Efficacy and tolerability of alosetron for the treatment of irritable bowel syndrome in women and men: a meta-analysis of eight randomized, placebo-controlled, 12-week trials

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CRD summary
This review concluded that alosetron was an effective treatment for irritable bowel syndrome when compared to placebo. Participants were predominantly women with diarrhoea-dominant irritable bowel syndrome, so the review findings may be only applicable to this group of patients. Overall, this was a well-conducted review and the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the efficacy and tolerability of alosetron for the management of irritable bowel syndrome.

Searching
PubMed, EMBASE, SCOPUS, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1966 to September 2007. Search terms were reported. Reference lists of relevant publications were also checked. No restrictions were placed on publication type or language.

Study selection
Randomised placebo-controlled trials (RCTs) that evaluated the efficacy and/or tolerability of alosetron in males and females with irritable bowel syndrome were eligible for inclusion. Trials were excluded if the patients received a dosage of less than 1mg/d, or if the duration of treatment was greater than 12 weeks. The primary outcomes were global improvement in irritable bowel syndrome symptoms and adequate relief of irritable bowel syndrome pain and discomfort. Adverse events were also assessed.

In all of the included trials, the patients met the Rome criteria for irritable bowel syndrome. All subtypes of irritable bowel syndrome were represented; the majority of patients had diarrhoea-predominant irritable bowel syndrome. All but one trial included high proportions of women; overall 80% of participants were women. The mean age of the participants ranged from 43.5 to 49.1 years. The daily dose of alosetron varied from 1mg to 16mg. In all trials, the treatment duration was 12 weeks and the duration of follow-up varied from 14 to 16 weeks.

Three reviewers independently selected the studies for inclusion.

Assessment of study quality
Study quality was assessed in terms of randomisation, double-blinding and withdrawals, using the Jadad scale to obtain a quality score out of 5 points.

Two reviewers independently applied the quality assessment criteria.

Data extraction
Three reviewers independently extracted data from the studies. The authors reported that there were no disagreements between the reviewers. Data were extracted in the form of 2x2 tables.

Methods of synthesis
A meta-analysis was used to estimate the pooled relative risks (RRs) with 95% confidence intervals (CIs). The trials were combined using either the Mantel-Haenszel fixed-effect model or the DerSimonian random-effects model, depending on whether or not heterogeneity was observed. Heterogeneity was assessed using the Breslow-Day test, and by examination of L'Abbe plot. Publication bias was assessed graphically using a funnel-plot, and statistically using the Egger test and Kendall's method. Subgroup analysis was conducted to assess effects of sex.
Results of the review
Eight RCTs (n=4,170) were included in the review.

Two studies had a quality score of 5 points, four had a quality score of 4 points, and two had a quality score of 3 points.

Global improvement in irritable bowel syndrome symptoms: There was a significant global improvement in irritable bowel syndrome symptoms with treatment compared to placebo (RR 1.60, 95% CI 1.44 to 1.76; three trials); there was no significant statistical heterogeneity between the studies.

Adequate relief of irritable bowel syndrome pain and discomfort: There was a significant difference in favour of alosetron compared to placebo (RR 1.31, 95% CI 1.20 to 1.43; six trials). There was no significant statistical heterogeneity between the trials. Results were similar when males and females were analysed separately.

Adverse events: Significantly more adverse events were reported in participants who received alosetron compared to placebo (RR 1.19, 95% CI 1.07 to 1.31; seven trials); there was significant statistical heterogeneity between the trials. When compared to placebo, there was significantly greater constipation (RR 4.35, 95% CI 3.01 to 6.26; eight trials) and abdominal pain and discomfort (RR 1.96, 95% CI 1.46 to 2.64; five trials) in participants who received alosetron. There were no significant differences between groups for nausea, ear, nose and throat infections, or headache. Ischaemic colitis (0.16%) and serious complications of constipation (0.08%) were reported in a small number of participants treated with alosetron.

Authors' conclusions
Alosetron was an effective treatment for irritable bowel syndrome in the sample evaluated. The most frequently reported adverse event was constipation.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion/exclusion criteria. A comprehensive search for published trials in any language was undertaken, and an assessment of publication bias was conducted. Validity was assessed according to published criteria, and detailed results of this assessment were presented. Comprehensive details of the included trials were provided. Appropriate methods were used to pool the results and to investigate statistical heterogeneity. More than one reviewer was involved in the selection of studies, data extraction and validity assessment processes, limiting reviewer error and bias. Participants were predominantly women with diarrhoea-dominant irritable bowel syndrome, so the review findings may be only applicable to this group of patients. Overall, this was a well-conducted review, and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that alosetron is recommended for patients with diarrhoea-predominant irritable bowel syndrome.

Research: The authors stated that multicentre clinical trials are needed to assess the effects of alosetron in men.

Funding
None.

Bibliographic details

PubMedID
18555935

DOI

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Carbolines /adverse effects /therapeutic use; Female; Humans; Irritable Bowel Syndrome /drug therapy /physiopathology; Male; Randomized Controlled Trials as Topic; Serotonin 5-HT3 Receptor Antagonists

Date bibliographic record published
03/11/2008

Date abstract record published
18/11/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.