Treatment of functional gastrointestinal disorders with antidepressant medications: a meta-analysis

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Authors' objectives
To determine the efficacy of antidepressant medications in the treatment of functional gastrointestinal disorders.

Searching
MEDLINE (1966 to December 1988), PsycLIT (1974 to December 1998) and EMBASE (1974 to December 1998) were searched (search terms listed). The Cochrane library Controlled Trials Register and the Cochrane Database of Systematic Reviews were searched. Federal Research in Progress was searched to identify unpublished literature. References of retrieved articles were searched for additional studies.

Study selection
Study designs of evaluations included in the review
Randomised, placebo controlled studies in which at least one group was receiving an antidepressant and which reported measurable outcomes were included.

Specific interventions included in the review
Tricyclic antidepressants: amitriptyline (25-75mg), clomipramine (75mg), desipramine(50-150mg), tramipramine (30-50mg) and doxepin (75mg).

Antiserotonin agents: mianserin (30-120mg) compared to placebo.

Participants included in the review
Patients with irritable bowel syndrome and/or non-ulcer dyspepsia.

Outcomes assessed in the review
Proportion of participants improved, abdominal pain scores. Drug side effects were also reported.

How were decisions on the relevance of primary studies made?
All primary and review articles, as well as their references, were reviewed independently in duplicate. Disagreements were arbitrated by consensus.

Assessment of study quality
Study quality was assessed using a six-item instrument that included description of randomisation, adequacy of blinding, description of withdrawals and drop-outs, appropriateness of statistical analysis, description of inclusion and exclusion criteria and method for assessing adverse treatment effects. Study quality was assessed independently in duplicate, with substantial interrater agreement. Disagreements were arbitrated by consensus; when consensus could not be achieved discordant scores were averaged.

Data extraction
Data were abstracted on setting, country of origin, treatment characteristics (dose, duration, follow-up), number and demographic characteristics of participants, assessment of comorbid psychiatric disease, follow-up losses, adverse effects, and outcomes. Outcomes were recorded as either dichotomous or continuous variables, depending on how they were reported in the studies.

Methods of synthesis
How were the studies combined?
The DerSimonian and Laird random-effects model was used to calculate the summary odds ratio, risk difference (and NNT) and standardised mean difference. Analysis of the continuous outcome of pain score involved comparing standardised differences in mean between the control and treatment groups. Sensitivity analyses were conducted to test the sensitivity of results to potential unpublished studies, the negative studies with variance and size equal to the average among included studies needed to negate the review findings was calculated. The relative influence of each study was determined by sequentially eliminating studies and calculating summary measures. The effects of year of publication, type of syndrome (irritable bowel versus non-ulcer dyspepsia), study quality scores, and drug types (tricyclic versus mianserin) were assessed using meta-regression.

How were differences between studies investigated?
Heterogeneity was assessed visually with forest plots and statistically using the Q (chi square) statistic.

Results of the review
Eleven randomised placebo-controlled trials (n=737).

Quality scores of all included studies moderate: mean 4.0 (se=1.7), range 2-7.

Dichotomous outcome (abdominal pain improvement or "response to treatment") (n=7):
Results showed no evidence of heterogeneity (p=0.35) and there was no evidence of publication bias (p=0.46). Pooled odds ratio for improvement on therapy = 4.2 (95% CI: 2.3, 7.9). Pooled risk difference = 0.32 (95% CI: 0.15, 0.48), equivalent to NNT of 3.2 (95% CI 2.1, 6.7).

Continuous outcome data (abdominal pain scores) (n=9):
Results showed no evidence of heterogeneity (p=0.12), but showed a borderline suggestion of publication bias (p=0.08). The standardised mean difference was 0.9 sd units (95% CI: 0.6, 1.2).

Sensitivity analysis showed that there would have to be 37 negative studies with dichotomous outcomes and 157 negative studies with continuous outcomes to negate the meta-analysis odds ratio or standardised mean differences. The findings were not overly influenced by any one study with the odds ratio varying from 3.2 to 4.9 and the standardised mean difference from 0.5 to 3.0 with the sequential exclusion of individual studies. Meta-regression found no significant effect of year of publication (p=0.26), type of syndrome (p=0.73), study quality (p=0.39) or drug type (p=0.47).

Authors’ conclusions
This meta-analysis of 11 published, randomised controlled trials suggests that antidepressants may reduce the symptoms of functional gastrointestinal disorders. These results were consistent whether assessing continuous or dichotomous measure of outcomes, and all published results indicated that treatment was effective. The magnitude of benefit also appears clinically important.

CRD commentary
A good review of the area. A thorough literature search was conducted, methodological details are clearly presented and a comprehensive quality assessment was conducted. Heterogeneity was investigated and pooling was appropriate for the data available. The authors conclusions follow from the results presented, and the authors mention a number of limitations which should be borne in mind when interpreting the results.

Implications of the review for practice and research
Practice: The authors state that 'a tailored approach to using antidepressants in combination with other beneficial treatments, including addressing the psychological needs of patients, may be the optimal approach to management'.
Research: The authors state that 'future trials investigating antidepressant effects in functional gastrointestinal disorders need to be larger, longer, and more rigorously blinded, and should pay closer attention to the issue of the effect of treatment on depression. They should include serotonin reuptake inhibitors and investigate the potential benefit from combining different treatment'.

Bibliographic details

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Other publications of related interest

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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.