Oregon Health Resources Commission

Newer Antiemetics

Subcommittee Report

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Health Resources Commission
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Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission to advise the Department of Human Services on this Plan.

In the winter of 2006 the Oregon Health Resources Commission (HRC) appointed a subcommittee to perform an evidence-based review of the use of Newer Antiemetic Drugs. Members of the subcommittee consisted of physicians, a pharmacist, a RN, and a family Nurse Practitioner. The subcommittee had three meetings. All meetings were held in public with appropriate notice provided.

Subcommittee members worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities.

Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC's report, "Drug Class Review on Newer Antiemetics" was completed in January 2006, circulated to subcommittee members and posted on the web. The subcommittee met on February 9, 2006 and March 23, 2006 to review the document and by consensus agreed to adopt the EPC report. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Newer Antiemetic Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services.

The Standing Update Committee of the HRC, working together with the EPCs, Center, OMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. The Newer Antiemetic report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a Newer Antiemetic's Subcommittee.

The full OHSU Evidence-based Practice Center's draft report, *Drug Class Review on Newer Antiemetics* is available on the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website: www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml .

You may request more information including copies of the draft report, minutes and tapes of subcommittee meetings, from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

John Santa, MD
Assistant Director for Health Projects
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There will be a charge for copying and handling in providing documents both from the Office of Oregon Health Policy & Research and from the Center.

Critical Policy:

- *Senate Bill 819*
  - "The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."

- *Health Resources Commission*
  - "Clinical outcomes are the most important indicators of comparative effectiveness";
  - "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Clinical Overview:

Nausea and vomiting associated with surgery, chemotherapy, radiotherapy, and pregnancy are thought to be induced by stimulating the dopamine, acetylcholine, histamine, and serotonin neuroreceptors involved in activating specific areas of the brain that coordinate the act of vomiting.

Post-operative nausea and vomiting (PONV) are frequent complications (25-30%) associated with surgery. The risk of PONV is multi-factorial and can be influenced by patient characteristics, type of surgery, and anesthesia. Surgical procedures with a high risk of PONV include: craniotomy, ENT procedures, breast surgery, strabismus, and laparoscopic surgery. Anesthesia-related factors include use of opioids, nitrous oxide, and volatile inhalational agents.

Nausea and vomiting are major concerns for patients undergoing chemotherapy and radiotherapy. Risk factors associated with chemotherapy-induced nausea and vomiting (CINV) include emetogenicity of the chemotherapy regimen, dose level, speed of IV infusion, and patient factors. Radiotherapy-induced nausea and vomiting (RINV) is influenced by site and total field size (particularly total body irradiation or radiation fields that include the abdomen), dose, and predisposition for emesis.

Finally nausea and vomiting are symptoms that are also commonly associated with pregnancy. The most severe form is Hyperemesis Gravidarum that can lead to dehydration, metabolic disturbances, hospitalization, and even mortality.

Definition of Newer Antiemetic Drugs:

This review is for 5-HT3's and Substance P drugs. Earlier pharmacologic agents commonly used as antiemetics included histamine-1 blockers, such as diphenhydramine, anticholinergics, and dopamine antagonists, including phenothiazines (e.g., chlorpromazine, perphenazine, prochlorperazine), metoclopramide and droperidol. A discovery that additional type 3 serotonin receptor-blocking properties were contributing to the development of one of the dopamine

antagonists, metoclopramide, eventually lead to the newer anti-serotoninergic drugs. There are currently four 5-HT3 receptor antagonists approved for use in the United States and Canada. The most recent research has focused on the potential role of Substance P in inducing emesis by binding to tachykinin neurokinin (NK_1) receptor sites and this led to the development of the novel substance P receptor antagonist, aprepitant.

- ***Interventions***

Generic	**Brand(s)**
Aprepitant	Emend
Dolasetron	Anzemet
Granisetron	Kytril
Ondansetron	Zofran
Palonosetron	Aloxi

- ***Populations***
  - Adults and children at risk with nausea and/or vomiting, including retching, related to the following therapies and conditions
    - Post-operative nausea and vomiting (PONV)
    - Chemotherapy induced nausea and vomiting (CINV)*
    - Radiation induced nausea and vomiting (RINV)
    - Pregancy

* In this report, we use the emetogenicity classification scale that Hesketh defined in 1997[1] and refined in 1999[2] to clarify the level of emetogenicity of the chemotherapeutic regiment with which the cancer population of the study is being treated. Chemotherapeutic agents rated as "1" on this scale have a low emetogenic potential, while agents rated as "5" are considered to be severely emetogenic (a >90% chance of emesis in patients).

