Meta-analysis: the effects of placebo treatment on gastro-oesophageal reflux disease
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CRD summary
The authors concluded that the placebo response rate in controlled trials of patients with gastro-oesophageal reflux disease was substantial; it appeared to be independent of erosive/non-erosive oesophagitis, but related to the class of acid suppression treatment studied. These conclusions appeared to reflect the evidence, but incomplete review methodology reporting and differences between trials make it difficult to assess their reliability.

Authors' objectives
To evaluate the size of the placebo response in randomised controlled trials (RCTs) of patients treated for gastro-oesophageal reflux disease and to identify factors influencing the placebo response rate.

Searching
MEDLINE, the Cochrane Register of Controlled Trials (CENTRAL) and EMBASE were searched from inception to 2009 for studies published in English. Search terms were reported. Reference lists of retrieved studies were screened.

Study selection
Double-blind, placebo-controlled randomised controlled trials (RCTs) of at least 20 patients who received acute treatment for gastro-oesophageal reflux disease with either a proton-pump inhibitor or an H$_2$-receptor antagonist for at least two weeks were eligible for inclusion. Eligible trials had to report relief of heartburn on the final day of the trial as a primary outcome. Trials were required report the number of patients responding (with relief of heartburn), provide an explicit definition of relief of heartburn, and restrict co-interventions for reflux except for rescue treatments (but excluding antisecretory drugs).

The included trials compared placebo with proton-pump inhibitors (dexlansoprazole MR, esomeprazole, omeprazole, pantoprazole or rabeprazole) or H$_2$-receptor antagonists (cimetidine, famotidine, nizatidine and ranitidine). The frequency of treatment generally ranged from one to twice daily. Most trials involved patients with non-erosive reflux disease; other trials included patients with erosive oesophagitis, or both erosive and non-erosive disease. Most trials were in patients of Caucasian or mixed ethnicity. The median age of patients was 49 years (range 18 to 85 years); just over half were women. Included trials used different definitions for relief of heartburn that ranged from ‘complete relief or resolution of 24-heartburns’ to ‘sufficient or substantial control of heartburn’ to ‘complete relief of upper gastrointestinal symptoms’. The included trials were conducted between 1983 and 2009.

The review also separately analysed trials that compared endoscopic procedures with placebo treatment in patients with gastro-oesophageal reflux disease, but it was not clear if this was part of a systematic review, so these data were not summarised in this abstract.

The authors did not state how papers were selected for the review.

Assessment of study quality
Three reviewers independently assessed trial quality using the Jadad criteria (reporting of randomisation, blinding and withdrawals). Disagreements were resolved by a fourth reviewer.

Data extraction
Three reviewers independently extracted sufficient data to permit calculation of an odds ratio (OR) with 95% confidence interval (CI). Placebo and treatment response rates and standard deviations (SDs) were calculated for each study. Disagreements were resolved by a fourth reviewer.

Methods of synthesis
Pooled odds ratios and 95% confidence intervals were calculated using a random-effects model. Statistical heterogeneity was assessed using the Q statistic and the $I^2$ statistic. Subgroup analysis was conducted to examine the
influence of the active drug type (proton-pump inhibitor or H₂ receptor antagonist).

Meta-regression was used to explore the association (measured using contingency coefficients) between placebo response rate and the following variables: Jadad score; duration of active treatment; number of visits during active treatment; frequency of treatment; and length of run-in period.

A cumulative meta-analysis was conducted to examine the influence of publication year.

The possibility of publication bias was explored using Begg and Mazumdar's test, Egger's test, and Rosenthal's classic fail-safe N.

**Results of the review**

Twenty-four double-blind RCTs were included in the review (n=9,988 patients from table 2). Jadad scores ranged from 2 to 5 of 5 points. The duration of active treatment ranged from 14 to 84 days; the duration of the run-in period ranged from none to 14 days.

The authors stated that significant heterogeneity was found (p=0.0001; $I^2=83\%$), but it was not clear which analysis this referred to.

The overall mean placebo response rate was 18.85% (SD 12.72%; range 2.94 to 47.06). The overall mean response rate for active treatment groups was 43.49% (SD 13.80%, range 21.59 to 70.22). Active treatment was associated with a significantly higher response rate than placebo (OR 3.71, 95% CI 2.78 to 4.96).

**Variables associated with placebo response rates**

Placebo response rates were lower (p=0.05) in trials of proton-pump inhibitor treatment (14.51%) compared with trials of H₂-receptor antagonist treatment (24.69%). These findings were also suggested by the subgroup analyses (OR 2.07, 95% CI 1.66 to 2.57, 10 H₂-receptor antagonist RCTs; OR 5.27, 95% CI 3.77 to 7.37, 14 proton-pump inhibitor RCTs). Meta-regression appeared to suggest no significant association between type of treatment and placebo response (p=0.16).

Placebo response rates were lower (but not statistically significant, p=0.246) in patients with erosive disease (11.87%) compared with non-erosive disease (18.31%). Meta-regression also suggested no significant association (p=0.896). Placebo response rates were not significantly correlated with other variables tested.

Cumulative meta-analysis showed that the odds ratio for treatment response declined from 1983 to 1991, then increased in 2009.

There was some evidence of publication bias (Begg and Mazumder's test p=0.094; Egger's test p=0.041).

**Authors' conclusions**

The placebo response rate in RCTs for gastro-oesophageal reflux disease was substantial. A lower placebo response was associated with testing of proton-pump inhibitors, but not the presence of erosive oesophagitis.

**CRD commentary**

The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched, but no attempts were made to minimise publication or language bias; tests suggested the presence of publication bias. Methods were used to minimise reviewer errors and bias in the extraction of data and assessment of validity, but it was not clear whether similar steps were taken for study selection.

Only double-blind RCTs were included, but other Jadad criteria were not reported in full, as only aggregate scores. Data were pooled using meta-analysis, but results of testing for statistical heterogeneity were not reported for all analyses. The influence of various factors on placebo response rates was examined. The authors acknowledged the heterogeneity among trials, but their analyses were unable to identify possible sources.
The authors’ conclusions appeared to reflect the evidence, but incomplete reporting of review methods and differences between trials make it difficult to assess their reliability.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that there is a need to investigate factors that influence the placebo response in gastro-oesophageal reflux disease trials and to use this information to design future clinical trials.

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