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# The Budgetary Impact of 5-HT$_3$ Receptor Antagonists in the Management of Chemotherapy-induced Emesis

**Alison L. Jones, Graham J. Lee and Nick Bosanquet**

**The study examined the budgetary implications of using 5-hydroxytryptamine$_3$ receptor antagonists(5-HT$_3$RA), granisetron or ondansetron, in the management of chemotherapy-induced emesis (CIE). A treatment model was constructed to represent a baseline of efficacy and costs for treating a cohort of patients with conventional antiemetics. Groups of patients who would be expected to receive the most benefit from 5-HT$_3$RA were then identified and the effect upon costs of using these compounds in a consecutively larger proportion of selected patients was calculated. On the basis of illustrative costs from The Cookridge Hospital in the UK, it was concluded that the new antiemetics can be used in acute emesis with substantial clinical benefit for an increase of 3–10% to total treatment costs. However, for delayed emesis these compounds have not yet shown a clinical advantage, and the increase in total costs of 12–34% is not justified.**
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## INTRODUCTION

NAUSEA AND vomiting are ranked by patients as the most distressing side-effects of cancer chemotherapy [1]. Although careful use of antiemetics can control emesis in approximately 60% of patients, some conventional antiemetic regimens also cause distressing side-effects, in particular extrapyramidal reactions (EPR). Thus, chemotherapy-induced emesis (CIE) remains a significant problem, which may severely undermine quality of life of patients undergoing treatment. The 5-hydroxytryptamine$_3$ receptor antagonists (5-HT$_3$RA) are a new class of antiemetic compounds, which may represent an opportunity to improve the management of CIE, thereby enhancing quality of

