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5-hydroxytryptamine-receptor antagonists versus prochlorperazine for control of delayed nausea caused by doxorubicin: a URCC CCOP randomised controlled trial

J T Hickok, MD, J A Roscoe, PhD, G R Morrow, PhD, and C W Bole, MA

Department of Radiation Oncology and James P Wilmot Cancer Center

H Zhao, PhD

Department of Biostatistics and James P Wilmot Cancer Center, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

K L Hoelzer, MD

Central Illinois Community Clinical Oncology Program (CCOP), Decatur Memorial Hospital, Decatur, IL, USA

S R Dakhil, MD

Wichita CCOP, Wichita, KS, USA

T Moore, MD

Columbus CCOP, Columbus, OH, USA and

T R Fitch, MD

Mayo Clinic Scottsdale CCOP, Scottsdale, AZ, USA

Summary

Background—Despite widespread use of short-acting antagonists for the 5-hydroxytryptamine (5-HT) receptor, about 50% of patients given moderately emetogenic chemotherapy have delayed nausea. We aimed to assess whether a 5-HT-receptor antagonist was more effective than was prochlorperazine for control of delayed nausea and delayed vomiting caused by doxorubicin.

Methods—691 patients who previously had not had chemotherapy and who were scheduled to receive doxorubicin were given a short-acting 5-HT-receptor antagonist and dexamethasone before doxorubicin (day 1), and were randomly assigned to one of three regimens for days 2 and 3: 10 mg prochlorperazine taken orally every 8 h; any first-generation 5-HT-receptor antagonist (except palonosetron) taken as standard dose intravenously or orally; or 10 mg prochlorperazine taken as needed. Nausea and vomiting were assessed by use of a home record. The primary endpoint was mean severity of delayed nausea. The secondary endpoint was quality of life. Analyses were done by intention to treat.

Findings—519 (77%) of the 671 evaluable patients had delayed nausea, with a mean severity of 3.33 (95% CI 3.22–3.44). 161 (71%) of 226 patients assigned prochlorperazine every 8 h reported delayed nausea (mean severity 3.37 [3.16–3.58]), as did 179 (79%) of 226 patients assigned 5-HT-

Correspondence to: Dr Jane T Hickok, James P Wilmot Cancer Center, University of Rochester, 601, Elmwood Avenue, Box 704, Rochester, NY 14642, USA Jane_Hickok@urmc.rochester.edu.

Conflict of interest We declare no conflicts of interest.

Contributors

J Hickok, J Roscoe, G Morrow, H Zhao, K Hoelzer, T Moore, T Fitch, and S Dakhil had a role in the concept and design of the original protocol; J Hickok was responsible for coordination of the study; K Hoelzer, T Moore, T Fitch, and S Dakhil obtained data; J Hickok, J Roscoe, and C Bole did data analyses and interpretation; J Hickok, J Roscoe, and G Morrow drafted the paper; G Morrow obtained funding; and all authors approved the final report.

receptor antagonists (3.29 [3.09–3.48]) and 179 (82%) of 219 patients assigned prochlorperazine as needed (3.33 [3.15–3.50]); groups did not differ in mean severity ($p=0.853$, one-way ANOVA). Patients allocated prochlorperazine every 8 h had less delayed nausea than did those allocated 5-HT-receptor antagonists ($p=0.05$, t test) and those allocated prochlorperazine as needed ($p=0.009$, t test).

Interpretation—Short-acting 5-HT-receptor antagonists are no better than is prochlorperazine in control of delayed nausea caused by doxorubicin. Although fewer patients taking prochlorperazine report delayed nausea, the proportion was unacceptably high.

