Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials
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CRD summary
This review analysed six trials on the effects of alosetron in irritable bowel syndrome (IBS). The authors concluded that alosetron can improve symptoms or decrease pain in female IBS patients without constipation. However, they also concluded that alosetron can have adverse effects, particularly constipation. The effects in men are unclear. These conclusions are appropriate given the evidence available.

Authors' objectives
To determine the effect of alosetron therapy on adequate relief of pain or global improvement of symptoms in patients with irritable bowel syndrome (IBS).

Searching
MEDLINE (from 1966 to 2002) and EMBASE (from 1988 to 2002) were searched electronically; the search terms were reported. The references of the included studies were also searched by hand.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included. The authors also stated that inclusion criteria incorporated quality criteria, although any cut-off point at which studies were considered to be of insufficient quality for inclusion was unclear.

Specific interventions included in the review
Studies of alosetron were included. Comparison was with placebo in all of the included studies. Within the selected studies, alosetron was given at daily doses of 0.2, 1, 2, 4, 8, 12 and 16 mg. Only participants who received at least 2 mg/day were included in the analysis.

Participants included in the review
The authors did not explicitly state any inclusion criteria relating to the participants. The participants in the selected studies all had IBS (defined by Rome I or II criteria) and were predominantly female (94.5%).

Outcomes assessed in the review
Studies were included if they used adequate relief of pain or global improvement of symptoms as outcome measures.

How were decisions on the relevance of primary studies made?
Two independent reviewers selected studies for inclusion in the review.

Assessment of study quality
The quality of the included studies was assessed according to published internal and external validity criteria and the quality of reporting (see other Publications of Related Interest). Two independent reviewers evaluated the validity of the included studies.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on: the participants’ IBS type, age and gender, treatment regimen, the length of follow-
up, the number of drop-outs, the number of responders, and adverse events. ‘Responders’ were defined as those participants who reported a positive outcome on at least 50% of the times it was measured in the study.

Methods of synthesis
How were the studies combined?
Outcomes and adverse events were assessed based on an intention-to-treat analysis using logistic regression. In the efficacy analysis, treatment was the independent variable and adequate pain relief or global improvement in symptoms was the dependent binary variable. The different studies were codified as dummy variables in the model to account for potential confounders. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived for individual studies and summary outcomes. The numbers-needed-to-treat were also calculated.

Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
Three sensitivity analyses were conducted: excluding one study that compared alosetron with mebeverine; excluding the largest study with the largest effect; and including only patients who received 2 mg alosetron daily.

Results of the review
Six RCTs (3,529 patients) were included in the review.

Alosetron was more effective than placebo for adequate relief of pain or global symptoms. The pooled OR for a positive outcome for all studies was 1.81 (95% CI: 1.57, 2.10, P<0.0001).

Alosetron remained more effective than placebo following the sensitivity analysis. The pooled OR for a positive outcome after excluding one study that compared alosetron with mebeverine was 1.85 (95% CI: 1.57, 2.18, P<0.0001).

The pooled OR for a positive outcome after excluding the largest study with the largest effect size was 1.49 (95% CI: 1.25, 1.73, P<0.0001).

The pooled OR for a positive outcome after including only those patients who received 2 mg alosetron daily was 1.96 (95% CI: 1.69, 2.28, P<0.0001).

Participants in the alosetron group were more likely to report constipation than the control group (OR 5.64, 95% CI: 4.40, 7.33, P<0.0001) and were generally more likely to report any adverse event (OR 1.70, 95% CI: 1.42, 2.04, P<0.0001).

Authors’ conclusions
The present analysis showed that alosetron 1 mg twice daily positively impacts on global symptoms and pain and discomfort in non-constipated female patients with IBS. One in four patients treated with alosetron may develop constipation. The efficacy of alosetron in male patients was unclear.

CRD commentary
The inclusion criteria relating to the interventions, study design and outcomes were specified and appropriate to the review question. The search of the published literature appeared adequate. The authors do not appear to have searched for unpublished or non-English language papers, but they did present a funnel plot that suggested there are unlikely to be sufficient small, unpublished trials to substantially change the results. Two independent reviewers assessed the validity of all studies, but it was unclear how this information was used in the synthesis. No analysis of statistical heterogeneity was reported, though the studies seemed clinically homogeneous from the information presented in the review. The authors’ general conclusions seem appropriate and follow from the evidence included in the review.

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

Research: The authors stated that post-marketing surveillance studies are required to establish the risk-to-benefit ratio associated with alosetron.

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