallel group or cross-over design that administered the pharmacological intervention to more than 10 patients for at least two weeks were eligible. Duration of studies ranged from 2 to 24 weeks (mean 7.5 weeks, median 6 weeks).

Specific interventions included in the review
Pharmacological interventions were eligible. The following pharmacological agents were included: bulking agents (psyllium, coarse or wheat bran, concentrated fibre, corn fibre, calcium polycarbophil, and ispaghula husk); smooth muscle relaxants (cimetropium, mebeverine, dicyclomine, trimebutine, rocuverine, diltiazem, pinaverium, otilonium, pirenzepine, and piriflum); prokinetic agents (domperidone and cisapride); peripheral opioid agonist (loperamide); 5-hydroxytryptamine-receptor antagonists (5-HT: ondansetron and aloestron); peripheral opioid k agonist (fedotozine); other agents (timolol, bisoprolol, lidamidine, and oxiglumide); psychotropic agents (nortryptylne, amitriptyline, desipramine, trimipramine, meprizazole, and meprobamate); and miscellaneous agents including peppermint oil, phentoin, sodium cromoglycate, galactosidase, Lactobacillus acidophilus, Streptococcus acidophilus, Streptococcus faecium and Chinese herbal medicine; and combinations of two to three of these agents.

Co-interventions included dietary changes such as high fibre diet, and concurrent use of other medications.

Participants included in the review
Adult patients with irritable bowel syndrome were eligible. Mean age ranged from 24 to 51 years (median 38 years). An average of 68% of participants were women. The following means were used to diagnose irritable bowel syndrome: standard criteria (including the Rome and Manning criteria); operational criteria based on a modification of standard criteria; method not specified; and work up to exclude organic disease including history, physical examination, and where appropriate, laboratory, radiologic and endoscopic evaluation. Predominant symptoms included abdominal pain, constipation and diarrhea.

Outcomes assessed in the review
Global or bowel-specific symptoms were eligible. Individual symptoms included: abdominal pain; bowel disturbance; constipation; distension; bowel satisfaction; stool frequency and consistency; anorectal symptoms; diarrhea; urgency; and flatulence. Outcome assessment was performed predominantly using data collected from a daily diary maintained by the patients or during periodic office visits with interviews or questionnaires.

How were decisions on the relevance of primary studies made?
All three authors independently applied the inclusion criteria to a subset of studies to assess interrater variation.
Assessment of study quality
The five following criteria were used to assess validity: clear inclusion criteria; baseline similarity of treatment and control group for symptom severity in parallel trials or absence of period or sequence effects in crossover trials; similar adherence in treatment and control group; patient-rated outcomes; and rigorous analysis preferably by the intention-to-treat principle. Analysis was judged satisfactory if the drop-out rate was less than 20% of non-adherent patients and those lost to follow-up were analysed within the groups to which they were initially assigned. All three authors independently applied validity criteria with resolution of disagreements by discussion. Each criterion was rated as present (1 point) or absent (0 points). Any trials satisfying at least four of the five criteria were judged as high quality.

Data extraction
The following data were extracted: criteria used to diagnose irritable bowel syndrome; characteristics of study sample; dose and length of pharmacological intervention; methodological characteristics of trial; reported outcomes; and statistical analysis with estimates of treatment effect and P values when available. Each trial was classified as positive or negative in terms of efficacy, with any trial reporting significant improvement in either global status or individual symptoms classified as positive. The absolute difference and 95% confidence intervals (CI) in frequency of any global improvement between intervention and control groups were calculated for each trial that provided sufficient data. The authors do not state how many of the reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review and by using a vote-counting approach using global improvement and improvement in specific symptoms of irritable bowel syndrome.

How were differences between studies investigated?
Sub-group analysis was conducted to compare high and low-quality trials and parallel and crossover trials.

Results of the review
Seventy studies were included (4836 patients), including thirty seven using a parallel design and thirty three using crossover design.

Use of diagnostic criteria: 17 (24%) trials used standard diagnostic criteria. 16 (23%) trials did not specify diagnostic criteria. 53% studies based diagnosis on a modification of standard criteria and 54 (77%) reported an adequate work up to exclude organic disease.

Methodological flaws included: lack of assessment of baseline comparability and co-intervention; variability in definition of symptoms; magnitude of improvement in global status was not well defined; few studies specified which adverse effects were measured or reported the number of patients experiencing adverse reactions; several outcomes were analysed without appropriate statistical adjustment; and some cross-over trials did not examine for period or sequence effects (or both). Statistical analysis: intention-to-treat (ITT) analysis was performed in most trials (80%). Drop-out rates ranged from 0% to 24% in trials judged to have used an ITT analysis. Only 2 studies reported any power calculation.