[1] Hesketh PJ, Kris MG, Grunberg SM et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *Journal of Clinical Oncology.* 1997;15(1):103-109.
[2] Hesketh PJ Defining the emetogenicity of cancer chemotherapy regimens: Relevance to clinical practice. *Oncologist.* 1999;4(3):191-196.

Table 1. Antiemetic Drug Indications and Recommended Doses

Generic Name	Trade Name	FDA Approved Indications and Dosage in Adults	FDA Approved Indications and Dosage in Children
Aprepitant	Emend®	**Chemotherapy:** Day 1: 125 mg po once Days 2 & 3: 80 mg po once *Emend is to be given for 3 days in conjunction with a regimen containing a 5HT3-antagonist and a corticosteroid*	**Chemotherapy:** Dose determined by doctor
Dolasetron	Anzemet®	**Chemotherapy:** 100 mg po once (up to 1 hr before chemo) 1.8 mg/kg iv once (up to 30 min before chemo); Alternatively, a fixed dose of 100mg iv can be administered over 30sec. **PONV, prevention:** 100 mg po once (up to 2 hrs before surgery) 12.5 mg iv once (15 min. before anesthesia ends) **PONV, established:** 12.5 mg iv once (at onset of symptoms)	**Chemotherapy (for children 2-16years):** 1.8 mg/kg po & iv once, max. 100mg (up to 30 min before chemo) **PONV, prevention:** 0.35 mg/kg iv once , max. 12.5 mg (15 min before anesthesia ends) 1.2 mg/kg po once , max. 100mg (up to 2 hrs before surgery) **PONV, established:** 0.35 mg/kg iv once, max. 12.5mg (at onset of symptoms)
Granisetron	Kytril®	**Chemotherapy:** 2 mg po once (up to 1 hr before chemo) 0.10mg/kg iv once (up to 30 min before chemo) **PONV, prevention:** 1 mg iv once (before induction or before reversal of anesthesia) **PONV, established:** 1 mg iv once **Radiation:** 2 mg po once	**Chemotherapy:** 0.10 mg/kg iv once (up to 30 min before chemo)
Ondansetron	Zofran®	**Chemotherapy:** *Moderately emetogenic:* 8 mg po (tablet or orally disintegrating tablet) OR 10 mL oral solution given twice daily *Highly emetogenic:* single 24 mg tablet 30 min before chemo; 32 mg iv once (30 min before chemo) or 0.15 mg/kg tid (1st dose is infused 30 min before chemo starts) **PONV, prevention:** 4 mg iv once (immediately before induction of anesthesia) 16 mg po (tablet or orally disintegrating tablet) once (1 hr before anesthesia induction) (*20 mL if oral solution given*) **PONV, established:** 4 mg iv or im once (at onset of symptoms) **Radiation:** 8 mg po (tablet or orally disintegrating tablet) X3 (*10 mL X3 if oral solution given*) (1st dose 1-2 hours before radiation)	**Chemotherapy** ***Moderately emetogenic:*** for patients aged 12 years and above, the dosage is the same as in adults; for patients 4-11 years the dose is 4 mg po (tablet or orally disintegrating tablet) OR 10 mL oral solution given three times daily 0.15mg/kg iv once (30 min before chemo) **PONV, prevention (the iv form is approved for use in patients 1 month to 12 years; the other forms have not been studied in children for PONV):** 0.1 mg/kg iv once if ≤40 kg; 4 mg iv once if >40 kg **PONV, established (the iv form is approved for use in patients 1 month to 12 years; the other forms have not been studied in children for PONV):** 0.1 mg/kg iv once if ≤40 kg; 4 mg iv once if >40 kg
Palonosetron	Aloxi®	**Chemotherapy:** 0.25 mg iv once (up to 30 minutes before chemo)	**Chemotherapy:** Dose determined by doctor

po = (*per os*) orally
iv = intravenous
im = intramuscular

Quality of the Evidence:

For quality of evidence the NAE subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period, and the end points of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

1) Methods used for randomization
2) Allocation concealment and blinding
3) Similarity of compared groups at baseline and maintenance of comparable groups
4) Adequate reporting of dropouts, attrition, and crossover
5) Loss to follow-up
6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

1) Adequate description of the study population
2) Similarity of patients to other populations to whom the intervention would be applied
3) Control group receiving comparable treatment
4) Funding source that might affect publication bias.

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency and power of the body of evidence relevant to that question.

Scope and Key Questions:

The purpose of this review is to compare the effectiveness and adverse effects of different pharmacologic treatments for nausea and vomiting.

