Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis

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CRD summary
The authors concluded that antidepressants were effective in the treatment of irritable bowel syndrome, and psychological therapies may be of comparable efficacy to antidepressants, but there was lack of high quality evidence. Given the risk of publication bias, the presence of statistical heterogeneity, and the low quality of available trials, the reliability of the authors’ conclusions regarding antidepressants is unclear.

Authors’ objectives
To assess the efficacy of anti-depressant medication and psychological therapies in alleviating symptoms of irritable bowel syndrome.

Searching
MEDLINE and EMBASE were searched up to May 2008. Cochrane Central Register of Controlled Trials (CENTRAL) was searched in 2007. Search terms were reported. No language restrictions were applied. Abstracts of conference proceedings and bibliographies of retrieved articles were handsearched.

Study selection
Randomised controlled trials (RCTs) of anti-depressants compared with placebo, or psychological therapies compared with control or treatment as usual, in adults (over 16 years) with a diagnosis of irritable bowel syndrome, were eligible for inclusion. Outcomes eligible for inclusion were global improvement of irritable bowel syndrome symptoms or improvement or cure of abdominal pain. The intervention had to last at least seven days, with a follow-up of at least seven days.

Included trials of antidepressants compared tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), or both (in varying doses) with placebo for a duration ranging from four weeks to three months. Included trials of psychological therapies compares self/therapist-administered cognitive behavioural therapy, multi-component psychological therapy, relaxation therapy, stress management programmes, dynamic psychotherapy or hypnotherapy (with symptom monitoring) with usual care, supportive therapy or placebo for a duration ranging from six weeks to six months. In all included trials, irritable bowel syndrome was diagnosed using clinical diagnosis, or Rome I or II criteria. The percentage of female participants in all included trials ranged from 44 to 100%. The majority of patients undergoing psychological therapy were in tertiary settings.

At the abstract stage, studies were selected by one reviewer. Retrieved articles were selected by two reviewers independently, with disagreements resolved by consensus.

Assessment of study quality
The methodological quality of the included trials was assessed using the Jadad scale. This was a three item checklist that assessed randomisation, allocation concealment and withdrawals/drop-outs; the maximum score was 5 points.

Two reviewers independently assessed the methodological quality of the included studies.

Data extraction
Outcomes were transformed into dichotomous outcomes of ‘symptom improvement’ or ‘no symptom improvement’. ‘Symptom improvement’ was defined as any improvement in outcomes on Likert scales, investigator defined improvement on continuous scales, or an improvement of more than one standard deviation on continuous scales. The number of patients showing symptom improvement was extracted for each group and used to calculate relative risks (RR) of symptoms or abdominal pain persisting, with 95% confidence intervals (CI).
The data were independently extracted by two reviewers on an intention-to-treat basis, where drop-outs were assumed to be treatment failures.

Methods of synthesis
Pooled relative risks with 95% confidence intervals were calculated using a random-effects model. One trial, with two separate treatment arms, was entered twice. Sensitivity analyses were conducted to explore potential sources of heterogeneity. The number-needed-to-treat (NNT), with 95% confidence intervals, was calculated from the reciprocal of the risk difference. Statistical heterogeneity was assessed using the $I^2$ statistic. Publication bias was assessed using funnel plots and Egger's test.

Results of the review
Thirty-two RCTs were included in the review (n=at least 2,239 patients); 19 trials assessed psychological therapies (n=1,278 patients), 12 trials assessed anti-depressants (n=789 patients) and one trial assessed both psychological and anti-depressant treatments (n=at least 172 patients). None of the trials of psychological therapies scored 4 or above on the Jadad scale; seven trials scored 3 and 12 trials scored 2 or less. Ten studies of anti-depressants scored 4 or more points on the Jadad scale; one trial scored 3 and two trials scored 2.

**Anti-Depressants:** Anti-depressant medication significantly improved symptoms of irritable bowel syndrome (IBS) (RR 0.66, 95% CI 0.57 to 0.78; 12 RCTs), but not abdominal pain (RR 0.66 95% CI: 0.41 to 1.06; five RCTs), compared with placebo. There was small but significant statistical heterogeneity ($I^2$=26.4%) and evidence of significant publication bias (p=0.02). The treatment effect was greatest in trials with low quality scores and in secondary care trials. There was no significant difference in treatment effect between tricyclic anti-depressants and tricyclic anti-depressants or in adverse effects between treatment and placebo groups.

**Psychological therapies:** IBS symptoms significantly improved with psychological therapies compared with treatment as usual or control therapy (RR 0.67, 95% CI: 0.57 to 0.79; 20 RCTs). There was evidence of significant statistical heterogeneity and publication bias ($I^2$ = 72.9%; Egger test p<0.0001). Subgroup analyses revealed that cognitive behavioural therapy, hypnotherapy, multi-component psychological therapy and dynamic psychotherapy all significantly improved IBS symptoms compared with control therapy or usual management by physicians. Relaxation training did not significantly improve symptoms. There was insufficient evidence to determine the impact of self-administered cognitive behavioural therapy or stress management.

Authors' conclusions
Anti-depressants were effective in the treatment of irritable bowel syndrome. Psychological therapies may be of comparable efficacy to anti-depressants, but there was a lack of high quality evidence.

CRD commentary
The review addressed a clear question with well-defined inclusion criteria. Three relevant databases were searched for articles in any language, reducing the risk of language bias. There was statistically significant evidence of publication bias. Appropriate steps were taken during the review process to minimise the risk of reviewer error and bias.

Suitable methods were taken to assess the methodological quality of the included trials. The quality of trials evaluating psychological therapies was low. There was evidence of statistical and clinical heterogeneity. Analyses were carried out to investigate potential sources of heterogeneity, but significant unexplained heterogeneity remained, so the pooling of trials may have limited value. Transforming continuous outcomes into dichotomous data meant that important data may have been lost and the definition of symptom improvement used made it difficult to assess whether the findings were clinically significant. Given the characteristics of the included trials, it was unclear the extent to which the findings may be generalised to primary care settings or to long-term outcomes. Also, given that there was only one trial directly comparing psychological therapies and anti-depressants, there was insufficient evidence to conclude that psychological therapies may have comparable efficacy to medication.

Given the risk of publication bias, the presence of statistical heterogeneity, and the quality of available trials, the reliability of the authors' conclusions regarding antidepressants is unclear, and there was insufficient evidence for their...
conclusions regarding psychological therapies.

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

**Practice:** The authors stated that current guidelines for the management of irritable bowel syndrome should be updated to include information on the efficacy of antidepressants and psychological therapies in the treatment of irritable bowel syndrome symptoms.

**Research:** The authors stated that further large, well-designed high quality RCTs are needed investigating the role of psychological therapies in the management of irritable bowel syndrome.

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