History of the Development of Antiemetic Guidelines at Mayo Clinic Rochester

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This article describes the historic experience of the development of antiemetic guidelines for patients taking chemotherapy drugs at Mayo Clinic Rochester. The initial guidelines for the use of serotonin (5-hydroxytryptamine 3) receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting were developed in early 1995 and implemented in September 1995. In February 1997, the guidelines were reviewed and modified. In the spring of 1998, major changes were made based on new data from the literature and discussions with antiemetic authorities.

Antiemetic treatment of patients with chemotherapy-induced nausea and vomiting was recently revolutionized because of the high degree of efficacy and low toxicity profile of serotonin (5-hydroxytryptamine, [5-HT$_3$]) receptor antagonists. Over the past decade, numerous studies have evaluated different 5-HT$_3$ receptor antagonists (including the 3 clinically available in the United States, ondansetron, granisetron, and dolasetron) and examined a myriad of doses and different routes of administration (primarily intravenous and oral). Many unanswered, clinically important questions remain, and multiple studies are currently ongoing to address these issues. In short, it has been difficult for all physicians to keep informed of this rapidly changing field.

The cost of these agents is substantial. In 1997, 5-HT$_3$ receptor antagonists accounted for approximately 5% of the overall pharmacy budget at Mayo Clinic Rochester, totaling approximately $1.5 million.

INITIAL GUIDELINE DEVELOPMENT
In early 1995, a decision was made to develop institutional guidelines for the use of 5-HT$_3$ receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. At that time, ondansetron was the most expensive of all the drugs in our dedicated chemotherapy pharmacy, representing a higher cost than any single cytotoxic chemotherapeutic agent. In addition, the use of 5-HT$_3$ receptor antagonists among the many medical oncologists at the clinic was diverse.

One clinical case was instrumental in initiating the development of guidelines. A hospitalized patient had pronounced chemotherapy-induced nausea and vomiting despite receiving 32 mg/d of ondansetron. He was given a continuous infusion of 1 mg/h of ondansetron. Because his nausea and emesis did not resolve, the infusion was increased to 2 mg/h and later to 3 mg/h. This patient was receiving hundreds of dollars worth of ondansetron per day in an unsuccessful attempt to alleviate his nausea and vomiting. Thus, 2 questions arose. First, have any studies suggested that a continuous infusion of ondansetron is more effective than a single daily dose? At that time, information was becoming available that a single daily dose was as effective as several split doses throughout the day. Second, have any data suggested that such high doses are more effective than substantially lower doses?

A committee of interested physicians, nurses, and pharmacists was formed, and the available literature was reviewed. The cytotoxic chemotherapeutic regimens used at our institution were graded in terms of expected emetogenicity from grade 1 (least) through grade 4 (worst). This grading system was eventually compared to that of Hesketh et al., and a remarkable consistency between the 2 methods was shown.
Standard Antiemetic Order Guidelines*—Revised 12/14/98

Scope: These guidelines describe antiemetic therapy for patients receiving cytotoxic chemotherapy.

Population: For patients 18 years and older who are receiving chemotherapy.

Aims: (1) To allow optimal antiemetic therapy at the most reasonable clinical cost.
(2) To facilitate easy standardization of antiemetic therapy.

A. Prophylactic therapy
Physician will write “standard antiemetics” on the physician order sheet. Nurse or pharmacist will use the “Emetogenic Potential for Mayo Non-Study Regimens” reference to obtain information on the emetogenicity of the treatment. Orders will be written on the order sheet and administered by the nurse as per the following guidelines.

Grade 4 emesis potential
1. Dexamethasone, 20 mg orally (po) pretreatment.
   Multiple trials have demonstrated that dexamethasone enhances the benefit of serotonin (5-hydroxytryptamine, [5-HT]) receptor antagonists. A 10- to 20-mg dose has been used in different trials, but experts believe that 20 mg is more effective than 10 mg.1-16
2. Granisetron, 1 mg po pretreatment. Multiple trials have proved that oral 5-HT, antagonists are as effective as intravenous (IV) 5-HT, antagonists. Although the Food and Drug Administration has approved a 2-mg po dose of granisetron as an effective antiemetic agent, other data are convincing that 1 mg is as efficacious (RJ Gralla, MD, unpublished data, 1998).17-21
3. Dexamethasone, 8 mg po twice a day (bid) for 2 d and then 4 mg po bid for 2 d. A standard approach by experts in the field is to use dexamethasone for prevention of delayed nausea and vomiting. Current evidence does not suggest that 5-HT receptor antagonists have additional benefit for delayed nausea and vomiting.
4. Prochlorperazine, 10 mg po every 6 h as needed (prn) (10f).
   Standard treatment of emesis.
5. Lorazepam, 1 mg po every 1 h pm; do not give if patient has excessive drowsiness (provide prescription or have nurse call in order pm for nausea and vomiting). Standard treatment of emesis.22-33

