Meta-analysis of antisecretory and gastrokinetic compounds in functional dyspepsia

Authors' objectives
To assess the efficacy of gastrokinetic and antisecretory compounds in the treatment of functional dyspepsia.

Searching
MEDLINE and 'other standard databases' were searched.

Study selection
Study designs of evaluations included in the review
Randomised, double-blind, placebo-controlled trials using parallel or crossover design. The studies were included if they fulfilled the following criteria:
- the trial provided a clear definition of the study protocol and results, with all patients accountable;
- the trial had success clearly defined in terms of patients without symptoms, or patients with significant improvement in symptoms or some other such equivalent criteria.

Trials were excluded if they were of less than 1 weeks' duration; if the assessment criteria (success and failure) were unclear; and if they related to individual symptoms or measures of intensity. A summary of the reasons for exclusion, and the number of studies excluded from the meta-analysis, was presented.

Specific interventions included in the review
Treatment with the antisecretory agents cimetidine and ranitidine, and the gastrokinetic compounds cisapride and domperidone. Dosage exceeding the recommended maxima of 80 mg/day for domperidone, 30 mg/day for cisapride, 800 mg/day for cimetidine, and 600 mg/day for ranitidine, were excluded.

Participants included in the review
Trials were only included if they used the current definition of functional dyspepsia (see Other Publications of Related Interest no.1).

Outcomes assessed in the review
Each treatment outcome was classified as a success or failure. Success was defined, in terms of the patient, as no symptoms or a significant improvement at the end of the trial period.

How were decisions on the relevance of primary studies made?
Each paper was assessed by two reviewers, with any differences being resolved by a member of the company's medical department.

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

Data extraction
When possible, relevant data were extracted for the intention-to-treat analysis and the per protocol analysis. Data from period 1 within the crossover trials were included when available. The differences in the success rates (active minus control) were calculated for each study, along with the 95% confidence intervals (CIs). No details were given of the methods used to extract the data.
Methods of synthesis

How were the studies combined?
Differences in the success rates were estimated for all trials using the intention-to-treat analysis, when possible, and the per protocol analysis. The method of Fleiss (see Other Publications of Related Interest no.2) was adopted. For both analyses, studies of each drug were combined. In addition, the results from each class of drug (antisecretory and gastrokinetic) were combined and the results for all drugs were combined.

How were differences between studies investigated?
The authors do not state how any differences between the studies were investigated.

Results of the review

A total of 18 randomised controlled trials (RCTs) were included.

The number of studies included in the intention-to-treat analysis was as follows: 4 RCTs (N=325) assessed cimetidine, 2 RCTs (N=303) assessed ranitidine, 8 RCTs (N=415) assessed cisapride, and 4 RCTs (N=181) assessed domperidone.

Intention-to-treat analysis (active minus control).

The difference was 14% (95% CI: 3, 24) for cimetidine, 33% (95% CI: 23, 43) for ranitidine, and 24% (95% CI: 17, 31) overall for antisecretory compounds. The difference was 36% (95% CI: 28, 44) for cisapride, 35% (95% CI: 24, 46) for domperidone, and 36% (95% CI: 29, 42) overall for gastrokinetic compounds.

The overall difference for all drugs was 31% (95% CI: 26, 35).

Per protocol analysis.

The difference was 13% (95% CI: 1, 24) for cimetidine, 30% (95% CI: 19, 40) for ranitidine, and 22% (95% CI: 14, 30) overall for antisecretory compounds. The difference was 36% (95% CI: 28, 45) for cisapride, 36% (95% CI: 25, 46) for domperidone, and 36% (95% CI: 30, 43) overall for gastrokinetic compounds.

The overall difference for all drugs was 30% (95% CI: 25, 35).

Authors' conclusions

The gastrokinetic compounds were superior to the antisecretory compounds in the treatment of functional dyspepsia, despite the well-established limitations of meta-analysis.

CRD commentary

This review was clearly presented and included a discussion of some of the limitations of the review.

The inclusion and exclusion criteria were clearly defined. The authors acknowledged the following limitations of their review: the analysis related to short-term efficacy because there were no long-term controlled studies available; only two studies were available to assess the efficacy of ranitidine; a large number of studies were excluded due to the strict inclusion criteria; there was difficulty in clinically diagnosing functional dyspepsia because no objective criteria exist; the assessment to response was subjective; there was a potential publication bias; and sponsorship by pharmaceutical companies was not readily identifiable. Differences in the success rates for the individual studies, and the summary results, were presented graphically.

Full details of the literature search are required; these should include a full list of the databases searched, the dates over which the search was conducted, and any language restrictions that were applied. No information was given of the method used to extract the data. Validity was not assessed. More comprehensive information on the primary studies would have been welcome, including the characteristics of the patients (e.g. age) and concurrent drug therapy, drug dosages, the number of drop-outs, adverse reactions, and the duration of follow-up. The results presented showed heterogeneity, and thus pooling was questionable. The intention-to-treat analysis included results from studies where
the intention-to-treat data were unavailable, and therefore, the per protocol analysis was used instead. Consideration
could have been given to conducting a separate analysis for those trials in which intention-to-treat data were available.
No comparative trials of antisecretory versus gastrokinetic agents were included, and thus any comparison between the
two classes of agent is invalid.

In view of the lack of validity assessment, a lack of consideration of adverse reactions, and the other aspects
highlighted, the evidence presented does not provide support for the authors' conclusions.

**Implications of the review for practice and research**
The authors suggest that a large study comparing the various treatments for functional dyspepsia is needed to confirm
the findings.

**Bibliographic details**

**PubMedID**
9649020

**Other publications of related interest**
randomised controlled clinical trials. J Clin Gastroenterol 1989;11:169-77. 2. Fleiss JL. The statistical basis of meta-

**Indexing Status**
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**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.