5-HT3 receptor antagonists vs traditional agents for the prophylaxis of postoperative nausea and vomiting

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Authors' objectives
To evaluate the effectiveness of 5HT3 receptor antagonists, compared with traditional anti-emetics, for the prevention of post-operative nausea and vomiting (PONV) in all types of surgery.

Searching
MEDLINE, EMBASE, and Pre-MEDLINE were searched from 1966 to October 1999 for articles published in the English language. References from retrieved articles were also manually searched. The search terms included 'nausea', 'vomiting', 'emesis', 'postoperative', 'surgery', 'ondansetron', 'granisetron', 'tropisetron', 'dolasetron', 'metoclopramide', 'droperidol', 'prochlorperazine', 'perphenazine', 'dimenhydrinate' and 'cyclizine'. Trials published more than once, data published in only abstract form, and unpublished data were excluded.

Study selection
Study designs of evaluations included in the review
Randomised, double-blinded controlled clinical trials were included.

Specific interventions included in the review
The studies had to compare any 5HT3 receptor antagonist (ondansetron, dolasetron, tropisetron, granisetron) with at least one other prophylactic drug therapy in order to be included. Studies comparing only combinations of anti-emetics were excluded.

Participants included in the review
Adults (over 18 years of age) receiving general anaesthesia were included.

Outcomes assessed in the review
Studies evaluating PONV, vomiting or nausea as an end point were included in the review.

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 a method for assessing validity, although assessment of methodological quality was built into the inclusion and exclusion criteria. The authors do not report a method for assessing validity, but each report was read by all three authors independently to assess adequacy of randomisation and blinding, and to assess description of withdrawals.

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. It is stated, however, that discrepancies of data extraction were resolved by group consensus. Data were extracted on the following: study; year; sample size; patient characteristics; surgery type; type of 5HT3 antagonist; type of traditional agent; dosage, timing and route of administration of anti-emetic agents; anaesthetic regimens; and incidences of PONV, vomiting, nausea and adverse events. Attempts were made to acquire additional information from investigators, as required.
Methods of synthesis
How were the studies combined?
The incidences of PONV, nausea, vomiting and adverse events were analysed separately. Odds ratios (ORs) with 95% confidence intervals (CIs), and the summary ORs were calculated using a random-effects model, according to the method of DerSimonian and Laird (see Other Publications of Related Interest no.1). Publication bias was investigated through visual inspection of funnel plots whereby ORs were plotted against study sample size (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
The Cochran Q method was used to test for heterogeneity (see Other Publications of Related Interest no.2). Homogeneity was assumed when the p-value was greater than 0.10. Heterogeneity was also evaluated visually using Galbraith plots (see Other Publications of Related Interest no.3). Where heterogeneity was detected, accepted methods for the exploration of statistical heterogeneity using clinical parameters were used (see Other Publications of Related Interest no.4). Trials were subgrouped by type of surgery, traditional anti-emetic agent, induction agent, previous history of PONV, and induction anaesthetic. Sensitivity analyses were performed by exploring for extremes of outcomes, with grouping by traditional anti-emetic agent and type of surgery. The robustness of the analysis was further evaluated using a technique based upon the 'file drawer' problem, whereby the number of unretrieved studies averaging null results required to bring the new overall p-value to the brink of significance (p=0.05) was calculated for each end point (see Other Publications of Related Interest no.5).

Results of the review
Forty-five trials were identified, of which 4 were excluded: one due to duplication of publication, one due to uninterpretable results, and two because patients did not receive general anaesthesia. In total, 41 RCTs were included in the review with a total of 6,638 participants: 2,855 receiving a 5HT3 antagonist and 3,783 receiving traditional agents.

The nausea end point was excluded from analysis because of the lack of a standard definition across trials.

PONV (32 studies): there was a 46% reduction in the odds of PONV in the 5HT3-treated group (OR=0.54, 95% CI: 0.42, 0.71, p<0.001; number-needed-to-treat, NNT=10, 95% CI: 7, 15)). The test for heterogeneity of treatment effect was non significant (p=0.21). Visual inspection of the corresponding funnel plots revealed no evidence of publication bias. A significant benefit favouring 5HT3 antagonists was found for gynaecological and orthopaedic surgery. In comparison with traditional anti-emetic agents, 5HT3 antagonists demonstrated a beneficial effect on the incidence of PONV: 5HT3 provided a 39% reduction compared with droperidol (OR=0.61; 95% CI: 0.42, 0.89, p<0.001; NNT=14, 95% CI: 8, 46) and a 56% reduction compared with metoclopramide (OR=0.44, 95% CI: 0.31, 0.62, p <0.001; NNT=6, 95% CI: 5, 10)). There were insufficient trials involving other traditional anti-emetics to justify further pooling.