Grade 3 emesis potential
1. Dexamethasone, 20 mg po pretreatment.
2. Ondansetron, 16 mg po pretreatment. (Studies illustrate that 16 mg of ondansetron is appropriate for treatment of moderately emetogenic chemotherapy.)
3. Dexamethasone, 4 mg po bid for 2 d (optional). (Since grade 3 emetogenic chemotherapy has less potential for causing delayed nausea and vomiting, we did not think that a subsequent dose of dexamethasone should be given to all patients. Thus, we allow this to be individualized.)
4. Prochlorperazine, 10 mg po every 6 h pm (10f).
5. Lorazepam, 1 mg po every 1 h pm; do not give if patient has excessive drowsiness (provide prescription or have nurse call in order pm for nausea and vomiting).

Grade 1 or 2 emesis potential
1. Dexamethasone, 20 mg po (optional).
2. Prochlorperazine, 10 mg po pretreatment (optional).
3. Prochlorperazine, 10 mg po every 6 h pm (10f).

B. Recommendations for nausea and vomiting that occur after chemotherapy
These standard treatments of nausea and vomiting are used when 5-HT, receptor antagonists are not effective.
One of the following can be used, but in general these medications should not be combined:
• Prochlorperazine, 10-mg tablets po every 6 h. 15-mg time-release capsules every 12 h, or 25 mg per rectum (pr) every 12 h pm for nausea, vomiting, or both.
• Haloperidol, 1 mg po every 4 h pm.
• Promethazine, 25-50 mg pr every 6 h pm.
• Lorazepam, 1 mg po every 1-2 h pm; do not give if patient has excessive drowsiness.
• Diphenhydramine, 50 mg po every 4-6 h pm.
• Dexamethasone, 4-8 mg po bid for maximum of 4 d.
• Promethazine, 25-50 mg pr every 6 h pm.
• Dronabinol, 2.5-7.5 mg po every 4 h pm.

C. Recommendations for subsequent cycle of the same chemotherapeutic regimen when patient experienced problems with the previous cycle of chemotherapy
The following seem to be reasonable intuitive recommendations but have not been studied in detail.
• If the patient had received grade 1-2 or grade 3 emetogenic chemotherapy, use the next level of antiemetic therapy (eg, grade 4 emesis treatments for patients who are receiving grade 3 emetogenic chemotherapy).
• If the patient had received grade 4 emetogenic therapy and had rapid onset of nausea or vomiting (within 24 h), 2 mg of po granisetron can be used. If the patient does not experience relief with the second regimen, use 1 mg po granisetron on subsequent cycles. If the patient is unable to take oral medication, granisetron may be administered IV at a dose of 0.01 mg/kg.
• If the patient experienced delayed nausea and vomiting, consider adding metoclopramide, 20 mg po every 6 h for 4 d.
• If the patient is receiving grade 4 emetogenic chemotherapy, continue this regimen and treat the nausea and vomiting per Section B. If this is not effective, consider changing to a different chemotherapeutic regimen.

D. Anticipatory nausea and vomiting
Anticipatory nausea and vomiting, phenomena of anxiety, may be treated with lorazepam, 1 mg po at bedtime the night before chemotherapy and 1 mg the morning of chemotherapy. Behavioral modification and biofeedback techniques may also be helpful.

