H2-receptor antagonists in the treatment of functional (nonulcer) dyspepsia: a meta-analysis of randomized controlled clinical trials

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Authors' objectives
To perform a meta-analysis evaluating the efficacy of H2-receptor antagonists in functional (nonulcer) dyspepsia.

Searching
MEDLINE was searched from 1966 to 1999 using the MeSH terms 'Dyspepsia' and 'Histamine-H2-Antagonists'. In addition, cited references were handsearched and the Cochrane Controlled Trials Register was searched. The search was limited to articles written in the English language and published in full. Abstracts were not evaluated.

Study selection
Study designs of evaluations included in the review
The included studies had to be randomised, double-blind, placebo-controlled trials of H2-blockers with a minimum of 20 patients enrolled. The studies used a parallel-group design, a two-period crossover design or a six-period multicrossover design. The duration of the studies ranged from 12 days to 6 weeks.

Specific interventions included in the review
Studies that investigated the treatment of functional dyspepsia with H2-receptor antagonists versus placebo were included. Fourteen studies used the drug cimetidine, with doses ranging from 0.8 to 1.2 g/day; 7 used ranitidine, all at a dose of 150 mg twice daily; and one used nizatidine at a dose of 300 mg/day.

Participants included in the review
Patients with functional dyspepsia, also called nonulcer or essential dyspepsia.

Fifteen studies specifically stated that patients with oesophagitis evident on endoscopy were excluded, while only one study appears to have included such patients; it was unclear in the remaining 6 studies whether patients with oesophagitis were included or excluded. Five studies specifically stated that patients with irritable bowel syndrome were excluded, while 9 studies included such patients; it was unclear in the remaining 8 studies whether patients with irritable bowel syndrome were included or excluded. Ten studies clearly excluded patients with a history of peptic ulcer disease; this was not an exclusion criteria in the remaining studies. Eleven studies specified stopping acid suppression therapy for a period of time (1 to 4 weeks) prior to endoscopy. The remaining studies did not specify whether or not the patients were taking acid suppression therapy prior to enrolment in the study.

The mean age of the patients in the included studies ranged from 28 to 51 years, and the proportion of male patients ranged from 30 to 65%.

Outcomes assessed in the review
The efficacy of H2-receptor antagonists was assessed. There was considerable variation in the outcome measures used by the different studies and how they were measured. The main outcome measures used for the meta-analysis were global assessment by the patient of the treatment effect, and epigastric pain or discomfort. The decision to use these outcome measures was dictated by the fact that they were reported in the most studies.

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. [A: One author initially assessed studies for relevance. The abstracts of potentially relevant articles were reviewed by two authors].

Assessment of study quality
The authors do not report the method used to assess validity, or how the validity assessment was performed. [A: Randomisation, blinding, use of placebo-controls and number of patients enrolled in each study were assessed; those studies which did not meet the pre-defined study design criteria were excluded. Validity was assessed independently by two authors and any disagreements were resolved through discussion.]

Data extraction
A data collection form was developed and was used to record methodological criteria such as study design, duration of treatment, drug regimen, age and gender of the patients, study protocol, and the outcome measures used to determine efficacy. For each study, the log odds ratio and a 95% confidence interval (CI) was calculated.

The authors do not state how many of the reviewers performed the data extraction. [A: Data extraction was performed collectively by all three authors.]

Methods of synthesis
How were the studies combined?
The results were combined by a meta-analysis, using the random-effects method of DerSimonian and Laird (see Other Publications of Related Interest). The overall odds ratio (OR) was reported, along with the 95% confidence interval (CI) and P-values. Publication bias was not assessed.

How were differences between studies investigated?
Before attempting to combine the results from different studies, the authors tested the homogeneity of the ORs using the Q-statistic.

Results of the review
Twenty-two randomised, double-blind, placebo-controlled trials with a total of 2,959 patients were included in the review. Fourteen trials used a parallel group design, 2 used a two-period crossover design, and 6 used a six-period multicrossover design. The sample sizes of the individual studies ranged from 21 to 509. The number of studies that could be used to pool the results for the different outcome measures varied: 7 studies (940 patients) were used for global assessment by the patient of the treatment effect; 5 studies (1,299 patients) were used for complete relief of pain; and 4 studies (589 patients) were used for improvement in pain.

