Treatment of non-ulcer dyspepsia: a meta-analysis of placebo-controlled prospective studies

Authors' objectives
To evaluate the efficacy of histamine H2-receptor antagonists and gastroprokinetics for non-ulcer dyspepsia, compared with placebos.

Searching
MEDLINE and PubMed were searched from 1978 to 1998. References in textbooks, review articles and previous systematic reviews were reviewed, and pharmaceutical companies were contacted for additional material.

Study selection
Study designs of evaluations included in the review
Randomised, double-blind placebo-controlled trials of at least 2 weeks' duration. Parallel and crossover designs were included. The duration of the trials ranged from 2 weeks (1 trial) to 6 weeks (3 trials), with the majority being 4 weeks.

Specific interventions included in the review
Studies were included if they compared H2-receptor antagonists (cimetidine or ranitidine) or gastroprokinetics (cisapride or domperidone) with placebo, and had a treatment duration of at least two weeks. The dose ranges were: cisapride, 12 to 30 mg/day; domperidone, 30 to 40 mg/day; cimetidine, 800 to 1,000 mg/day; ranitidine, 300 mg/day.

Participants included in the review
Participants who were being treated for non-ulcer or functional dyspepsia, including those with symptoms of early satiety, postprandial fullness, nausea, bloating, epigastric pain, or heartburn. However, it was not a requirement in all trials that patients had undergone endoscopy to rule out peptic ulcer or gastro-oesophageal reflux. Studies which included patients with Helicobacter pylori infection were not excluded.

Outcomes assessed in the review
The number of patients categorised as treatment success. This was defined as without symptoms, with excellent or good results, with significant improvement of symptoms, or equivalent phrases. Trials were included only if they had clear clinical criteria of treatment success.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not report the method used to assess validity, other than the inclusion criterion for trial design.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on the study design (parallel or crossover), treatment duration and dosage, the numbers of participants in each treatment group, and the numbers of treatment successes.

Methods of synthesis
How were the studies combined?
The effect size was estimated as the difference in treatment success between the drug and placebo, with confidence intervals (CIs) calculated by Yates' correction for continuity (see Other Publications of Related Interest no.1).
effects were combined using the DerSimonian and Laird random-effects model (see Other Publications of Related Interest no.2). There was no indication as to the method used to include crossover trials in the meta-analysis.

How were differences between studies investigated?
The homogeneity of the results of the included trials was assessed using the test suggested by Hedges and Olkin. (See Other Publications of Related Interest nos.3) and the recommendations of Whitehead and Whitehead (see Other Publications of Related Interest no.4). Where heterogeneity was detected in relation to the differences found between the treatment and placebo groups, the homogeneity of the success rates of the placebo groups was subsequently tested. (see Other Publications of Related Interest no.5). There was no further investigation of the possible sources of heterogeneity.

Results of the review
Nineteen trials of gastroprokinetics (n=1,091) were included: 13 of cisapride and 6 of domperidone. Ten trials of histamine H2-receptor antagonists (n=1,540) were included: 7 of cimetidine and 3 of ranitidine.

The treatment success was defined as the difference between the proportion of successes under the treatment and the proportion under placebo. For example, 0.40 indicates that an estimated 40% more patients would be successfully treated with the treatment than with placebo. Gastroprokinetics.

The pooled estimate of treatment success for cisapride versus placebo was 0.34 (95% CI: 0.21, 0.46) in favour of cisapride. There was significant statistical heterogeneity between the studies. The pooled estimate of treatment success for domperidone versus placebo was 0.56 (95% CI: 0.48, 0.64) in favour of domperidone. Statistical heterogeneity was not significant.

The overall pooled estimate of treatment success for both gastroprokinetics was 0.40 (95% CI: 0.30, 0.50) in favour of treatment, although statistical heterogeneity was highly significant (P<0.00001). When the success rates of the placebo groups were tested for heterogeneity, it was not statistically significant among the cisapride studies or when all the gastroprokinetic studies were pooled. However, it was significant among the domperidone studies alone. All meta-analyses were conducted using a random-effects model, because of the apparent heterogeneity.

Histamine H2-receptor antagonists.

The pooled estimate of treatment success for cimetidine versus placebo was 0.18 (95% CI: 0.11, 0.25) in favour of cimetidine. Statistical heterogeneity was not significant. The pooled estimate of treatment success for ranitidine versus placebo was 0.27 (95% CI: 0.09, 0.45) in favour of ranitidine. There was significant statistical heterogeneity between the studies.

The overall pooled estimate of treatment success for both histamine H2-receptor antagonists was 0.20 (95% CI: 0.13, 0.28) in favour of treatment, although statistical heterogeneity was significant (P=0.03). When the success rates of the placebo groups were tested for heterogeneity, it was not statistically significant among the cimetidine studies, the ranitidine studies, or when all the histamine H2-antagonist studies were pooled. All meta-analyses were conducted using a random-effects model, because of the apparent heterogeneity.

Both class of drug showed a positive effect compared with placebo. The pooled estimates of the difference in proportion of success from placebo, along with 95% confidence limits, were as follows:

for cisapride, 0.34 (95% CI: 0.21, 0.46, P<0.05);
for domperidone, 0.56 (95% CI: 0.48, 0.64, P<0.05);
for the gastroprokinetics (cisapride and domperidone), 0.40 (95% CI: 0.30, 0.51, P<0.05);
for cimetidine, 0.18 (95% CI: 0.11, 0.25, P<0.05);
for ranitidine, 0.27 (95% CI: 0.09, 0.45, P<0.05);
for histamine H2-receptor antagonists (cimetidine and ranitidine), 0.20 (95% CI: 0.12, 0.28, P<0.05).

**Authors' conclusions**
Based on these data, both treatments were significantly more effective than placebo. The gastroprokinetics (cisapride and domperidone) were more effective than the histamine H2-receptor antagonists (cimetidine and ranitidine).

**CRD commentary**
The review addressed a well-defined question and had clear inclusion criteria. The search strategy was reasonable, although it is possible that trials were missed. Double-blind, randomised controlled trials provide a good evidence base provided they are well-conducted, which we were not able to determine; there was no report of any further validity assessment beyond inclusion of the stated study design. The processes of determining eligibility and extracting the data were not described, and thus could not be evaluated. The basic characteristics of the individual studies were well-presented, but there were no comments on particular characteristics, such as details of the participants. It was not stated whether an intention to treat-analysis was carried out. The possibility of publication bias was mentioned but not investigated.

Heterogeneity was assessed, and was explored in relation to differential placebo effects. A sensitivity analysis would have been useful to investigate this hypothesis further, together with the assessment of other possible sources of heterogeneity.

The evidence supported the authors' general conclusion that the four drugs were effective compared with placebo. However, their relative effectiveness was much less certain, due to the heterogeneity found in relation to the cisapride and ranitidine trial results, which was not fully explored in this review. Consequently, the estimated treatment effects (see the 'Results' section) should be treated with caution in terms of the relative effectiveness. It cannot be concluded from the evidence presented in this review that gastroprokinetics are more effective than histamine H2-receptor antagonists, since none of the included trials compared one drug with another; this comparison should be considered only as hypothesis.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors conclude that there is a need for trials of longer duration, given that the condition being treated is often a long-term one and that the identified trials were of 2 to 6 weeks' duration.

**Bibliographic details**

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**Other publications of related interest**

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Subject indexing assigned by NLM

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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.