Introduction

Antagonists for the 5-hydroxytryptamine (5-HT) receptor such as ondansetron and granisetron decrease the frequency of vomiting in patients given emetogenic chemotherapy. However, control of nausea, particularly delayed nausea (ie, that which is experienced on the days after chemotherapy is given), remains elusive. Delayed nausea is more than twice as frequent than is acute nausea (defined as that which occurs on the same day chemotherapy is given) after treatment with highly emetogenic chemotherapy (eg, cisplatin) or with moderate to highly emetogenic chemotherapy agents (eg, doxorubicin and epirubicin) and combination regimens.¹

In a Community Clinical Oncology Program (CCOP) study,² 234 (73%) of 322 patients who previously had not received chemotherapy and who were given regimens containing cisplatin, carboplatin, or doxorubicin had nausea on days 2–5 after starting the first chemotherapy cycle. All patients received ondansetron with dexamethasone on the day of treatment—antiemetic therapy regarded as standard at the practice sites that participated in the study. Patients also received any additional (ie, rescue) treatments needed for control of symptoms caused by the cancer or its treatment on the days after chemotherapy.

Physicians and nurses who specialise in oncology might underestimate substantially the extent to which symptoms occur, especially those that are delayed,¹ possibly because patients are at home by the time these side-effects become apparent. There is little consensus regarding guidelines for the prophylactic control of delayed emesis, and confidence in the recommendations is also weak.^{3–5}

We therefore aimed to survey the 27 private-practice oncologists who were principal investigators in our CCOP network (University of Rochester CCOP Research Base, NY, USA) regarding the antiemetic regimen they prescribed for patients with newly diagnosed breast cancer who were scheduled to receive first-line treatment with cyclophosphamide and doxorubicin, and to design a protocol for the assessment of various antiemetic strategies for use with emetogenic chemotherapy. 25 of 27 respondents reported adherence to the guidelines of the American Society of Clinical Oncology for the prevention of acute emesis,³ and reported that they gave a 5-HT-receptor antagonist with a corticosteroid on the day of treatment. However, no consensus emerged for the prophylactic control of nausea and vomiting on days 2–4 after starting treatment. Nine different antiemetic regimens were reported to be in use, none of which were endorsed by more than eight respondents, and some respondents prescribed more than one type of antiemetic regimen. 18 respondents prescribed prochlorperazine, either alone or in combination with other drugs; 14 respondents prescribed a 5-HT-receptor antagonist, either alone or in combination with other drugs. In addition to the differences in the drugs prescribed, there was no consensus on whether they should be taken irrespective of the presence of symptoms or only as needed.

We aimed to assess whether a 5-HT-receptor antagonist was more effective than was prochlorperazine in controlling the frequency and severity of delayed nausea and vomiting caused by doxorubicin when given on days 2–3 after appropriate antiemetic treatment had been

given on day 1 of starting chemotherapy that contained doxorubicin. Furthermore, we aimed to investigate whether prochlorperazine taken on a preventive basis was more effective than was prochlorperazine taken as needed for control of delayed nausea and vomiting.

Methods

Patients

Eligible patients were those who: previously had not had chemotherapy; were aged 18 years or older; had any cancer diagnosis; and were scheduled to receive their first treatment with a chemotherapy regimen containing doxorubicin (Adriamycin, Bedford Laboratories, Bedford, OH, USA) and antiemetic prophylaxis with a 5-HT-receptor antagonist, ondansetron (Zofran[®], GlaxoSmithKline, Research Triangle Park, NC, USA), granisetron (Kytril[®], Roche Laboratories, Nutley, NJ, USA), or dolasetron (Anzemet[®], Aventis Pharmaceuticals, Bridgewater, NJ, USA) plus dexamethasone (Decadron[®], Merck and Co, West Point, PA, USA) or the equivalent dose of intravenous methylprednisolone (Depo-Medrol[®], Pharmacia and Upjohn, New York, NY, USA) on the day of treatment with doxorubicin (ie, day 1).