Key Question 1	**What is the comparative effectiveness of Newer Antiemetics in treating or preventing nausea and/or vomiting?**
Key Question 2	**What is the comparative tolerability and safety of Newer Antiemetics when used to treat or prevent nausea and/or vomiting?**
Key Question 3	**Are there subgroups of patients based on demographics (age, racial groups, gender), pregnancy, other medications, or co-morbidities for which one Newer Antiemetic is more effective or associated with fewer adverse events?**

Summary of Results:

Key Question 1a **What is the comparative effectiveness of Newer Antiemetics in treating or preventing nausea and/or vomiting for patients with post-operative nausea and vomiting (PONV)?**

The direct comparison of dolasetron vs. ondansetron (5 trials in adults, 3 trials in children) or granisetron vs. ondansetron (2 trials adults, 5 trials children) revealed no consistent differences in efficacy. Although active and placebo-controlled trials of dolasetron and granisetron showed efficacy in adults or children undergoing various surgical procedures; the indirect comparison of these drugs was limited by the heterogeneity of these trials and was not adequate to establish a difference in response rate between these drugs. Aprepitant and palonosetron were not studied for PONV.

Key Question 1b **What is the comparative effectiveness of Newer Antiemetics in treating or preventing nausea and/or vomiting for patients with chemotherapy-induced nausea and vomiting (CINV)?**

When dealing with CINV, the questions is divided into acute and delayed primary prevention. There is no consistent difference in efficacy of oral (1 trial) or parenteral (5 trials) between granisetron vs. ondansetron. There is no data on palonosetron for CINV in children. There is no data supporting repeating the same antiemetic agent if there was break-through nausea and vomiting.

IV palonosetron vs. IV dolasetron or IV ondansetron in two fair-to-poor trials with females undergoing moderately emetogenic (Hesketh levels 3-4) chemotherapy for breast cancer showed that palonosetron was superior in acute/delayed complete response rates. The differences however may be attributable to the longer duration of action of palonosetron.

Aprepitant has been studied only as an add-on to "standard therapy" (granisetron or ondansetron plus dexamethasone) for the prevention of highly or moderately emetogenic chemotherapy-induced nausea and vomiting. In all studies a significantly higher proportion of patients receiving the aprepitant regimen had a complete response compared with patients receiving standard therapy in the acute and delayed phases of treatment.

Key Question 1c **What is the comparative effectiveness of Newer Antiemetics in treating or preventing nausea and/or vomiting for patients with radiation-induced nausea and vomiting (RINV)?**

There were no fair or good quality head-to-head studies for the antiemetics studied. There is limited evidence from historical active-controlled trials that granisetron and ondansetron showed no difference in efficacy. No indirect comparisons were possible for dolasetron, granisetron and ondansetron due to heterogeneity and variability of those trials in underlying risk, clinical settings, comparators, radiotherapy regimen and endpoints. A trial for IV ondansetron reported superiority compared to placebo during total-body irradiation (TBI) for bone-marrow transplantation conditioning regimen, but not 6-12 hours after, in preventing these patients from any emetic event or nausea/retching. There were no trials of newer antiemetics for prevention of radiation-associated nausea and vomiting in children.

Key Question 1d **What is the comparative effectiveness of Newer Antiemetics in treating or preventing nausea and/or vomiting for pregnant patients?**

Evidence on the use of newer antiemetics in pregnant women is extremely limited, and non-comparative for our purposes. The only trial that was identified (rated poor) compared ondansetron and promethazine in 30 women hospitalized with Hyperemesis Gravidarum and found no differences on any outcome measure.

The NAE Subcommittee agrees by consensus that:

1a. In patients with PONV:
- **dolasetron, granisetron and ondansetron are equally effective in preventing PONV in adults or children.**
- **dolasetron, granisetron and ondansetron are less effective in treating established nausea and vomiting.**
- **aprepitant and palonosetron were not studied.**

1b. In patients with CINV:
- **there is no difference in efficacy between oral granisetron and ondansetron.**
- **IV dolasetron vs. IV granisetron were similarly effective.**
- **if there was break-through nausea and vomiting, repeating the same antiemetic agent is not effective.**
- **palonosetron may be superior to dolasetron and ondansetron for acute/delayed complete response rates, but the evidence requires further refinement to eliminate consideration of half-life of single dose of these drugs.**
- **aprepitant has been studied only as an add-on for standard therapy with granisetron or ondansetron.**

1c. In patients with RINV:
- **limited evidence reveals that granisetron and ondansetron showed no difference in efficacy.**

1d. In pregnant patients with Hyperemesis Gravidarum:
- **only ondansetron has been studied in one poor active-controlled trial that showed no superiority over promethazine.**

Key Question 2 **What is the comparative tolerability and safety of Newer Antiemetics when used to treat or prevent nausea and/or vomiting?**

The head-to-head trials are heterogeneous for non-pre-specified adverse events. Specifically, it was unclear as to whether adverse events reported included those that the investigators considered unrelated and impossible to determine whether they were non-biased. It was also unclear whether adverse event reporting included all levels of severity.