*Virtually all the medications can be given intravenously at similar doses if the patient is unable to take oral medication.
†Total number of tablets per prescription.
Table 1. Antiemetic Guideline Summaries for Patients Receiving Chemotherapy*†‡

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<tr>
<td>Grade 4 (with cisplatin)</td>
<td>Dexmethasone, 20 mg IV; granisetron, 10 μg/kg IV; ondansetron, 8 mg po every 12 h for 4 doses; prochlorperazine, 10 mg po every 6 h pm</td>
<td>Dexmethasone, 10 mg IV; granisetron, 10 μg/kg IV or 2 mg po; ondansetron, 8 mg po every 8 h for 7 doses; dexmethasone, 4 mg po bid for 5 doses; prochlorperazine, 10 mg po every 6 h pm</td>
<td>Dexmethasone, 20 mg po; granisetron, 1 mg po; metoclopramide, 40 mg bid for 4 d; dexmethasone, 8 mg po bid for 4 d and then 4 mg po bid for 2 d; prochlorperazine, 10 mg po every 6 h pm; lorazepam, 1 mg po every 1 h pm; metoclopramide, no longer used</td>
<td>Dexmethasone, 20 mg po; granisetron, 1 mg po; dexamethasone, 8 mg po bid for 4 d and then 4 mg po bid for 2 d; prochlorperazine, 10 mg po every 6 h pm; lorazepam, 1 mg po every 1 h pm; metoclopramide, no longer used</td>
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<tr>
<td>Grade 4 (without cisplatin)</td>
<td>Dexmethasone, 20 mg IV; granisetron, 10 μg/kg IV; prochlorperazine, 10 mg po every 6 h pm</td>
<td>Dexmethasone, 10 mg IV; granisetron, 10 μg/kg IV or 2 mg po; ondansetron, 8 mg po every 12 h for 5 doses; dexmethasone, 4 mg po bid for 5 doses; prochlorperazine, 10 mg po every 6 h pm</td>
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<td>Grade 3</td>
<td>Dexmethasone, 10 mg IV; ondansetron, 10 mg IV; prochlorperazine, 10 mg po every 6 h pm</td>
<td>Dexmethasone, 10 mg IV; ondansetron, 10 mg IV; prochlorperazine, 10 mg po every 6 h pm</td>
<td>Dexmethasone, 20 mg po; ondansetron, 16 mg po; dexmethasone, 4 mg po bid for 2 d; prochlorperazine, 10 mg po every 6 h pm; lorazepam, 1 mg po every 1 h pm</td>
<td>Dexmethasone, 20 mg po; ondansetron, 16 mg po; dexmethasone, 4 mg po bid for 2 d; prochlorperazine, 10 mg po every 6 h pm; lorazepam, 1 mg po every 1 h pm</td>
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<tr>
<td>Grade 1 or 2</td>
<td>Prochlorperazine, 10 mg po every 6 h pm</td>
<td>Prochlorperazine, 10 mg po every 6 h pm</td>
<td>Prochlorperazine, 10 mg po every 6 h pm</td>
<td>Prochlorperazine, 10 mg po every 6 h pm</td>
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*bid = twice a day; IV = intravenously; po = orally; pm = as needed.
†Italicized entries represent changes from the previous guidelines.
‡These guidelines also provided recommendations for the treatment of nausea and vomiting that occurred despite standard prophylactic therapy.
§For inpatients, ondansetron could be given as an 8-mg IV bolus followed by 1 mg/h of continuous infusion.
∥Optional.

Antiemetic treatment regimens were developed for each of the grades of emetogenicity. These guidelines were discussed with all the medical oncologists. When implemented in September 1995, these guidelines allowed physicians to indicate on a chemotherapy form that the patient should receive standard antiemetics when a new chemotherapeutic regimen was initiated. The nurses and pharmacists relied on the grading system to determine the emetogenicity of the chemotherapeutic regimen mentioned, and then they gave the patient the appropriate antiemetic treatment regimen as per the antiemetic guidelines. These initial antiemetic guidelines are summarized in Table 1.

Of note, these initial guidelines attempted to identify the most appropriate therapy as determined by the literature. However, there were biases and practices inherent to our system that were allowed in the initial guidelines to increase acceptance by involved parties. For example, the initial guidelines allowed a continuous infusion of ondansetron at 1 mg/h, but no more. This approach was based primarily on clinical experience and opinion that, in some patients, control is better with continuous infusion of ondansetron when bolus doses of this drug are ineffective. We recognized that such improvement may have been because of the passage of time alone, knowing that chemotherapy-induced nausea and vomiting diminish with time.