Patients from 18 private-practice oncology groups in the USA funded through the CCOP were enrolled by research personnel at every CCOP site from June 12, 2001, to June 11, 2004. The choice of which 5-HT-receptor antagonist to prescribe and the method by which the drugs were given (ie, orally or intravenously), was decided by the patient's oncologist. Patients scheduled to receive liposomal doxorubicin, cisplatin, doxorubicin for more than 1 day, dacarbazine, altretamine, nitrosoureas, or streptozocin, and those scheduled to receive radiotherapy or interferon concurrently with chemotherapy, were not eligible. Patients with clinical evidence (as judged by the treating oncologist) of current or impending bowel obstruction or symptomatic brain metastases were not eligible. Chemotherapy agents other than those listed above could be given: orally, intravenously, or by continuous infusion on one or several days; in an adjuvant or neoadjuvant setting; and with curative or palliative intent. The institutional review board of the University of Rochester and every participating site approved the protocol in accordance with an assurance filed with, and approved by, the US Department of Health and Human Services. Patients gave written informed consent.

Randomisation

A random-numbers table generated in the Department of Biostatistics, University of Rochester, with the SAS computer program was used to assign patients to one of three groups (figure 1). The allocation sequence was generated by a programmer at the Department of Biostatistics, who had no further role in the trial. Randomisation, stratified by CCOP site by use of separate blocked lists of three, was done centrally via a secure internet connection owned by the University of Rochester and maintained by an information analyst for the CCOP, and was followed immediately by an automated email confirmation of University of Rochester Cancer Center (URCC) CCOP web registration and the randomisation result.

An open-label study design was used—ie, oncologists, patients, and investigators were not masked as to the drugs they were assigned. On the day of starting chemotherapy with doxorubicin, all patients were given a 5-HT-receptor antagonist with dexamethasone (12 mg orally or 10 mg intravenously), or the equivalent dose of intravenous methylprednisolone, about 30 min before doxorubicin infusion. On day 1, patients assigned to group one were given a prescription for prochlorperazine tablets (Compazine[®], GlaxoSmithKline, Research Triangle Park, NC, USA), and were instructed to take the tablets as outlined in the protocol, starting on day 2, whether or not they had any symptoms of nausea or vomiting. Patients assigned to group two were prescribed any first-generation 5-HT-receptor antagonist (except palonosetron) as standard dose,³ and were instructed to take the tablets as outlined, starting on day 2. Patients

assigned to group three were prescribed prochlorperazine tablets and instructed to take one tablet by mouth as needed to control symptoms of nausea or vomiting, starting on day 2 (figure 1). Oncologists could prescribe additional (ie, rescue) drugs as needed to alleviate symptoms of nausea and vomiting. No free or discounted drugs were supplied for any patients or any sites.

The primary endpoint was mean severity of delayed nausea. The secondary endpoint was quality of life, data for which are not presented in this report. Furthermore, we assessed severity of acute nausea, frequency of acute and delayed nausea, frequency of acute and delayed vomiting, and compliance. Analyses were by intention to treat.

Assessments

On enrollment, patients completed pretreatment assessments of: an on-study interview with questions about marital status, sex, age, ethnic origin, occupation, education, previous treatment, alcohol consumption, susceptibility to motion sickness, history of pregnancy-related nausea and vomiting, susceptibility to nausea and vomiting compared with family and friends, and expectation of nausea and vomiting compared with other patients receiving the same treatment; a questionnaire about expectations of having nausea, vomiting, fatigue, and hair loss; and a quality-of-life questionnaire (FACT-G). Pretreatment assessments were completed in the clinic before chemotherapy or at home before the first chemotherapy appointment. The clinical research associate at every site was responsible for coordinating the completion of these forms.

Patients were given a home-record card by the clinical research associate at the site, who instructed the patients on how to complete the form. Patients recorded nausea and vomiting on day 1 while at the clinic, and continued to complete the card at home for days 2 and 3. The home-record card was to be returned to the treatment site in a postage-paid envelope. A phone-call reminder was made by clinic personnel on the third day after treatment. The home-record card enables the patient to note nausea, vomiting, and use of antiemetic drugs.^{6,7} Every day is divided into four segments (morning, afternoon, evening, and night), and patients report the severity of nausea and number of vomiting episodes for the periods of that day. Severity of nausea was assessed by use of a 7-point semantic rating scale, ranging from 1 ("not at all nauseated") to 7 ("extremely nauseated").