In adults the majority (82%) of trials reported adverse event outcomes, but without statistically significant differences for the newer antiemetics. Two trials showed that ondansetron was associated with higher rates of dizziness, blurred vision and constipation than dolasetron; whereas, higher rates of diarrhea and abdominal pain were reported for dolasetron.

Evidence regarding comparative tolerability of newer antiemetics in children is severely limited and indicates no differences in adverse event rates for oral solution and IV forms of ondansetron. There are no comparative tests of newer antiemetic drugs for safety in children.

The only study done comparing ondansetron vs. promethazine in patients with Hyperemesis Gravidarum showed significantly more women experienced sedation with promethazine. No other side effects were noted. A prospective observational study assessed birth outcomes in women and infants exposed to ondansetron during early pregnancy. The study enrolled 188 pregnancies with exposure to ondansetron during 5-9 weeks gestation. No differences were found between the ondansetron and the active control groups for number of live births, proportion of infant deformities, and birth weight.

The NAE Subcommittee agrees by consensus that:

- **Heterogeneity of trials preclude accurate assessment of comparative tolerability or safety for the newer antiemetic drugs.**
- **In adults the only statistically significant difference between ondansetron and dolesetron was the former was associated with more dizziness, blurred vision, and constipation and the latter with more diarrhea.**
- **Comparative evidence in children was severely limited, but IV and oral administration of ondansetron were well tolerated.**
- **In Hyperemesis Gravidarum of pregnancy, ondansetron is less sedating than the active control promethazine. Long term studies of birth outcomes show no difference in number of live births, proportion of infant deformities, and birth weight between ondansetron and the active control group.**
- **Aprepitant and palonosetron were not studied.**

Summary of Results:

Key Question 3 **Are there subgroups of patients based on demographics (age, racial groups, gender), pregnancy, other medications, or co-morbidities for which one Newer Antiemetic is more effective or associated with fewer adverse events?**

Analysis of the comparative efficacy of newer antiemetics in subpopulations was reported only by a few studies focused on PONV and emetogenic CINV. Race or ethnicity was not reported in most trials, thus nothing about differences in effectiveness or safety can be determined from these limited data.

Co-morbidities that were often excluded from these trials included obesity, gastroesophageal reflux disease, cardiovascular disease, diabetes and other serious conditions. Even if the trials allowed patients with one or more of these co-morbidities to enter, they failed to analyze the effects in these subgroups.

There were no consistent differences between dolasetron, granisetron, and ondansetron in rates of complete emetic control in subpopulations based on demographics such as age or gender.

As far as other medications, the only significant finding was that the use of dexamethasone pre-operatively or pre-chemotherapy resulted in higher overall response to the concomitant newer antiemetic used.

Evidence from post-hoc subgroup analysis of a trial of patients receiving emetogenic chemotherapy suggested that ondansetron may be significantly better in preventing vomiting than granisetron in patients with a predisposition to nausea/vomiting. However authors note that these outcomes could be due to chance given that the numbers of patients in these subgroups were relatively small.

The NAE Subcommittee agrees by consensus that:

- **For adults there is no difference in complete response rates in subpopulations based on age, gender or use of concomitant medications between dolasetron, granisetron, or ondansetron.**
- **For children there is no difference in complete response rates in subpopulations based on age for ondansetron.**
- **Aprepitant and palonosetron were not reported.**

Conclusion

It is the decision of the AP Subcommittee that:

1. **In patients with PONV or CINV:**
   - **dolasetron, granisetron and ondansetron are equally effective in preventing nausea or vomiting.**
   - **palonosetron may be superior to dolasetron and ondansetronin for acute/delayed complete response rates.**
   - **aprepitant has been studied as an add-on for standard therapy.**
2. **In patients with RINV:**
   - **granisetron and ondansetron showed no difference in efficacy.**
3. **In pregnant patients:**
   - **ondansetron was not superior to promethazine for effectiveness, but was less sedating.**
   - **Long term studies show no difference in number of live births, proportion of infant deformities, and birth weight between ondansetron and the active control groups.**
4. **Heterogeneity of trials precludes accurate assessment of comparative tolerability or safety for the newer antiemetic drugs.**
5. **Ondansetron is superior to granisetron for complete response rates in subpopulations based on a predisposition to nausea/vomiting such as motion sickness or previous treatment with emetogenic chemotherapy.**

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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.