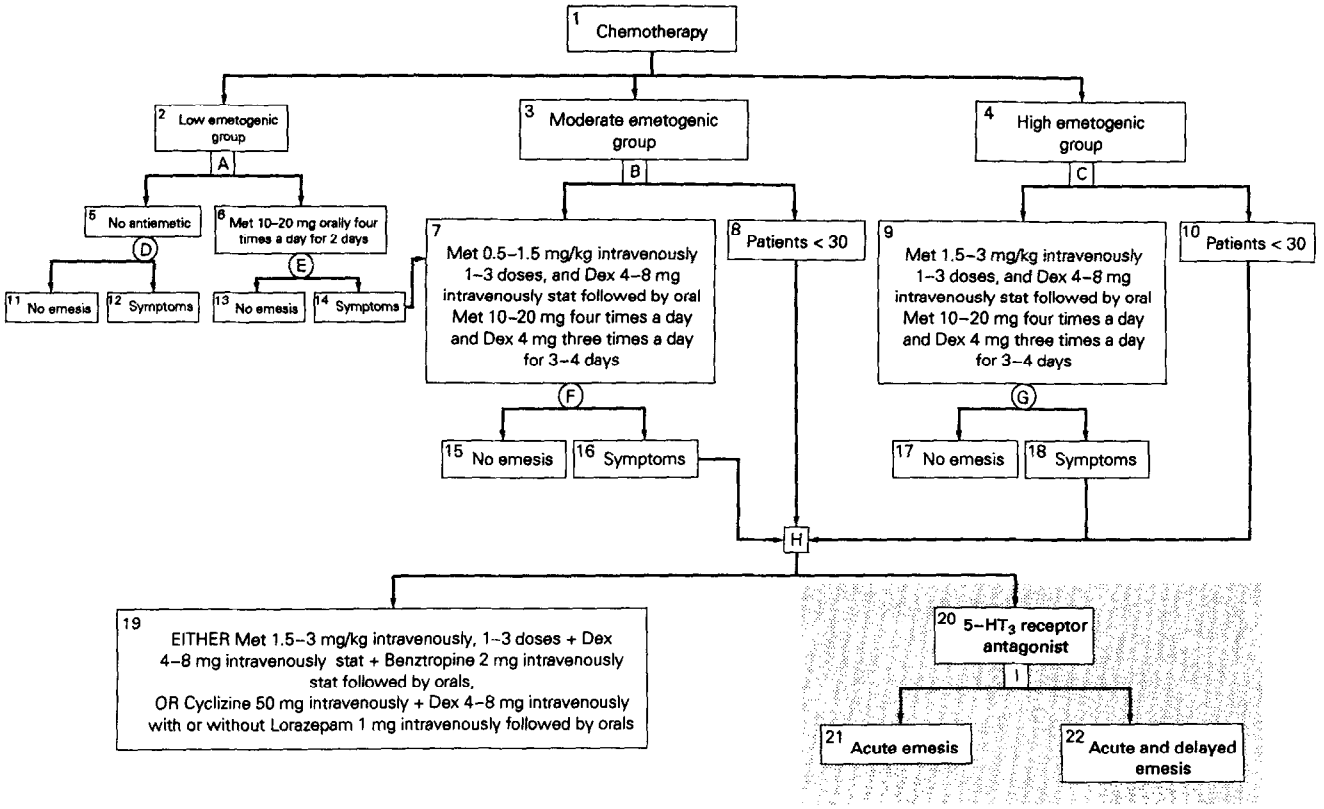


**Fig. 1. Treatment model. Met = metoclopramide; Dex = dexamethasone.**

life of patients receiving chemotherapy. However, from the perspective of budget holders, these new drugs may cause concern. The costs of the first commercially available 5-$HT_3$RA, granisetron and ondansetron, are higher than conventional antiemetic regimens, and it is possible that use of these compounds for CIE will add substantially to the total costs of chemotherapy. Clinicians and health managers need to be able to identify and target patient groups for whom the benefits are considered to justify the additional costs.

In order to address this issue a study was designed to examine the marginal costs of different usage patterns of 5-$HT_3$RA in the management of CIE. A model was constructed to represent the baseline or typical pattern of treatment with conventional antiemetics for a cohort of patients receiving chemotherapy. Then, based upon the clinical benefit of using 5-$HT_3$RA for specific groups of patients, a series of antiemetic strategies was considered in which a successively larger proportion of treatments were with 5-$HT_3$RA. The incremental costs of using these drugs according to each strategy were evaluated in relation to costs for the baseline strategy. The use of the model as a framework for evaluating the budgetary implications of 5-$HT_3$RA in a particular cancer centre was illustrated for The Cookridge Hospital (The Yorkshire Regional Centre for Cancer Treatment) in the UK. The total annual budgetary impact of each antiemetic strategy was calculated for treating a cohort of 1000 cancer patients. Conclusions about the appropriate use of 5-$HT_3$RA were drawn from this analysis.

Correspondence to A.L. Jones.
A.L. Jones is at the Department of Medicine, The Royal Marsden Hospital, Fulham Road, London, SW3 6JJ; G.J. Lee is at the Policy and Economics Group, Cambridge Pharma Consultancy, St. John's Innovation Centre, Cowley Road, Cambridge, CB4 4WS; and N. Bosanquet is at the Department of Social Policy, Royal Holloway and Bedford New College, University of London, Egham, Surrey, U.K.
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## MATERIALS AND METHODS

*Treatment model*

The treatment model shown in Fig. 1 was initially constructed to represent the management of CIE with the most effective conventional antiemetics; the 5-$HT_3$RA arm of the model (shaded area) was added subsequently. Small squares represent decision nodes, the point at which the clinician makes a therapeutic decision, and small circles represent chance nodes, the point at which there is a chance probability of a certain treatment outcome.

*Conventional antiemetics and treatment model*

It is assumed that group 1 consists of a cohort of 1000 patients receiving chemotherapy. This group is divided into three groups according to the emetogenic potential of the cytotoxic regimen, defined in terms of the percentage of patients who experience emesis (Table 1). Several publications classify the emetogenic potential of cytotoxic drugs into five groups [2–4]. A broader regrouping of these categories has been used here to reflect the working classifications that are commonly made in British clinical practice. It is assumed that 15% of patients will be in the low emetogenic group, 75% in the moderate emetogenic group and 10% in the high emetogenic group.

The choice and use of conventional antiemetics in the model are based upon a comprehensive literature review and comments from three oncologists. The assumptions governing the flow of patients through the treatment model are as follows:

*Table 1. Emetogenic potential of cytotoxic drugs*

| | |
|---|---|
| High | Cisplatin |
| | Dacarbazine |
| | Cyclophosphamide (intravenous high dose) |
| | Melphalan (intravenous high dose) |
| | Mustine |
| | Actinomycin D |
| Moderate | Doxorubicin |
| | Epirubicin |
| | Cyclophosphamide (oral) |
| | Carboplatin |
| | Fluorouracil (intravenous bolus) |
| | Etoposide (intravenous) |
| | Mitozantrone |
| Low | Chlorambucil |
| | Mitomycin |
| | Methotrexate |
| | Melphalan (oral low dose) |
| | Fluorouracil (oral or intravenous infusion) |
| | Bleomycin |
| | Vinblastine |
| | Vincristine |

For combination chemotherapy, the emetogenic potential equals that of the most emetogenic drug in the combination.