Mean scores of nausea severity were obtained from the afternoon, evening, and night reporting periods on day 1 (ie, for assessment of acute nausea) and from morning, afternoon, evening, and night reporting periods from days 2 and 3 (ie, for assessment of delayed nausea). Mean severity of delayed nausea was calculated by obtaining the mean of recorded values for the eight reporting periods of days 2 and 3. The number of patients who reported nausea (ie, score >1 for any reporting period) and who reported vomiting (ie, any number >0 for any reporting period) was calculated. All analyses were done at the URCC by JAR and JTH. We used scannable forms, data from which were automatically entered into an ACCESS database; an information analyst checked all data processing. Missing data for nausea severity for any reporting period were substituted with the mean nausea severity for the remaining periods of that day for a patient. If all data for nausea severity were absent for any one day, the data was classed as missing and the patient's data were not evaluable.

Statistical analyses

ANOVA and two-sided *t* tests were used to compare mean severity of delayed nausea between groups. Separate regression models with nausea occurrence (yes vs no) and mean severity of delayed nausea as the dependent variables were generated to test for differences between

groups, while controlling for possible predictor variables. Data are reported for days 1, 2, and 3.

On the basis of data for a previous URCC CCOP Research Base protocol, we expected mean severity of delayed nausea in patients receiving doxorubicin to be 2.14 (SD 1.17). 600 evaluable patients (ie, 200 per group) would provide 80% power to detect an 18% difference in mean severity of nausea between groups. To account for 10% of randomised patients to have no information on the outcome variables after first-line chemotherapy, a total enrollment of 670 patients was planned. No interim analyses were planned or done. Although analyses were done by intention to treat, 20 patients had no outcome data, and were therefore excluded from analyses.

We used SPSS version 12 for all analyses. Statistical tests were two-tailed with a level of significance of 5%. A Bonferroni correction was used to control the overall significance level of all three pairwise comparisons to 0.05.

Role of the funding source

The sponsor of the study had no role in the design of the study; in the collection, analysis, or interpretation of data; or in the writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

691 patients were enrolled onto the study and randomised to one of the three groups, 671 of whom had evaluable data (figure 2). Table 1 shows the baseline characteristics by treatment group. Mean severity of delayed nausea for all 671 patients was 2.29 (95% CI 2.18–2.39). Mean severity of delayed nausea for the 226 patients in group one assigned prochlorperazine every 8 h was 2.25 (2.06–2.43), for the 226 patients in group two assigned 5-HT-receptor antagonist 2.33 (2.13–2.50), and for the 219 patients assigned prochlorperazine as needed 2.30 (2.14–2.48). One-way ANOVA showed that groups did not differ in mean severity of delayed nausea ($p=0.814$).

519 (77%) of the 671 patients had delayed nausea, with a mean severity of 3.33 (3.22–3.44). 161 (71%) of 226 patients assigned prochlorperazine every 8 h reported delayed nausea (mean severity 3.37 [3.16–3.58]), as did 179 (79%) of 226 patients assigned 5-HT-receptor antagonists (3.29 [3.09–3.48]) and 179 (82%) of 219 patients assigned prochlorperazine as needed (3.33 [3.15–3.50]). One-way ANOVA showed that these groups did not differ in mean severity ($p=0.853$). 152 (23%) of 671 patients reported severe nausea (ie, score 6 or 7) at least once during the 2 days, with no difference between groups by use of ANOVA ($p=0.895$).

Table 2 shows data for acute nausea and vomiting for all patients. Figure 3 shows mean severity of acute and delayed nausea, and maximum severity of acute and delayed nausea for those who reported it. Neither maximum acute nausea differed between groups ($p=0.387$) nor that of maximum delayed nausea ($p=0.572$). In all instances, all underlying assumptions for use of ANOVA were met.

