Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis: systematic re-evaluation of clinical evidence and drug cost implications

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined the extended use of 5-hydroxytryptamine-3 receptor (5-HT3) antagonists in order to prevent delayed emesis in post-chemotherapy patients.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
Adult cancer patients receiving moderately or highly emetogenic chemotherapy represented the study population.

Setting
The setting was secondary care. The economic study was carried out in Hawaii, USA.

Dates to which data relate
The effectiveness data were collected from studies dating from 1992 to 2000. Resource use was based upon an average of unit doses required per patient, as reported in the included studies. The price year was 2004.

Source of effectiveness data
The effectiveness data were derived from a systematic review of the literature.

Outcomes assessed in the review
The primary outcome was the proportion of patients with complete control of delayed emesis. Delayed emesis was defined as at least one episode of vomiting occurring more than 24 hours after commencement of chemotherapy administration. A re-analysis of previously collected data led to the outcomes being expressed as the absolute risk reduction (ARR) and the number-needed-to-treat (NNT). The NNT indicates the number of patients who need to receive a 5-HT3 antagonist beyond the first 24 hours after chemotherapy to prevent delayed emesis in one patient.

Study designs and other criteria for inclusion in the review
Randomised placebo-controlled clinical trials were included in the review. A full list of inclusion and exclusion criteria was detailed in the Practice Guideline (Cancer Care Ontario Practice Guideline Initiative 2003).
Sources searched to identify primary studies

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Ten randomised, placebo-controlled trials with a total of 3,956 assessable patients were included in the review. Five studies compared a 5-HT3 antagonist with placebo (1,716 assessable patients), while the other five compared 5-HT3 antagonists plus dexamethasone with dexamethasone monotherapy (2,240 assessable patients).

Methods of combining primary studies
The primary studies were combined in a meta-analysis using weighted pooled estimates of ARR and NNT, along with 95% confidence intervals (CIs). A fixed-effect model was used because there were too few studies to estimate random effects.

Investigation of differences between primary studies
The authors did not report whether differences between the primary studies were investigated.

Results of the review
The results were reported separately for studies assessing 5-HT3 antagonist monotherapy and 5-HT3 antagonist combination therapy.

The meta-analysis showed that a 5-HT3 antagonist (ondansetron) used as a monotherapy resulted in a statistically significant ARR of 8.2% (95% CI: 3.0 - 13.4).

Twelve patients would need to be treated with ondansetron for more than 24 hours after chemotherapy to protect one patient from delayed emesis (NNT 12.2, 95% CI: 7.5 - 33.4).

The meta-analysis addressing 5-HT3 antagonist combined with dexamethasone found no significant difference in the control of delayed emesis when compared with dexamethasone monotherapy. The ARR was 2.6% (95% CI: -0.6 - 5.8) and the NNT was 38.8 (95% CI: 17.3 - infinity; p not significant).

Measure of benefits used in the economic analysis
No summary benefit measure was used in the economic analysis. The study was, therefore, a cost-consequences analysis.

Direct costs
Drug acquisition costs were included, drawing on a sample of US price data from www.drugstore.com and from a selected pharmacy or medical centre (June 2004). Resource use was determined by multiplying the NNT in the effectiveness analysis by the mean number of unit doses required for each treated patient, which was derived from a single study. The cost estimates were reported separately from other model parameters. No discounting was carried out.
as the costs were incurred during less than 2 years. The price year was 2004.

Statistical analysis of costs
The cost data were deterministic. No statistical analysis of the costs was carried out.

Indirect Costs
In line with the chosen perspective (i.e. the health care system), the indirect costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
The results were presented using three different prices for the drug. These prices were derived from www.drugstore.com, Longs Drugs Pharmacy, or Queens Medical Center. The authors' conclusions were based upon the lowest price ($30.45 per 8-mg oral ondansetron tablet from www.drugstore.com).

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
Assuming a cost of $30.45 per tablet, the drug acquisition cost per patient was:

for 5-HT3 antagonist (ondansetron) as monotherapy, $2,265 per cycle (95% CI: 1,392 - 6,203); and

for 5-HT 3 antagonist in combination with dexamethasone, $12,877 (95% CI: 5,743 - infinity).

At a cost of $47.55 per tablet, the results were $3,538 (95% CI: 2,173 - 9,686) for monotherapy and $20,109 (95% CI: 8,968 - infinity) for combination therapy.

At a cost of $56.25 per tablet, the results were $4,185 (95% CI: 2,571 - 11,458) for monotherapy and $23,788 (95% CI: 10,609 - infinity) for combined therapy.

Synthesis of costs and benefits
The costs and benefits were not combined.

Authors' conclusions
Economic and effectiveness evidence suggest there is no justification for the extended use of 5-hydroxytryptamine-3-receptor (5-HT3) antagonists (24 hours post chemotherapy) in the prevention of delayed emesis.

CRD COMMENTARY - Selection of comparators
The technology was chosen on the basis of its standard use in clinical practice. You should decide if this represents a widely used technology in your own setting.

Validity of estimate of measure of effectiveness
The review was supported by a comprehensive and systematic search of the literature. However, other biases in the review process could not be ruled out given the lack of information on how the studies were selected and the data extracted. The absence of a validity assessment is also a potential threat to the reliability of the findings. A meta-analysis was carried out to synthesise the data. The appropriateness of this was unclear since there was no reported investigation of differences between the studies in this update study. The reporting of the NNT is meaningful for contextual clinical decision-making, and it represents a strong feature of the review.

**Validity of estimate of measure of benefit**
No summary measure of benefit was derived. The reader is referred to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

**Validity of estimate of costs**
The analysis of the costs was performed from the perspective of the health care system. The narrow perspective of costs (drug acquisition prices only) should be borne in mind when interpreting the results. The costs were reported separately from the quantities, which will aid the reproducibility of the study in other settings. Resource use was appropriately presented as mean data derived from the included studies, and this potentially aids the generalisability of the findings to other settings. No statistical, sensitivity or other analysis of the quantities was conducted. The prices were taken from a web source and from selected clinical settings. The economic analysis reflected this range of prices and the conclusions were based on the lowest estimate. The price year was reported and this will aid any future reflation exercises. Discounting was not applied, which was appropriate given the short time horizon of the analysis.

**Other issues**
The authors were not able to compare their results with those of other studies since their specific comparisons had not been addressed before. The issue of the generalisability of the results to other settings was not directly addressed. The authors acknowledged two limitations to their study. First, nausea-related end points were excluded from the meta-analysis. Therefore, from a combined end point of complete control of nausea and vomiting, 5-HT3 antagonists would be expected to be even less effective than for the end point used in the present analysis. Second, continuing the administration of 5-HT3 antagonists for more than 24 hours would result in an increased incidence of adverse effects. These may further reduce the net benefit accrued from treatment with these agents.

**Implications of the study**
The authors advised against the use of 5-HT3 antagonists in this clinical setting, stating that no further research is required to support this recommendation.

**Source of funding**
None stated.

**Bibliographic details**
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**Other publications of related interest**
Cancer Care Ontario Practice Guideline Initiative. Use of 5-HT 3 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy. Practice Guideline Report 12-3. Available from: URL:

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