H2-receptor antagonists were found to be superior to placebo in 15 of the 22 studies. However, the number of studies that could be used for pooling the results varied for the different outcome measures.

Global assessment: only 7 studies provided sufficient data to calculate the number of patients who were improved; these 7 studies were combined in a meta-analysis. A moderate beneficial effect of H2-receptor antagonists was demonstrated for global assessment of dyspepsia symptoms with an OR of 1.48 (95% CI: 0.94, 2.32). The P-value for the homogeneity test was 0.047, suggesting that there was significant heterogeneity among the studies. Results in favour of H2-blockers were seen in the studies that did not state that patients with a prior peptic ulcer disease were excluded. Similarly, in 4 of the 5 studies in favour of H2-blockers, oesophagitis was not clearly stated as a reason for exclusion from the study. The 2 studies that excluded both previous peptic ulcers and oesophagitis did not demonstrate a benefit of active treatment over placebo.

Epigastric pain: based on 7 studies, the OR for complete relief of pain for drug- versus placebo-treated patients was 1.81 (95% CI: 1.15, 2.84, P<0.01). The P-value for the homogeneity test was 0.017, suggesting that there was significant heterogeneity among the studies. The OR for improvement of pain was 2.33 (95% CI: 1.63, 3.32, P<0.0001). The P-value for the homogeneity test was 0.67, suggesting that for this outcome measure there was no significant heterogeneity among the studies. Thus, showing a clear benefit of H2-antagonists for the relief or improvement of epigastric pain. As with the global assessment outcome measure for absence or improvement of epigastric pain, studies that excluded previous peptic ulcer disease did not show a benefit of the H2-receptor antagonists.
Authors' conclusions
There was some evidence to suggest that H2-receptor antagonists are superior to placebo in functional dyspepsia.

CRD commentary
The authors stated their review question and the inclusion criteria clearly. The literature search was described clearly, but only two databases were searched and the authors restricted their search to English language articles published in full. This narrow search strategy may have missed relevant studies, allowing the introduction of selection bias. No analyses were conducted to assess publication bias.

The validity of the individual studies was not formally assessed. The authors did not report details of the decision-making process involved in study selection and data extraction, such as how many of the reviewers were involved, whether the studies were examined independently, or whether the reviewers were blinded to source.

Details of the studies were reported adequately in tabular format, supplemented by narrative discussion. However, the authors stated that some important information was lacking from some of the individual studies, such as whether patients with other gastrointestinal disorders were excluded from the studies and whether the patients were taking acid suppression therapy prior to enrolment in the study.

Twenty-two studies were identified by the review, but only five could be combined in the meta-analysis of complete relief of epigastric pain, four in the meta-analysis for improvement of epigastric pain, and seven in the meta-analysis of global assessment by the patient, due to the variation in the outcome measures used in the individual studies. The authors stated that the lack of consensus on how to measure outcome, and the absence of a validation of the outcome measures, has been identified as a problem in studies of functional dyspepsia. They acknowledge that the combined number of patients for the meta-analysis of each outcome measure was relatively small.

There was only significant homogeneity for the outcome of improvement of pain. Therefore, it may not have been appropriate to pool the results for global assessment by the patient of treatment effect, and for complete relief of pain. The authors pointed out that studies which excluded patients with previous peptic ulcer disease, and those that did not exclude such patients, had results in different directions. Therefore, it may not have been appropriate to pool the results of these two groups of studies.

The authors identified limitations with crossover design studies in this area, which may not have a washout period and may not demonstrate a return to baseline. The authors also acknowledged the problems of dosage and duration of therapy, which may not have been optimal in the included studies.

The authors' conclusions should be interpreted with caution owing to the limitations highlighted.

Implications of the review for practice and research
Practice: The authors state that it is probably not unreasonable to prescribe H2-blockers for functional dyspepsia patients.

Research: The authors state that larger studies evaluating higher doses of H2-receptor antagonists and of longer duration are necessary to determine the exact effect size. They also state that, given the recent promising data on the use of proton-pump inhibitors in functional dyspepsia, comparisons with H2-blockers will be necessary to better define the most efficacious treatments.

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Other publications of related interest

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