Overall, 561 (84%) of the 671 patients reported nausea, 347 (52%) of whom noted acute nausea (table 2). The overall frequency of delayed nausea was greater than that of acute nausea. Patients allocated prochlorperazine every 8 h had less delayed nausea than did those allocated 5-HT-receptor antagonists ($p=0.05$, t test) and those allocated prochlorperazine as needed ($p=0.009$, t test). Patients assigned 5-HT-receptor antagonists did not differ from those assigned prochlorperazine as needed in the frequency of delayed nausea ($p=0.501$, t test). Further analysis showed that, irrespective of treatment group, more patients had nausea on day 3

compared with on day 2 (475 [71%] of 671) vs 425 [63%] of 671; $p<0.0001$, χ^2 test). Figure 4 shows the proportion of patients who had acute nausea and delayed nausea (difference between groups for delayed nausea $p=0.022$, ANOVA).

Age, sex, expectation of having nausea, history of motion sickness, and acute vomiting were significantly associated with severity of delayed nausea (table 3). Linear-regression analysis, controlling for these variables, confirmed that the type of antiemetic given on days 2 and 3 did not affect the mean severity of delayed nausea (table 3). Age younger than 53 years, women, a history of motion sickness, and an expectation of nausea accounted for 10% of the variance in mean severity of delayed nausea (table 3). Acute vomiting (ie, yes vs no) contributed an additional 7% of the variance in mean severity of delayed nausea when entered as step two in the analyses (table 3).

Logistic-regression analysis with delayed nausea (ie, yes vs no) as the outcome measure confirmed that treatment group was a significant factor in determining the occurrence of delayed nausea (table 4). Furthermore, patients who had acute nausea were more likely to develop delayed nausea compared with those who had no acute nausea ($p<0.0001$, t test), and the severity of their nausea was also greater than for patients who did not have acute nausea ($p<0.0001$, t test).

121 (18%) of 671 patients had one episode of acute vomiting, and 194 (29%) had at least one episode of delayed vomiting (129 [19%] on day 2 and 142 [21%] on day 3). Groups did not differ in the frequency of acute vomiting (table 2) or delayed vomiting ($p=0.332$). Patients who reported acute vomiting had more delayed vomiting than did patients without acute vomiting ($p<0.0001$, χ^2 test). Figure 5 shows the frequency of acute vomiting and delayed vomiting; table 5 shows the mean number of vomits and mean severity of nausea according to whether patients reported the symptom on day 1.

219 (97%) of 226 patients assigned prochlorperazine every 8 h complied with treatment, as did 220 (97%) of 226 assigned 5-HT-receptor antagonists. 178 (81%) of 219 assigned prochlorperazine as needed took at least one tablet during days 2 and 3. Patients allocated prochlorperazine as needed took fewer tablets on days 2 and 3 than did those allocated prochlorperazine every 8 h (1.7 [SD 1.7] vs 2.8 [1.0] mean tablets per day on day 2 [$p<0.0001$, t test]; 1.7 [1.7] vs 2.7 [1.7] mean tablets per day on day 3 [$p<0.0001$]).

165 (25%) of the 671 patients took additional rescue drugs to control nausea or vomiting. The proportion of patients taking additional drugs differed significantly between groups: 77 (34%) of the 226 patients assigned a 5-HT-receptor antagonist compared with 47 (21%) of 226 patients assigned prochlorperazine every 8 h ($p<0.0001$, χ^2 test), and with 41 (19%) of 219 assigned prochlorperazine as needed ($p<0.0001$, χ^2 test). The two groups assigned prochlorperazine did not differ in the use of additional drugs ($p=0.334$). Dexamethasone was seldom prescribed after the first day of treatment, and the proportion of patients taking this drug did not differ between groups (eight (4%) of 226 patients assigned prochlorperazine every 8 h vs nine (4%) of 226 assigned 5-HT-receptor antagonists vs ten (5%) of 219 assigned prochlorperazine as needed; $p=0.863$). No serious, unexpected, or treatment-related adverse events were reported, and the study did not identify any new safety concerns related to these drugs.

