Discontinuation rates of Helicobacter pylori treatment regimens: a meta-analysis
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Authors' objectives
To determine what factors in treatment regimes for Helicobacter pylori (H pylori) are associated with increased discontinuation rates.

Searching
Articles published in the English language were sought in MEDLINE from 1990 to 1996 using the following terms: 'Helicobacter pylori'; 'drug therapy' (explode); PT = 'clinical trials'; and TG 'human'. Bibliographies of review articles on H pylori were examined.

Study selection
Study designs of evaluations included in the review
Prospective, comparative clinical trials were included.

Specific interventions included in the review
Drug regimes in the treatment of H pylori infection were included. Regimes consisted of the combinations of the following drugs: bismuth; omeprazole; amoxicillin; clarithromycin; metronidazole; azithromycin; tetracycline; ranitidine; sucralfate; cimetidine; doxycycline; lansoprazole; ciprofloxacin; and famotidine. Number of doses per day ranged from 1 to 16. Drugs that were unavailable in the United States (e.g. plaunatol, tinidazole, spiramycin) and drugs traditionally not effective against H pylori (e.g. cefixime, clindamycin) were excluded.

Participants included in the review
Adult patients (18 years of age or more) diagnosed with duodenal ulcer, gastric ulcer or non ulcer dyspepsia were included. Children (age < 18 years) and patients with gastric malignancy were excluded.

Outcomes assessed in the review
Drop-out rates (categorized as due to adverse-effects, noncompliance, lost to follow-up, or unknown) and factors that could potentially affect drop-out rates were assessed.

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 reviewers performed the selection.

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

Data extraction
The following factors that could potentially affect drop-out rates were extracted: number of drugs and doses per day, duration of therapy, whether regime contained a bismuth compound or proton pump inhibitor, whether patients received compliance counselling, whether adverse effects were documented, and whether pill counts were performed. In addition, tables reported in the review included sample size, treatment, and total number of drop-outs. The authors do not state how data were extracted for the review, or how many of the reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
Results from all studies were pooled to consider risk of drop-out as a function of number of daily doses, number of drugs and doses per day, bismuth or proton pump inhibitor use, compliance counselling, ADR documentation, pill...
counting, and number of agents. Univariate analysis was conducted with each potential factor to determine an association between that factor and drop-out. The association was also tested after controlling for the number of daily doses. Multivariate analysis, using logistic regression, was used to determine the effect of each factor after controlling for all others. A probability of 0.05 or less was accepted as statistically significant and the Bonferroni correction was used for multiple analysis. Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
Heterogeneity was tested using the Q statistic.

**Results of the review**
Sixty-three studies were included (5996 patients).

Association of various factors:

Influence of number of drugs in regime.

Regimes containing three or more agents had higher drop-out rates in univariate analysis than those with one of two (P = 0.039). After controlling for all other characteristics, regimes with more than two drugs had a lower drop-out rate (P = 0.0124).

There was no statistical significance in drop-out rates due to adverse effects based on the number of agents in a regime.

The number of drugs in the regime had a significant impact on drop-out rates due to noncompliance in univariate analysis (P = 0.001). After controlling for number of doses per day, the drop-out rate was significantly lower with regimes of three or more agents compared with those of one or two (P = 0.0001).

Influence of the number of doses per day.

Regimes containing three or fewer doses/day had a lower drop-out rate than regimes with 4 to 6 doses/day (P = 0.001), 7 to 11 doses/day (P = 0.009) or 12 or more (P < 0.0001). Rates were similar in regimes with 4 to 6 and 7 to 11 doses/day. Patients taking 7 to 11 doses/day were less likely to drop-out than those taking 12 or more (P = 0.0018).

After controlling for the number of doses/day, drug regimes with adverse reaction counselling (P = 0.0001), short duration of therapy (P = 0.0110), and fewer agents (P = 0.0322) had higher drop-out rates.

After controlling for other factors, regimes with a proton pump inhibitor (P = 0.0343), and compliance counselling (P = 0.0322) had lower rates.

Drop-out due to adverse effects.

After controlling for the number of doses/day, regimes with bismuth (P = 0.0001), and ADR documentation (P = 0.0080) had significantly high drop-out rates due to adverse reactions and those with a proton pump inhibitor has significantly low rates (P = 0.0168).

Multivariate analysis controlling for all other factors, showed higher drop-out rates for regimes with bismuth and ADR documentation.

Drop-out due to noncompliance.

Multivariate analysis showed no changes in drop-outs due to noncompliance.

Heterogeneity and publication bias.

There was no evidence of heterogeneity for total drop-outs (Q = 26.46, P = 0.99), drop-outs due to side-effects (Q = 7.68, P = 0.94), or those due to noncompliance (Q = 2.92, P = 0.89).
There was no evidence of publication bias in the symmetry of the funnel plot.

**Authors' conclusions**
The main finding was that drug regimes for eradication of H pylori that have a high number of doses per day result in higher discontinuation rates than regimes with fewer doses per day.

**CRD commentary**
The aims were stated and inclusion criteria defined in terms of study design, intervention and participants. By restricting primary studies to those published in the English language and identified in one database, other relevant studies may have been omitted. No attempt was made to locate unpublished material, thus raising the possibility of publication bias and methods used to select studies were not described. Some relevant information on the included studies was presented in tabular format but there was no mention of criteria used to diagnose participants as having peptic ulcer or non ulcer dyspepsia or to determine H pylori status. No comment was made on the potential influence of the efficacy of different regimes on drop-out rates. Statistical heterogeneity and publication bias were assessed. Validity was not assessed and no account was taken of study validity in the analysis.

Evidence supports the author's conclusions, though interpretation of the results is not complete without taking the relative efficacy of the various regimes into account.

**Implications of the review for practice and research**
Practice: The authors state that regimens containing three or fewer doses per day are ideal.

Research: The authors state that future trials in H. pylori-induced peptic ulcer disease should include minimum compliance standards, adverse effect diaries or interviews, and intention-to-treat analysis. Based on these results, investigating multiple-drug dosage forms in a large scale clinical trial could be the next step.

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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.