Vomiting (34 studies): there was a 38% reduction in the odds of vomiting in the 5HT3-treated group (OR=0.62, 95% CI: 0.48, 0.81, p<0.001; NNT=16, 95% CI: 10, 44). The test for heterogeneity of treatment effect was non significant (p=0.19). Visual inspection of the corresponding funnel plots revealed no evidence of publication bias. A benefit favouring 5HT3 antagonists was found for gynaecological surgery only (OR=0.61, 95% CI: 0.44, 0.85, p <0.001; NNT=22, 95% CI: 11, infinity). Compared with traditional anti-emetic agents, 5HT3 demonstrated a beneficial effect on vomiting over droperidol (OR=0.56, 95% CI: 0.41, 0.76, p<0.001; NNT=12, 95% CI: 7, 32) and metoclopramide (OR=0.50, 95% CI: 0.32, 0.77, p<0.001; NNT=10, 95% CI: 7, 23)). There were insufficient trials involving other traditional anti-emetics to justify further pooling.

Adverse events: there were no differences between the 5HT3 antagonists and the traditional anti-emetics in the overall rate of adverse reactions. Headache was the most commonly experienced adverse effect, occurring in 14.6% of patients in whom it was evaluated (12 trials); it was more common in the 5HT3 group than in the traditional anti-emetic group (OR=1.65, 95% CI: 1.35, 2.02, p<0.001; number- needed-to-harm, NNH=28, 95% CI: 15, 200). Sedation, which occurred in 9.6% of the patients evaluated (11 trials), was more common in the traditional anti-emetic group than in the 5HT3 group (OR=0.47, 95% CI: 0.32, 0.64, p<0.001; NNH=14, 95% CI: 9, 26). Dizziness was found in 7.6% of patients evaluated (10 trials); the incidence was not different between the two groups. Compared with droperidol, 5HT3 antagonists were associated with a higher incidence of headache (OR=1.68, 95% CI: 1.34, 2.11, p<0.001; NNH=15, 95% CI: 10, 35) and a lower incidence of sedation (OR=0.39, 95% CI: 0.29, 0.54, p<0.001; NNH=12, 95% CI: 8, 20).
No differences were detected between 5HT3 antagonists and metoclopramide for the adverse effects evaluated.

Heterogeneity analyses: for the PONV end point, 7 trials fell outside the area in which 95% of trial results would be expected to lie, and were therefore, thought to be statistically heterogeneous. There was no common factor among these trials which could explain their dissimilar results from the aggregate. For the vomiting end point, 5 trials fell outside the region of homogeneity; similarly, there was no common factor among them that could explain the differences. The overall analyses of these two end points were repeated without the anomalous trials; this further strengthened the estimated beneficial effects of 5HT3 antagonists on PONV (OR=0.44, 95% CI: 0.35, 0.55; test for heterogeneity, p=0.46; NNT=6) and vomiting (OR=0.57, 95% CI: 0.46, 0.70; test for heterogeneity, p=0.42; NNT=13).

Sensitivity analyses: when grouped by traditional anti-emetic and type of induction anaesthetic, the results of all the analyses were robust to varying the extremes of the outcomes. When the results were pooled by surgery type, the 5HT3 receptor antagonists were only superior to traditional agents for both PONV and vomiting end points in gynaecological surgery. The number of unretrieved trials averaging null results that would be required to bring the p-value up to 0.05 were 598 and 245 for PONV and vomiting, respectively. The limit of robustness was defined as 5k + 10 trials where k equals the number of trials included in the analysis. By this method, the threshold values for PONV and vomiting would be 170 and 180 trials, respectively, indicating that the results of the review are robust.

**Authors' conclusions**
The 5HT3 receptor antagonists are superior to traditional anti-emetic agents for the prevention of PONV and vomiting. The reduction in the odds of PONV and vomiting is significant in both the overall analysis, and the subgroup analyses comparing 5HT3 receptor antagonists with droperidol and metoclopramide.

**CRD commentary**
The review question was clearly stated and was well supported by the inclusion criteria. The literature search was adequate, but it was restricted to English language articles and excluded unpublished studies. There was no formal assessment of validity although aspects of the methodological quality of studies were taken into account in the inclusion and exclusion criteria. The data were appropriately synthesised, both quantitatively and narratively. Publication bias and heterogeneity were also appropriately investigated. Some details regarding the explanation of the review process were provided, such as how judgements of validity were made, whereas other details, such as how decisions were made on the relevance of primary studies and how data were extracted from primary studies, were not provided. The authors' conclusions follow from their findings, but should be viewed with some caution given the above mentioned limitations.

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

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