Discussion

We have shown that neither short-acting 5-HT-receptor antagonists nor prochlorperazine adequately control delayed nausea in patients given a chemotherapy regimen containing doxorubicin. 5-HT-receptor antagonists given on days 2 and 3 after chemotherapy were no more effective than was prochlorperazine in controlling the severity of delayed nausea. About three-quarters of the patients had delayed nausea at least once, the severity of which was greater

than that of acute nausea. Although patients assigned prochlorperazine every 8 h reported less delayed nausea than did those assigned 5-HT-receptor antagonists or prochlorperazine as needed, the proportion was unacceptably high.

Consistent with the findings of previous studies,^{1,8} we found that the strongest predictor of delayed nausea and vomiting was the occurrence of acute nausea and vomiting. However, we² and others¹ have noted that delayed nausea arises in the absence of acute symptoms in 18–24% of patients. Our findings confirm those from previous studies in that patients aged 52 years or younger and women were more likely to have delayed nausea than were those older than 52 years and men, and that a high expectation of nausea was a significant predictor of more severe nausea.

Several studies^{1,9,10} suggest that 5-HT-receptor antagonists are not significantly better than are their earlier counterparts (ie, compazine and metoclopramide) in the prevention of delayed nausea and vomiting after moderately emetogenic chemotherapy. Grunberg and colleagues¹ found that 119 (52%) of 227 patients receiving moderately emetogenic chemotherapy had delayed nausea; 71% had been given a 5-HT-receptor antagonist for at least 3 days and 55% had taken dexamethasone for at least 3 days. Comparisons^{9,10} of a 5-HT-receptor antagonist plus dexamethasone with metoclopramide plus dexamethasone, in a total of 368 patients, found no significant differences between study groups in the control of delayed nausea or delayed vomiting. However, in a trial¹¹ of 407 patients, a 5-HT-receptor antagonist combined with dexamethasone provided better control of delayed nausea than did dexamethasone alone. A review by Roila and colleagues¹² concluded that use of 5-HT-receptor antagonists did not adequately control delayed vomiting, consistent with previous reports.^{11,13,14} Furthermore, a meta-analysis of 5-HT-receptor antagonists¹⁵ concluded that there was insufficient clinical evidence for use of these antagonists for the prevention of delayed vomiting.

A limitation of our study is that we do not present data for nausea and vomiting after day 3. Although the duration of nausea and vomiting would be interesting to analyse, we have shown¹⁶ that the frequency and severity of nausea are at their maximum on the morning of day 3, and that the frequency and severity of vomiting remain fairly constant during the first 4 days of a chemotherapy cycle. Extension of the assessment period during chemotherapy might be useful and ensure better comparisons with findings from other studies. We did not specify any dose restrictions for doxorubicin or obtain information on the dose given to patients. Doxorubicin is not given at a dose of more than 60 mg/m² in every cycle; as part of the TAC (docetaxel, doxorubicin, and cyclophosphamide) regimen 50 mg/m² can be given, but this combination is not used often. Most patients probably received the full, planned dose of doxorubicin because the study analysed only the first cycle of chemotherapy.

Published guidelines have focused their recommendations strongly on the control of vomiting, and generally accepted classification schemes for chemotherapy agents rank these drugs according to their propensity to cause vomiting rather than their tendency to cause nausea.¹⁷ Although current guidelines for the prevention of delayed nausea and vomiting in patients receiving moderately emetogenic chemotherapy consistently recommend the use of a 5-HT-receptor antagonist plus dexamethasone for prevention of acute symptoms, they continue to recommend several alternative regimens for prevention of delayed symptoms, reflecting the uncertainty of panel members and the weakness of published evidence.^{3,4,18} Even though these guidelines may outline optimum treatment for control of vomiting, these drugs do not seem to be adequate for control of delayed nausea.

