Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptom relief and constipation in nonconstipated irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials
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CRD summary
This review evaluated the effectiveness of 5-hydroxytryptamine (serotonin) antagonists in treating irritable bowel syndrome (IBS). The authors concluded that 5-hydroxytryptamine antagonists significantly improved symptoms of nonconstipated IBS and diarrhoea predominant IBS in men and women, but there was an increased risk of constipation. The authors’ conclusions reflect the evidence presented and are likely to be reliable.

Authors’ objectives
To evaluate the effectiveness of 5-hydroxytryptamine (serotonin) antagonists in patients with non-constipated or diarrhoea-predominant irritable bowel syndrome (IBS).

Searching
The databases MEDLINE (January 1966 to December 2006), EMBASE (January 1988 to December 2006) and Web of Science (January 1990 to December 2006) were searched. No publication status or language restrictions were applied. Search terms were reported. Reference lists of included studies were also scanned.

Study selection
Eligible for inclusion in the review were randomised controlled trials (RCTs) evaluating the effects of 5-hydroxytryptamine antagonists on the relief of abdominal pain and discomfort, or global improvement, in irritable bowel syndrome (IBS). Review or animal studies, studies with pharmacodynamic endpoints, duplicate publications and non-IBS studies were excluded. Outcomes of interest were relief of abdominal pain and discomfort, global improvement of IBS symptoms, and constipation rate.

In included trials, 5-hydroxytryptamine antagonists were alosetron and cilansetron. Controls were placebo or mebeverine. Gender breakdown varied between included trials. The mean age of patients was approximately the same for both genders (43 to 49 years). Some included trials had patients with diarrhoea-predominant IBS and patients with non-constipated IBS, whilst other trials had patients with diarrhoea-predominant IBS only.

Two reviewers independently selected the studies for inclusion in the review. It was not reported how disagreements were resolved.

Assessment of study quality
Trial quality was assessed using the criteria of: a control group; random allocation; blinding of patients and investigators; parallel group design; validated disease definition (Rome I and II criteria); validated outcome measures; attrition bias; loss to follow-up; adequate power; definition of responder included a priori; and use of intention-to-treat analysis.

Two reviewers independently assessed study quality. It was not reported how disagreements were resolved.

Data extraction
Data was extracted in order to calculate risk ratios (RR) with 95% confidence intervals (CI).

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
Methods of synthesis
Risk ratios were combined in a meta-analysis using the random-effects model. Heterogeneity was assessed using the $I^2$ test. Sub-group analyses were performed according to study population, gender, medication used, dose, treatment duration, comparator, outcome definition, outcome estimation and publication status.

Results of the review
Fourteen RCTs (n=7,984 patients) were included in the meta-analysis. Of these fourteen RCTs, four were abstracts and ten were full articles. The full articles met all the quality criteria. Funnel plot analysis did not show any evidence of publication bias.

Abdominal pain and discomfort relief: 5-hydroxytryptamine antagonists were associated with statistically significant relief of abdominal pain and discomfort compared to control (RR 1.30, 95% CI 1.22 to 1.39; 10 RCTs). The calculated number-needed-to-treat was 7.7. There was no evidence of statistically significant heterogeneity.

Global improvement of IBS symptoms: Compared to patients receiving control, those receiving 5-hydroxytryptamine antagonists had a statistically significant increase in global improvement of IBS symptoms (RR 1.60, 95% CI 1.49 to 1.72; seven RCTs). The number-needed-to-treat was 4.2. There was also no evidence of statistically significant heterogeneity.

Constipation: Patients receiving 5-hydroxytryptamine antagonists were statistically significantly more likely to report constipation (RR 4.28, 95% CI 3.28 to 5.60, 14 RCTs) compared to those in the control group. The calculated overall number-needed-to-harm was 4.7. However, there was evidence of statistically significant heterogeneity ($I^2$=65%). The authors stated that this heterogeneity was due to constipation being reported as adverse events by patients in some trials and identified from bowel habit diaries in other trials. Results of subgroup analyses were reported (see full article).

Authors' conclusions
5-hydroxytryptamine antagonists significantly improved symptoms of non-constipated IBS or diarrhoea-predominant IBS in men and women. There was an increased risk of constipation with 5-hydroxytryptamine antagonists, although the risk was lower in those with diarrhoea-predominant IBS.

CRD commentary
The review addressed a clear research question and was supported by adequate inclusion criteria. The search strategy was adequate and included studies in languages other than English, which reduced the possibility of language bias. Adequate details of the included studies were provided and synthesis methods were appropriate. This was a well-conducted review with sufficient attempts to minimise errors and bias, although it was not reported how many reviewers performed data extraction. The authors' conclusion reflect the evidence presented and are likely to be reliable.

Some of the data used in the review was obtained from manufacturers of two drugs included in the review (GlaxoSmithKline and Solvay). Some of the authors reported previously working as consultants for these manufacturers.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors did not state any implications for research.

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