*Table 2. Antiemetics—relative efficacy scale (based on [5])*

| Antiemetic treatment regimen | Relative efficacy | 5-HT$_3$RA |
|---|---|---|
| Strong | | |
| Metoclopramide 3 mg/kg + corticosteroid (+ benzodiazepine) | 4.0 | = Granisetron |
| Benzodiazepine + corticosteroid + phenothiazine | 3.5 | |
| Metoclopramide 3 mg/kg + benzodiazepine | 3.5 | |
| Moderate | | |
| Corticosteroid + phenothiazine | 3.0 | |
| Benzodiazepine + corticosteroid | 3.0 | |
| Metoclopramide 3 mg/kg | 3.0 | < Ondansetron |
| Benzodiazepine + phenothiazine | 2.5 | |
| Corticosteroid | 2.5 | |
| Weak | | |
| Metoclopramide 0.1–0.3 mg/kg | 2.0 | |
| Phenothiazine | 2.0 | |
| Benzodiazepine | 1.0 | |

*Low emetogenic group.* At decision node A, it is assumed that 30% of patients receive no antiemetic (group 5), and 70% receive a regimen of oral metoclopramide (group 6). The use of an alternative conventional oral antiemetic, e.g. dexamethasone or a phenothiazine, will not significantly affect the costing of this model. Patients who experience no emesis (group 11 or group 13) will receive the same antiemetic regimen on subsequent cycles. Patients who experience emesis or side-effects (group 12 or group 14) will receive, on subsequent cycles, an alternative antiemetic regimen comparable with that used for patients in the moderate emetogenic group.

*Moderate and high emetogenic groups.* For the moderate and high emetogenic groups the distinction between acute and delayed emesis is relevant. Acute emesis refers to nausea and vomiting during the first 24 h after chemotherapy. Delayed emesis develops later than 24 h after chemotherapy and may persist for up to 6–7 days. Delayed emesis is particularly associated with cisplatin and dacarbazine, but may occur to a lesser degree with most chemotherapy regimens. Clinical trials have largely focused on acute emesis, and a relative efficacy scale for conventional antiemetics has been developed (Table 2) [5]. High-dose metoclopramide (2–3 mg/kg) was the most effective single-agent antiemetic, but combination regimens are superior [6]. For example, the addition of dexamethasone enhances antiemetic efficacy of most drugs and in combination with high-dose metoclopramide, achieves major control of acute emesis in 60–70% of patients receiving highly emetogenic chemotherapy [7]. For delayed emesis, the combination of oral metoclopramide and dexamethasone at low dose was found to be superior to placebo or dexamethasone alone in patients receiving cisplatin [8]. Therefore, in our treatment model it is assumed that at either decision node B (moderately emetogenic chemotherapy) or C (highly emetogenic chemotherapy), most patients (85%) receive a combination of intravenous metoclopramide and dexamethasone for acute emesis, and oral metoclopramide and dexamethasone for 4 days for delayed emesis. The efficacy of this regimen has been demonstrated in clinical trials [7–10] and is reflected in the chance outcomes for the moderate (node F) and high (node G) emetogenic groups.

At chance node F (moderately emetogenic chemotherapy), it is assumed that 74% of patients experience no emesis and continue with this antiemetic regimen for subsequent treatments (group 15). The remaining patients (26%) who experience emesis, EPR, or other side-effects (group 16) receive alternative therapy, such as the addition of an anticholinergic to control EPR, e.g. benztropine, or a different regimen such as cyclizine, dexamethasone and lorazepam (group 19). Patients aged less than 30 years are separated in the model (group 8), since they are more susceptible to EPR with metoclopramide or other dopamine antagonists [11,12]. These patients receive the alternative regimen first-line.

At chance node G (highly emetogenic chemotherapy), it is assumed that 55% of patients experience no emesis or side-effects and continue with this antiemetic regimen for subsequent treatments (group 17). Patients who experience emesis or side-effects (group 18), together with those patients aged less than 30 years (group 10) receive an alternative regimen (group 19) as described above.

