Efficacy of tricyclic antidepressants in irritable bowel syndrome: a meta-analysis
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CRD summary
This review concluded that low-dose tricyclic antidepressants (TCAs) exhibited clinically and statistically significant control of irritable bowel syndrome (IBS) symptoms. Caution is warranted in the application of the results as reported TCA effects may have been overestimated given the small number of studies and patients reviewed.

Authors' objectives
To assess the efficacy of tricyclic antidepressants (TCAs) in patients with irritable bowel syndrome (IBS).

Searching
PubMed, Scopus, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) were searched (from 1966 to September 2008) for English-language papers. Search terms were reported. Reference lists of retrieved articles were handsearched. Abstracts of conference meetings were considered.

Study selection
Randomised controlled trials (RCTs) that compared TCAs with placebo in the management of patients with IBS were eligible for inclusion. Outcomes of interest were global improvement of symptoms and adequate relief of pain and discomfort.

TCAs evaluated included amitriptyline, imipramine, desipramine, doxepin and trimipramine. Duration of treatment/follow-up was varied and ranged from four to 12 weeks. Doses of TCAs were varied: initial doses ranged from 10mg to 75mg; and subsequent doses ranged from 50mg to 150mg. Patients in the included studies had diarrhea predominant-IBS (D-IBS), constipation predominant-IBS (C-IBS) and alternating-IBS (Alt-IBS). Approximately half of the patients were female. Mean age, where reported, ranged from 32.5 to 45.2 years. Definitions of clinical response were varied.

Three reviewers independently screened studies for inclusion. Disagreements were assessed through consensus discussion.

Assessment of study quality
The methodological quality of included studies was assessed using the Jadad scale: studies were awarded a score of between 0 and 5 based on adequacy of criteria of randomisation, blinding and level of dropouts (withdrawals).

The authors did not state how many reviewers performed the validity assessment.

Data extraction
At least two reviewers independently extracted data on the number of patients with outcomes to calculate relative risks (RRs) and 95% confidence intervals (CIs) for dichotomous outcomes (such as clinical response) and mean differences for continuous outcomes (such as change in abdominal pain scores). Data were extracted into 2x2 tables. Disagreements were resolved through consensus discussion.

Methods of synthesis
A fixed-effect model was used to combine relative risks using the Mantel-Haenszel method and weighted mean differences (WMDs) using the Mulrow-Oxman method where there was no evidence for statistically significant heterogeneity; otherwise a random-effects model was used. Statistical heterogeneity was assessed using the Cochran Q test and further explored using L’Abbe plot. Analyses were performed to test sensitivity of the results to exclusion of one study with a Jadad score of 2. Publication bias was assessed using funnel plots and Kendall’s t test. Results for statistical tests were reported.
Results of the review

Seven RCTs (n=257) were included in the review. Sample sizes ranged from 22 to 50. Most included studies were of medium quality. Jadad scores were: 3 points (five studies), 2 points (one study) and 4 points (one study).

TCA therapy compared to placebo was associated with significant improvement in clinical response (RR 1.93, 95% CI 1.44 to 2.6, p<0.0001; seven RCTs) and a reduction in abdominal pain score (WMD -44.15, 95% CI -53.27 to -35.04, p<0.0001; two RCTs). There was no evidence of statistically significant heterogeneity. There was conflicting evidence on the possible presence of publication bias.

Authors' conclusions

Low dose TCAs exhibited clinically and statistically significant control of IBS symptoms.

CRD commentary

The review question and inclusion criteria were clearly defined with respect to participants, study designs and interventions. Inclusion criteria for outcomes were not explicitly stated. Relevant sources were searched for papers in English and so language bias could not be ruled out. Assessment of publication bias yielded mixed results, which made interpretation about publication bias difficult. Methods to minimise reviewer bias and error were reported for study selection and data extraction, but not for assessment of validity. Validity assessment was performed using an appropriate scale and most studies were of moderate quality. The decision to combine study results using a fixed-effects model was supported by the absence of statistical heterogeneity. Statistical outcome data were reported for both outcomes considered. The authors’ conclusions reflected the evidence of the review. However, as the authors acknowledged, some caution may be warranted due to possible publication bias and the small numbers and sizes of included studies.

Implications of the review for practice and research

Practice: The authors stated that use of TCAs should be limited to moderate and severe IBS given their numerous adverse effects. Patients should be started on subtherapeutic doses for depression. TCA formulations should be selected on an individual basis. Further recommendations included TCAs with the least anticholinergic effects for elderly patients or C-IBS and imipramine or amitriptyline for D-IBS and patients with insomnia.

Research: The authors stated that additional large RCTs with strict surveillance on compliance were needed to further explain the role of antidepressants for management of IBS in routine practice.

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