Prochlorperazine has not been studied extensively for its ability to control delayed nausea and vomiting. Studies^{19,20} have shown a small effect of dopamine-receptor antagonists against delayed nausea in patients receiving non-cisplatin chemotherapy. A small comparison¹⁹ of

domperidone with ondansetron and with placebo for delayed nausea and delayed vomiting in patients receiving cisplatin or doxorubicin with cyclophosphamide found that domperidone was more effective than was ondansetron for the prevention of the delayed nausea and vomiting.

The effectiveness of dexamethasone in the control of delayed nausea is unclear. Whereas some studies²¹ have shown that dexamethasone was more effective against delayed nausea than were 5-HT-receptor antagonists, others^{22–24} have found dexamethasone combined with a 5-HT-receptor antagonist to be no more effective than was dexamethasone alone. A large, well designed study¹³ recorded that the addition of dexamethasone to an antiemetic regimen of ondansetron, as favoured in most guidelines, did not decrease markedly the incidence of delayed nausea in patients who had had acute vomiting. In our study, dexamethasone use was low, possibly because its use was not preplanned and by the time patients requested additional antiemetic support, physicians were reluctant to begin a course of this drug. Moreover, not all oncologists are comfortable with prescribing more than one dose of dexamethasone for several days after chemotherapy.²⁵ In view of the ease of availability, low cost, and evidence for the efficacy of dexamethasone for control of chemotherapy-related nausea and vomiting, a study to clarify its role in the delayed phase is needed.

Two new antiemetics not available at the time this study started might be more effective than 5-HT-receptor antagonists and therefore need further assessment. Antagonists for neurokinin receptor 1, such as aprepitant, are promising drugs and should be tested in the setting of a randomized controlled trial for patients receiving moderately emetogenic chemotherapy. However, a placebo-controlled phase III trial²⁵ of women with breast cancer given cyclophosphamide-based chemotherapy found no benefit in control of nausea for the addition of aprepitant to oral ondansetron and dexamethasone on day 1 of chemotherapy and compared with ondansetron alone after the first 24 h of chemotherapy. Palonosetron, a selective 5-HT-receptor antagonist with a high binding affinity for the 5-HT receptor and a half-life of about 40 h, has been approved by the US Food and Drug Administration for the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic and highly emetogenic chemotherapy. Results of registration trials^{26–28} suggested that palonosetron is equally as, or more, efficacious than are 5-HT-receptor antagonists in the control of acute and delayed nausea and vomiting. Palonosetron is the first, and at present the only, 5-HT-receptor antagonist to have a specific indication for the prevention of chemotherapy-induced delayed nausea and vomiting in patients receiving moderately-emetogenic drugs, and should be tested in the community oncology setting.

Further research into the causative mechanisms of nausea, especially delayed nausea, is needed, and the introduction of new agents should be preceded by basic research into the physiological mechanisms of nausea such as disorders of the autonomic nervous system. Oncology organizations should consider the development of specific guidelines for nausea, including delayed nausea, to complement those that exist for vomiting.

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Figure 1. Study scheme
Day 1=day of doxorubicin treatment.

Figure 2.
Trial profile

Figure 3. Severity of acute and delayed nausea in patients who reported nausea (A) Mean severity. (B) Maximum severity. Vertical bars are SE.

Figure 4. Proportion of patients with acute and delayed nausea
Vertical bars are upper limit of the 95% CI.

Figure 5. Proportion of patients with acute and delayed vomiting
Vertical bars are upper limit of the 95% CI.