There is a range of alternative antiemetics that can be used instead of those described here, according to clinical preference. For example, dexamethasone alone may be used as first-line treatment for patients receiving moderately emetogenic chemotherapy. These differences would not substantially change the logic, costing or outcome of our treatment model.

*5-HT$_3$RA and treatment model*

The strategies for the potential use of 5-HT$_3$RA were derived from an analysis of the reported clinical trials for granisetron and ondansetron. There is, as yet, no direct comparison of these compounds. Furthermore, different efficacy criteria and comparators have been used in the respective clinical programmes. Ondansetron was shown to be superior to single-agent, high-dose metoclopramide in patients receiving cisplatin and non-cisplatin treatment [13–15], from which we can infer that ondansetron has a relative efficacy of > 3.0 (Table 2). In

*Table 3. Antiemetic treatment strategies*

| Pattern of antiemetic use | % Patients receiving 5-$HT_3$RA for acute or acute and delayed emesis |
|---|---|
| Baseline | |
| H: Conventional antiemetics | 0 |
| M: Conventional antiemetics | |
| Strategy 1 | |
| H/M: First-line use in patients < 30 | 28 |
| H/M: Second-line use in patients > 30 | |
| Strategy 2 | |
| H: First-line use in all patients | 34 |
| M: Second-line use in patients > 30 | |
| Strategy 3 | |
| H: First-line use in all patients | 86 |
| M: First-line use in all patients | |

H = High emetogenic group; M = moderate emetogenic group.

contrast, the key comparator for granisetron has been the combination of high-dose metoclopramide and dexamethasone [16], and granisetron has been shown to have equivalent efficacy to this comparator. Therefore, we can infer that granisetron has a relative efficacy of 4.0.

The low incidence of side-effects with 5-$HT_3$RA compared favourably with conventional antiemetic regimens. There have been only anecdotal reports of EPR with ondansetron [17, 18], in contrast to the incidence with metoclopramide [11, 12, 16]. The most commonly reported side-effect with 5-$HT_3$RA is mild to moderate headache in 10–15% of patients, which is readily controlled with paracetamol.

The mechanisms underlying delayed emesis are not clear. Although ondansetron is effective in control of acute emesis, there is no evidence that oral ondansetron is more effective than conventional antiemetics in control of delayed vomiting. Indeed metoclopramide and/or dexamethasone has been shown to give superior control of delayed nausea compared with ondansetron against cisplatin or moderately emetogenic chemotherapy [19, 20]. Granisetron has a longer half-life than ondansetron, and it has been suggested that a single infusion of granisetron at the time of chemotherapy not only controlled acute nausea and vomiting but also controlled delayed emesis for 7 days in over 60% of patients [21]. This observation requires confirmation in controlled trials.

This review indicates that 5-$HT_3$RA are at least as effective as the best conventional antiemetic regimens in control of acute emesis for platinum- or non-platinum-containing therapies. Absence of EPR and ease of administration may be important advantages. For delayed emesis however, there is no advantage for 5-$HT_3$RA.

*5-$HT_3$RA treatment strategies*

The benefit of 5-$HT_3$RA will be greatest for patients in moderate and high emetogenic groups, where significant numbers experience EPR or other side-effects. It is assumed that patients in the low emetogenic group are adequately treated with conventional antiemetics. For the other two groups, three different treatment strategies were considered (strategies 1, 2 and 3). In each strategy an increasing proportion of patients were treated with 5-$HT_3$RA. Each treatment strategy was subdivided into two according to whether 5-$HT_3$RA were used for acute emesis or for acute and delayed emesis (Table 3).

In strategy 1 the number of patients in each group up to decision node H is the same as for the baseline strategy. At decision node H the alternative antiemetic regimen (group 19) for patients in the moderate or high emetogenic groups is replaced by use of 5-$HT_3$RA (group 20). According to this strategy, 28% of all treatments are with 5-$HT_3$RA.

In strategy 2, the proportion of treatments with 5-$HT_3$RA (group 20) is increased to 34%. All patients in the high emetogenic group (group 4) receive 5-$HT_3$RA as first-line treatment. Patients in the moderate emetogenic group are treated as for strategy 1.

In strategy 3 the proportion of treatments with 5-$HT_3$RA (group 20) is increased to 86%. All patients in the high and moderate emetogenic groups receive 5-$HT_3$RA as first-line treatment.