**FIRST REVISION**

When guidelines are developed, they should be reviewed at appropriate intervals to ensure that they are updated. We reviewed and modified the antiemetic guidelines in February 1997. The changes made are summarized as follows.

- Intravenous doses of dexamethasone were decreased from 20 mg to 10 mg because, at that time, there was no evidence that 20 mg was substantially more effective than 10 mg.
There was an option to use 2 mg of oral granisetron instead of an intravenous dose of 10 μg/kg.

On days after chemotherapy administration, the dosage of oral ondansetron was increased from 8 mg every 12 hours for 4 doses to 8 mg every 8 hours for 7 doses for grade 4 emetogenic chemotherapy that contained cisplatin and to 5 doses for grade 4 emetogenic chemotherapy that did not include cisplatin.

These revised guidelines are summarized in Table 1. Of note, no data showed that continued oral ondansetron was beneficial, but, nonetheless, it became part of the guideline because of the potential for additional benefit.

REVISED GUIDELINES JULY 1998
The antiemetic guidelines were reviewed again in the spring of 1998. Major changes were made based on new data from the literature and dedicated discussions with antiemetic authorities in the United States. The changes occurred primarily in 2 areas. First, the route of administration of 5-HT3 receptor antagonists was changed from intravenous to oral. Second, relatively low doses of metoclopramide were substituted for ondansetron on the 4 days after administration of chemotherapy. In addition, we resumed the 20-mg dose of dexamethasone but changed the route from intravenous to oral. These revised guidelines are summarized in Table 1.

Because the guidelines were changed substantially, prospective data were obtained before these revised guidelines were implemented. These data were collected for all patients receiving their first cycle of grade 3 or grade 4 emetogenic chemotherapy. Patients were given a daily diary whereby they were asked to rate their nausea from grade 0 (none) to grade 3 (severe) for 5 days after administration of chemotherapy to identify the number of vomiting episodes on each of these 5 days and to address their satisfaction with their antiemetic therapy. After implementation of the new guidelines on July 1, 1998, similar information was collected for approximately 1 month.

After the revised guidelines were instituted, but before the availability of the efficacy data tabulation, some health care providers expressed concern that the severity of nausea and vomiting had increased since the new antiemetic guidelines had been established. The data demonstrated that, although some patients had nausea and vomiting despite the new antiemetic guidelines, the degree did not seem to be any greater than that with the previously used antiemetic guidelines (Figures 1 and 2). Patient satisfaction with the antiemetic regimen is illustrated in Table 2. A virtually identical experience was reported from another institution when the route of administration of 5-HT3 receptor antagonists was changed from intravenous to oral.

REVISED GUIDELINES DECEMBER 1998
After the revised guidelines were instituted in July 1998, when we started using metoclopramide, the oncology nurses perceived a considerably higher incidence of patient complaints of restlessness, agitation, drowsiness, and sleeplessness. This led to several discussions and an eventual decision to discontinue using metoclopramide. Based on data that supported the theory that dexamethasone alone was as effective as a 5-HT3 receptor antagonist for preventing delayed nausea and vomiting, we did not add another 5-HT3 receptor antagonist. We again prospectively monitored nausea and vomiting for 5 days in patients, but only in those receiving grade 4 emetogenic chemotherapy. As illustrated in Figure 1, right and Figure 2, right, there was no suggestion of any decrease.
in antiemetic control when metoclopramide was no longer used. Concomitantly, the nurses reported dramatically fewer telephone calls regarding symptoms of restlessness, agitation, drowsiness, and sleeplessness.

COST COMPARISON
In addition to analyzing antiemetic efficacy with the revised guidelines, we evaluated the costs of the February 1997 antiemetic guideline regimen and the newest antiemetic regimen established in December 1998. Data provided in Table 3 illustrate an almost 75% reduction in costs for the revised antiemetic regimen for highly emetogenic chemotherapy.

FUTURE CONSIDERATIONS
These cost-effective antiemetic guidelines should allow us to incorporate the next step in antiemetic treatment of chemotherapy-induced nausea and vomiting. This step is the expected availability of a new class of antiemetic agents, the neurokinin, receptor inhibitors, which seem to decrease chemotherapy-induced sudden-onset nausea and vomiting, and, to a larger degree, they seem to decrease chemotherapy-induced delayed nausea and vomiting (which occur on days 2 through 4 after therapy).