Validity: mean quality score was 3.2, median was 3. 28 trials were judged as high quality.

1. Bulking agents (13 RCTs): results were inconsistent with only four trials reporting benefit. Of the 7 high quality RCTs (341 patients), 3 reported benefit in either global status or individual symptoms (ease of stool passage, bowel satisfaction and constipation).

2. Smooth-muscle relaxants (16 RCTs): results were inconsistent though, with 13 RCTs reporting benefit, tended to favour the active drug. All 7 high quality RCTs (601 patients) reported improvement in abdominal pain with 2 trials reporting a significant improvement in constipation. In all but one of the high quality RCTs, anticholinergic side effects...
were similar between active drug and placebo.

3. Prokinetic agents (6 RCTs): results were inconsistent with only one RCT reporting benefit. Of the 4 high quality RCTs (266 patients), 3 RCTs reported no benefit in global status and 2 reporting no benefit in individual symptoms.

4. Loperamide (4 RCTs): all 4 RCTs reported an improvement in diarrhea and the 2 RCTs that reported global status reported improvement. The 2 high quality RCTs (100 patients) both reported significant improvement in diarrhea, including decreased frequency of bowel movements and improved stool consistency but no improvement in abdominal pain and distention.

5. Psychotropic agents (7 RCTs): results were inconsistent with 3 of the 5 RCTs that measured global improvement, reporting benefit and 4 of the 7 RCTs reporting improvement in abdominal pain and diarrhea but none reporting any difference in constipation. Only one high quality RCT (14 patients) was identified and this reported global improvement but did not report on individual symptoms.

6. Other agents: results given below are limited to those from more than one trial. Other results were reported in the review.
   a) Ondansetron (2 RCTs, including one high quality RCT with 50 patients): both reported significant improvement in global status and stool consistency in patients with predominant diarrhea but no improvement in abdominal pain and distension.
   b) Diphenylhydantoin (2 RCTs, including one high quality RCT with 14 patients): inconsistent results with the one high quality RCT reporting no benefit and the other RCT reporting global improvement.
   c) Peppermint oil (3 RCTs, including one high quality RCT with 110 patients): inconsistent results with the high quality RCT reporting improvement and the others reporting no benefit.

Authors' conclusions
Smooth muscle relaxants are beneficial when abdominal pain is the predominant symptom. In contrast, the efficacy of bulking agents has not been established. Loperamide is effective for diarrhea. Evidence for use of psychotropic agents is inconclusive; more high-quality trials of longer duration are needed. Evidence for the efficacy of 5-HT-receptor antagonists seems favourable, although more studies are needed.

CRD commentary
The aims were stated and inclusion criteria defined in terms of intervention, participants, study design and outcome. Several potential sources were searched for relevant articles, though studies were limited to those published in the English language and no attempt was made to locate unpublished material which raises the possibility of publication bias; a bias which was acknowledged by the authors. Methods used to select studies and validity were described. Validity was formally assessed using defined criteria and methodological flaws discussed.

Relevant detail of the high-quality studies was presented in tabular format with further information provided in the text. Given the heterogeneity among studies, a narrative review with vote-counting was appropriate. In pooling the studies, account was taken of study validity. The discussion includes mention of the possibility of publication bias and the following limitations of the review: trials were of short duration; most patients were enrolled from gastroenterology practice settings rather than primary care and thus may have had more severe or atypical symptoms.

The evidence supports the authors' conclusions.

Implications of the review for practice and research
Practice: The authors state that pharmacological treatments should be targeted at the major symptom, and treatment should be carefully monitored for adverse effects that can mitigate the benefit of an intervention. They further report that there was reasonable evidence supporting the use of smooth-muscle relaxants for abdominal pain, benefits of
bulking agents remain unproven despite a large number of trials, and loperamide appears to be effective in diarrhoea.

Research: The authors state that future trials of antidepressants (including the selective serotonin re-uptake inhibitors) should examine long-term outcomes, the need for long-term therapy, and the relation between depressive states and treatment efficacy. They also suggest that future studies should consider published guidelines for proper study design and stratification of patient subgroups on the basis of symptom severity and/or the predominant symptom, and should assess both side-effects and overall health-related quality of life by using validated measures. Further trials are required for 5-HT-receptor antagonists and psychotropic agents.

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