*Costs*

Antiemetic costs are based upon British list prices. The price of granisetron is £36 per patient, based upon the recommended dose of a single 3-mg infusion for acute emesis. The cost of ondansetron is more complicated to calculate due to the range of recommended doses. Most clinical trials have used 24–32 mg of ondansetron (intravenous and/or oral) for acute emesis, followed by 24 mg orally per day for up to 5 days. Two studies reported the use of single doses of 8 mg intravenously for acute emesis, one study showing equivalent efficacy to a 32-mg dose, and another showing inferior efficacy [22]. In another study ondansetron 8 mg twice a day was as effective as 8 mg three times a day in delayed emesis [23]. Appropriate doses of ondansetron for different chemotherapy regimens are not yet established, and since it is likely that different patients will require different doses, the costs used here are based upon an average of a range of doses. Assuming one third of ondansetron treatments for acute emesis are at 8 mg intravenously, one third at 8 mg intravenously followed by two oral 8 mg doses, and one third at 32 mg intravenously, the cost for acute emesis is £36. Assuming a dose of ondansetron 8 mg orally twice a day for delayed emesis, the cost is £18 per day. The effect of alternative doses of ondansetron on costs is addressed in the sensitivity analysis.

Use of the antiemetic model as a framework for measuring the budgetary impact of 5-$HT_3$RA within a treatment centre is illustrated for The Cookridge Hospital (The Yorkshire Regional Centre for Cancer Treatment). Analysis of the total costs of chemotherapy at the centre was carried out in order to place the costs of the new antiemetics into context. Although there is variability in the costs of cancer treatment for different patients, average costs were used in the model since individual patient costs did not reflect the emetic risk or the suitability for treatment with 5-$HT_3$RA. For example, the cost per cycle of highly emetogenic cisplatin treatment varied between £10 and £300 depending upon the use of other cytotoxics in combination with cisplatin. The average number of cycles of chemotherapy for 1000 patients was four. Staff, in-patient and diagnostic costs were derived from hospital accounts. The total cost of treating 1000 cancer patients at The Cookridge Hospital with chemotherapy and controlling the associated emesis with conventional antiemetics, as described for the treatment model, is £1 018 000 (Table 4). This cost represents the baseline with which the additional cost of each 5-$HT_3$RA strategy was compared.

*Table 4. Annual costs for 1000 patients*

| Item | Cost (£000s) |
|---|---|
| Cytotoxic drugs | 408 |
| Staff (medical and nursing) | 396 |
| In-patient bed stays | 136 |
| Conventional antiemetics | 30 |
| Diagnostic procedures | 48 |
| Total | 1018 |

## RESULTS

Results of the analysis for The Cookridge Hospital are shown in Table 5. Annual, incremental and total treatment costs are shown for a cohort of 1000 patients. The percentage change columns show the percentage increase in total costs for each strategy compared with baseline. As anticipated, 5-HT$_3$RA increase total treatment costs. However, there is considerable variation in the cost implications of different treatment strategies. Where 5-HT$_3$RA are used for acute emesis only, the additional cost is £32 000–£106 000, an increase in total costs of 3–10%. If used for acute and delayed emesis, the additional cost is £118 000–£342 000, an increase in total costs of 12–34%.

Within the range of treatment strategies that were considered, there are two decisions for use of 5-HT$_3$RA that have an incremental budgetary impact greater than £50 000. One is extension to first-line use in patients receiving moderately emetogenic chemotherapy (i.e. the cost increment from strategy 2 to strategy 3 for acute emesis), for which the cost is £70 000. The second is extension of 5-HT$_3$RA to use in delayed emesis, for which the incremental cost is £86 000–£236 000, relative to the costs for acute emesis.

*Sensitivity analysis*

Since the model is based upon a number of assumptions, these were tested in sensitivity analyses to determine their impact on the conclusions. The proportion of patients in each group (low, moderate and high), the percentage of patients less than 30 years old and the efficacy rates of conventional antiemetics were all tested. Although all affected the budgetary impact of 5-HT$_3$RA, none altered the conclusions of the model. The biggest change occurred if the high emetogenic group represented a significantly greater proportion of patients. Increasing this from 10 to 25% of all patients increased costs by a maximum of £10 000 if the new antiemetics were used for acute emesis, and by £49 000 if used for acute and delayed emesis.