NEW RESEARCH PROJECT
In investigating the use of 5-HT3 receptor antagonists in our practice and developing the aforementioned guidelines, we noted that these drugs have been used in patients with nausea and vomiting from causes other than those associated with cytotoxic chemotherapy or anesthetic drugs. Data are sparse regarding the utility of these drugs in patients with nausea and vomiting associated with entities such as bowel obstruction, pancreatitis, narcotics, viral syndromes, or advanced cancer in general. A few anecdotal experiences and pilot projects have implicated some efficacy. Currently, we are developing a placebo-controlled clinical trial to ascertain the efficacy of 5-HT3 receptor antagonists for these entities.

SUMMARY REMARKS
In conclusion, it is important to determine whether the development of these antiemetic guidelines and their continual revisions have been worthwhile. This effort has been the result of considerable work from a large number of participants. Has this effort been justified? We believe the answer is "yes." The hours of work entailed in this effort have led to a large number of valuable discussions with physicians, nurses, and pharmacists. We had numerous opportunities to review the literature and to talk with established antiemetic experts in the field. This has led to a group of local health care providers with new expertise regarding antiemetic drugs.

The most recent version of these guidelines is currently used at Mayo Clinic Rochester, and, although they are

<table>
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<th>Emetogenic chemotherapy</th>
<th>Patient satisfaction</th>
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<tr>
<td></td>
<td>February 1997 regimen, No. (%)</td>
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<tr>
<td>Grade 3</td>
<td>7/8 (88)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>16/23 (70)</td>
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</table>

*As per a question on day 5 after chemotherapy.
 voluntary, they are routinely used in both the outpatient and the inpatient settings. The physician does not need to remember the specific emesis potential grade for each chemotherapeutic regimen or the specifics of the antiemetic regimen for each patient. Rather, when a patient starts a new chemotherapeutic regimen, the physician needs only to write "standard antiemetics" on the chemotherapy form and then the oncology nurses and pharmacists can determine the emesis potential grade and the antiemetic treatment. This user-friendly procedure has encouraged compliance with these guidelines. The guidelines, even in their most recent format, are not guaranteed to be the best available. Other groups have developed guidelines that differ from ours. A cross-comparison of different sets of guidelines allows for appropriate introspection of each guideline to address whether the local guidelines seem appropriate. The guidelines we established in December 1998 will clearly change, potentially before the results of this current work are published.

Overall, this guideline development process for antiemetic use has been a way we have been able to attempt to fulfill the primary Mayo vision: "Mayo aspires to provide the highest quality, compassionate patient care at a reasonable cost through a physician-led team of diverse people working together in clinical practice, education and research in a unified multi-campus system."

REFERENCES


12. Cunningham D, Dicato M, Verweij J, et al. Optimum anti-emetic therapy for cisplatin induced emesis over repeat courses: ondan-

Table 3. Cost Comparison Between Regimen Instituted in February 1997 and Newest Regimen Instituted in December 1998

<table>
<thead>
<tr>
<th>February 1997 antiemetic regimen</th>
<th>Cost</th>
<th>December 1998 antiemetic regimen</th>
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<tbody>
<tr>
<td>Dexamethasone, 10 mg IV pretreatment</td>
<td>$1.08</td>
<td>Dexamethasone, 20 mg po pretreatment</td>
<td>$1.85</td>
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<tr>
<td>Granisetron, 700 μg IV pretreatment</td>
<td>$124.18</td>
<td>Granisetron, 1 mg po pretreatment</td>
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<tr>
<td>Ondansetron, 8 mg po every 8 h for 7 doses</td>
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<td>Dexamethasone, 8 mg po bid for 2 d and then 4 mg po bid for 2 d</td>
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<td>Dexamethasone, 4 mg po bid for 5 doses</td>
<td>$1.85</td>
<td>Prochlorperazine, 10 mg po every 6 h pm (10x)</td>
<td>$8.10</td>
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<tr>
<td>Prochlorperazine, 10 mg po every 6 h pm (10x)</td>
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<td>Lorazepam, 1 mg po every 1 h pm (5x)</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>$289.21</strong></td>
<td><strong>Total</strong></td>
<td><strong>$58.94</strong></td>
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*Average wholesale price.
†bid = twice a day; IV = intravenously; po = orally; pm = as needed.
‡Total number of tablets per prescription.