Table 1

Baseline characteristics by study group

	Prochlorperazine every 8 h (n=226)	5-HT-receptor antagonist (n=226)	Prochlorperazine as needed (n=219)
Age			
Mean (SD)	52 (11.4)	54 (10.8)	52 (11.2)
Sex			
Men	16 (7%)	10 (4%)	12 (6%)
Women	210 (93%)	216 (96%)	207 (95%)
Ethnic origin			
White	197 (87%)	201 (89%)	193 (88%)
Black	22 (10%)	20 (9%)	15 (7%)
Other	7 (3%)*	5 (2%) [†]	11 (5%) [‡]
Education			
Beyond high school	139 (62%)	132 (58%)	126 (58%)
High School or less	87 (38%)	94 (42%)	93 (42%)
History of motion sickness			
Yes	70 (31%)	69 (30%)	79 (36%)
No	156 (69%)	157 (70%)	140 (64%)
Diagnosis			
Breast cancer	204 (90%)	206 (91%)	194 (89%)
Lymphoma	21 (9%)	17 (8%)	25 (11%)
Other	1 (1%) [§]	3 (1%) [¶]	0
Previous treatment			
Surgery	192 (85%)	208 (92%)	183 (84%)
Chemotherapy	2 (1%)	2 (1%)	3 (1%)
Radiotherapy	2 (1%)	8 (4%)	6 (3%)
None	30 (13%)	8 (4%)	27 (12%)

Data might not add to 100% because of rounding.

* 3 Hispanic, 2 Asian, 1 Native American, and 1 unknown.

[†] 2 Hispanic, 1 Asian, and 2 Native American.[‡] 6 Hispanic, 2 Asian, 2 Native American, and 1 unknown.[§] Urinary bladder cancer.[¶] 1 multiple myeloma, 1 endometrial cancer, and 1 soft-tissue sarcoma.

Table 2

Acute nausea and vomiting

	Prochlorperazine every 8 h (n=226)	5-HT-receptor antagonist (n=226)	Prochlorperazine as needed (n=219)	p
Nausea				
Proportion of patients	117 (52%)	115 (51%)	115 (53%)	0.937
Mean severity (95% CI)	2.0 (1.8–2.2)	1.9 (1.8–2.1)	2.0 (1.8–2.2)	0.833
Maximum severity (95% CI) *	2.7 (2.4–3.0)	2.5 (2.3–2.8)	2.6 (2.3–2.9)	0.73
Vomiting				
Proportion of patients	42 (19%)	35 (16%)	44 (20%)	0.435

Data are for day 1 of treatment.

* Mean highest nausea severity.

Table 3

Linear regression: prediction of mean delayed nausea severity

	R	R²	Adjusted R²	p
Nausea expectation, sex, motion sickness, age	0.314	0.099	0.093	<0.0001
Nausea expectation, sex, motion sickness, age, acute vomiting	0.409	0.167	0.161	<0.0001
Nausea expectation, sex, motion sickness, age, acute vomiting, study group	0.409	0.167	0.160	0.637

Table 4
Stepwise logistic regression: prediction of delayed nausea

	Coefficient	Coefficient/SE	Odds ratio (95% CI)	p
Step 1: age-group				
≤52 years vs ≥53 years	1.025	4.95	2.79 (1.86–4.18)	<0.001
Step 2: sex				
Women vs men	0.926	2.54	2.52 (1.24–5.16)	0.015
Step 3: acute vomiting				
Yes vs no	0.922	2.81	2.52 (1.32–4.78)	0.006
Step 4: study group				
5-HT-receptor antagonist vs prochlorperazine every 8 h	0.561	2.42	1.75 (1.11–2.76)	0.019
Prochlorperazine as needed vs prochlorperazine every 8 h	0.651	2.72	1.92 (1.20–3.06)	0.014

Table 5

Acute vomiting and nausea: effect on delayed vomiting and delayed nausea

	Proportion of patients (%)	Mean severity of delayed event (SE)	p [*]
Acute vomiting[†]			
No	547 (82%)	0.88 (0.13) [‡]	<0.0001
Yes	119 (18%)	4.0 (0.49) [‡]	
Acute nausea[§]			
No	320 (48%)	1.7 (0.05) [¶]	<0.0001
Yes	347 (52%)	2.8 (0.08) [¶]	

* t test.

[†] Data for acute vomiting missing for 3 patients, and data for delayed vomiting for 2 patients.

[‡] Mean severity of delayed vomiting.

[§] Data for acute nausea missing for 4 patients.

[¶] Mean severity of delayed nausea.