All strategies were, however, sensitive to the average dose of ondansetron for acute emesis. If the dose was 8 mg intravenously for patients in the moderate emetogenic group, the cost increase would be £16 000–£52 000, representing an overall budgetary impact of 2–5% if use was limited to the acute phase, and an increase of £102 000–£288 000, representing a total budgetary impact of 10–28%, if use was extended to delayed emesis.

## DISCUSSION

In the absence of prospective studies, health managers and clinicians have to make decisions about the use of new drugs, and a treatment model can be a useful tool for evaluating the implications of treatment decisions. The model presented here for the management of CIE enables assessment of the economic impact of a range of strategies for the use of 5-HT$_3$RA.

The 5-HT$_3$RA have been shown to be equivalent or superior to conventional antiemetics for acute emesis induced by high or moderate emetogenic chemotherapy. However, in delayed emesis 5-HT$_3$RA have not yet shown any clinical benefit over conventional antiemetic regimens [19, 20]. The 5-HT$_3$RA have a lower incidence of side-effects than conventional regimens and are simpler to use. There is also evidence emerging which suggests that efficacy in acute emesis may be improved when used in combination with dexamethasone [24–26].

Analysis of the budgetary impact of different antiemetic strategies according to costs at The Cookridge Hospital indicates a wide variation in the potential cost burden of using 5-HT$_3$RA in the management of CIE. Broad conclusions of the model are likely to be applicable to other cancer treatment centres, although the absolute numbers are probably not. However, the model can be used as a basis for calculating the budgetary impact in other centres.

Two broad conclusions are drawn from the study. First, the budgetary impact of these new antiemetics will not automatically lead to an escalation in costs. More than a third of a cohort of 1000 cancer patients at The Cookridge Hospital can receive 5-HT$_3$RA for acute emesis for an additional cost of £36 000 per year, representing an overall budgetary increase of 3.5%. Such a cost for using 5-HT$_3$RA first-line for acute emesis in patients receiving highly emetogenic chemotherapy (strategy 2) seems to be justified by the clinical benefits. It may even be argued on clinical judgement, that the further benefit of extending first-line use of 5-HT$_3$RA to patients in the moderate emetogenic group (strategy 3) warrants the further additional cost of £70 000, representing an annual, total budgetary increase of 6.9%.

The second conclusion concerns the use of 5-HT$_3$RA for delayed emesis. These strategies will lead to an additional increase in costs, over that already established for acute emesis, of £86 000 for strategy 1, £101 000 for strategy 2, and £236 000 for strategy 3. There is no evidence to suggest that this cost

*Table 5. Annual budgetary impact of 5-HT$_3$RA*

| 5-HT$_3$RA strategy (cohort = 1000 patients) | Acute emesis | | | Acute and delayed emesis | | |
|---|---|---|---|---|---|---|
| | Incremental costs (£000s) | Total costs (£000s) | Percentage change | Incremental costs (£000s) | Total costs (£000s) | Percentage change |
| 1 | 32 | 1050 | + 3.1 | 118 | 1136 | +11.6 |
| 2 | 36 | 1054 | + 3.5 | 137 | 1155 | +13.4 |
| 3 | 106 | 1124 | +10.4 | 342 | 1360 | +33.6 |

increase will be matched by a commensurate clinical benefit. On the basis of current clinical evidence 5-$HT_3$RA should not be used for delayed emesis; any budget available for delayed emesis can be more effectively directed to funding use of 5-$HT_3$RA for acute emesis.

The 5-$HT_3$RA may have further economic and clinical impacts, besides those addressed in our model. Potentially reduced costs of patient management due to improved emetic control could be investigated in a prospective study. Other potential factors include improved efficacy in acute emesis when used in combination with dexamethasone, reduced costs due to lower doses of ondansetron, and control of acute and delayed emesis with single doses of granisetron. Since these are likely to reduce costs or improve management of acute emesis, they would reinforce our conclusion that use in acute emesis is justified.

This study demonstrates that it is important to optimise those treatment decisions that are made at the margins. The consecutive addition of different groups of patients into the treatment group alters the balance of costs and benefits. A point will be reached where the marginal costs of extending treatment to another patient group will be too high in relation to the benefits it brings. For 5-$HT_3$RA we have shown that a major cut-off point is between use of these drugs in acute and delayed emesis. On the basis of current evidence, use of 5-$HT_3$RA should be focused on the acute emetic phase and relative efficacy and ease of use in the acute phase should be the primary determinant of which of the available drugs to choose.


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