Evaluation of harm in the pharmacotherapy of irritable bowel syndrome
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CRD summary
Tricyclic antidepressants and alosetron were associated with significant numbers needed to harm, compared with rifaximin, for diarrhoea. Selective serotonin re-uptake inhibitors and lubiprostone seemed to be safe, for constipation. The authors’ conclusions reflected the evidence presented, but lack of quality assessment, different trial lengths, and small samples in some trials mean that the reliability of the results is unclear.

Authors' objectives
To compare the number needed to harm for drug interventions for patients with irritable bowel syndrome.

Searching
MEDLINE (1950 to April 2011), EMBASE (1980 to April 2011) and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched, without language restrictions. Reference lists from relevant meta-analysis publications were handsearched.

Study selection
Randomised, double-blind, placebo-controlled trials that included adult patients with irritable bowel syndrome were eligible for inclusion. Trials had to report adverse events and the number of patients who discontinued treatment because of an adverse event. They had to assess drugs rated as Grade 1 by the American College of Gastroenterology Task Force, such as alosetron, tricyclic antidepressants, or rifaximin for diarrhoea, or lubiprostone or selective serotonin re-uptake inhibitors for constipation, in irritable bowel syndrome. Trials of Grade 2 or other medications were excluded.

The primary endpoint was the number needed to harm; secondary endpoints were the numbers of adverse events and serious adverse events. An intention-to-treat analysis was used to compare the patients who withdrew due to adverse events in each medication group. Drug dosages varied in the included trials. Trial length ranged from 10 days treatment plus 10 days follow-up to 48 weeks.

Two reviewers selected the trials and any disagreements were resolved through consensus.

Assessment of study quality
The authors did not state that they assessed methodological quality.

Data extraction
The relative risk of experiencing an adverse event that required discontinuation of treatment was extracted to calculate the number needed to harm and the 95% confidence interval. Risk differences between each two trial groups were extracted.

The authors did not report how many reviewers extracted the data.

Methods of synthesis
The pooled relative risk of experiencing an adverse event, with 95% confidence interval, was calculated for each drug, using the DerSimonian and Laird random-effects model. Heterogeneity was assessed using I². Harbord's test (a modified version of the Egger test) was used to assess funnel plot asymmetry to detect publication bias.

The number needed to harm was calculated from the reciprocal of the absolute value of the risk difference (the risk of the outcome in the treatment group minus its risk in the control group). To compare the incidence of side-effects, a X² test was used. The number needed to treat was calculated.

Results of the review
Twenty-six trials were included, with four on selective serotonin re-uptake inhibitors, three on lubiprostone, six on...
tricyclic antidepressants, eight on alosetron, and five on rifaximin. There were 8,595 participants (range 23 to 1,171). Follow-up ranged from 10 days to 10 weeks (where reported).

**Constipation:** There was no difference in dropouts due to adverse events between lubiprostone and placebo. The four trials of selective serotonin reuptake inhibitors did not supply enough data for a reliable meta-analysis of harm, but the drugs seemed to be safe, with 7.8% dropout from treatment and 9.2% dropout from placebo.

**Diarrhoea:** The pooled number needed to harm was 18.3 (95% CI 5.8 to 217.4) for tricyclic antidepressants, 19.4 (95% CI 8.5 to 90.1) for alosetron, and 8,971 for rifaximin. The relative risk was 2.71 (95% CI 1.14 to 6.44) with tricyclic antidepressants, 2.00 (95% CI 1.22 to 3.30) with alosetron, and 1.01 (95% CI 0.50 to 2.02) with rifaximin. Apart from alosetron (I²=71.8%), no statistical heterogeneity was observed in the pooled relative risks. No publication bias was found.

The number needed to treat to benefit one patient was 8.0 for tricyclic antidepressants, 7.5 for alosetron, and 10.6 for rifaximin. For tricyclic antidepressants 2.3 patients and for alosetron 2.6 patients benefited from treatment before one harm occurred. For rifaximin, 846 patients benefited before one harm. Adverse events were more common with tricyclic antidepressants and alosetron.

**Authors’ conclusions**
Tricyclic antidepressants and alosetron were associated with significant numbers needed to harm, compared with rifaximin, for diarrhoea. Selective serotonin re-uptake inhibitors and lubiprostone seemed to be safe, for constipation.

**CRD commentary**
The review addressed a clear question and was supported by appropriate inclusion criteria. Relevant sources were searched, with no language restrictions. No attempts were made to locate unpublished studies, but funnel plots suggested no evidence of publication bias. No quality assessment (randomisation, allocation concealment, etc.) was reported, so the risk of bias in the included trials was unclear. Two reviewers were selected the trials, but the authors did not report how many reviewers extracted the data, so reviewer bias and error cannot be ruled out.

The authors’ conclusions reflected the evidence presented, but the lack of quality assessment, the different lengths of the trials, and small samples in some trials mean that the reliability of the results is not clear.

**Implications of the review for practice and research**

**Practice:** The authors stated that instead of simply focusing on the number needed to treat, clinicians should be aware of harm when selecting pharmacotherapy for irritable bowel syndrome.

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

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