Chemotherapy-induced nausea and vomiting (CINV) is among the most significant adverse effects in patients treated for cancer. CINV is categorized into three phases: acute, delayed, and anticipatory. The likelihood of developing CINV is driven by patient risk factors such as age and gender, as well the emetogenicity of the prescribed chemotherapeutic regimen. Antiemetic drugs have significantly improved the control of acute CINV due to moderately and highly emetogenic chemotherapy. Because CINV can persist for several days and many patients continue to have suboptimal control of delayed emesis, multiple doses or an antiemetic agent with a long duration of action may be needed to prevent this delayed adverse effect.

The most effective class of anti-emetics for CINV is the serotonin 5-HT\textsubscript{3} receptor antagonists (5-HT\textsubscript{3}s). Three first-generation 5-HT\textsubscript{3}s, ondansetron (ZOFTRAN), dolasetron (ANZEMET) and granisetron (KYTRIL), and one second-generation agent, palonosetron (ALOXI), are available in the United States. Little difference in efficacy and tolerability between first-generation agents has been demonstrated in clinical trials. Furthermore, recent guidelines indicate older 5-HT\textsubscript{3}s
are therapeutically interchangeable.\textsuperscript{4,5} When compared with the first-generation agents, palonosetron has a 100-fold higher binding affinity for the 5-HT\textsubscript{3} receptor and a longer plasma elimination half-life (40 hours) than the first-generation agents.\textsuperscript{6} These characteristics are potential explanations for the prolonged antiemetic activity and efficacy, especially in delayed emesis, of palonosetron compared with first-generation agents.\textsuperscript{7,8}

Substantial differences exist among the 5-HT\textsubscript{3}s in terms of cost, and pharmacy benefit administrators actively manage these products with formulary restrictions, prior authorization, and competitive acquisition practices. From a direct drug cost perspective, one would expect that higher-costing agents would increase the overall costs associated with the prevention and treatment of CINV. However, dosing regimens and efficacy in delayed CINV may affect utilization of supplemental or rescue antiemetic therapy, as well as fewer physician office visits, emergency department visits, or hospitalizations for treatment of uncontrolled CINV.

To examine this matter further, we utilized blinded paid medical and pharmacy claims to evaluate the cost impact of palonosetron compared with the first-generation 5-HT\textsubscript{3}s in the prevention and management of CINV.

\textbf{Methods}

We conducted a cost impact analysis utilizing blinded paid medical and pharmacy claims from two commercial health plans. The plans collectively had more than $15 million in annual expenditures of 5-HT\textsubscript{3}s and no restrictions on their use with pharmacy utilization management techniques. Paid claims from July 1, 2004, to June 30, 2005, were utilized in the analysis.

\textbf{Identification of claims}

Patients with breast, lung, colorectal, ovarian cancers and lymphomas treated with moderate and highly emetogenic chemotherapy (see Table 1) were identified. Additionally, patients had to receive at least one dose of a 5-HT\textsubscript{3} to be included in the analysis. Both pharmacy and medical benefits had to be available from the same insurer. CPT, ICD-9 codes, HCPCS, NDC were captured for all claims during the study period. Finally, patients were enrolled in their plan for at least 1 month prior to and 3 months following 5-HT\textsubscript{3} administration.

\textbf{CINV is categorized into three phases: acute, delayed, and anticipatory.} The likelihood of developing CINV is driven by patient risk factors such as age and gender, as well the emetogenicity of the prescribed chemotherapeutic regimen.\textsuperscript{2}

\textbf{Analytical approach}

Demographic and descriptive data, including claim numbers, member and provider IDs, age, gender, duration of enrollment, and incidence of prior CINV were extracted. Members meeting the inclusion criteria were categorized into either the palonosetron (Aloxi), ondansetron (Zofran), dolasetron (Anzemet) or granisetron (Kytril) groups based upon the first agent utilized during their chemotherapy cycle. Costs included were the actual payor costs for drugs and ancillary services associated with the prevention and treatment of CINV. Any paid claim associated with uncontrolled CINV events for day 0 to 5 following chemotherapy administration were captured and imputed into the cost per patient. These charges included additional anti-emetic therapy, intravenous fluids, and office or emergency department visits for the treatment of nausea, vomiting, and dehydration from day 0 to 5 after chemotherapy (for analytical definitions, see Table 2).

\textbf{Statistical analysis}

There are numerous prognostic factors that increase the likelihood of CINV such as age and history of motion-sickness. Many of these factors are not available via member enrollment or claims data. Also the occurrence of CINV will increase the

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Highly} & \textbf{Moderately} & \textbf{Highly} & \textbf{Moderately} \\
\hline
Cisplatin \textgreater= 50 mg/m\textsuperscript{2} & Oxaliplatin \textgreater= 75 mg/m\textsuperscript{2} & Daunorubicin & Dactinomycin \\
Mechlorethamine & Carboplatin & Daunorubicin & Melphalan \textgreater= 50 mg/m\textsuperscript{2} \\
Streptozocin & Cyclophosphamide \textgreater= 1500 mg/m\textsuperscript{2} & Idarubicin & Methotrexate \\
Cyclophosphamide > 1500 mg/m\textsuperscript{2} & Doxorubicin & Temozolomide & Procarbazine \\
Carmustine \textgreater= 250 mg/m\textsuperscript{2} & Epirubicin & Imatinib & Ifosfamide \\
Dacarbazine & Irinotecan & Carmustine < 250 mg/m\textsuperscript{2} & Lomustine \\
Hexamethylmelamine & Etoposide & Cisplatin \textless 50 mg/m\textsuperscript{2} & Mitoxantrone \\
& Vinorelbine & Amifostine \textgreater= 500 mg/m\textsuperscript{2} & Pemetrexed \\
& Cytarabine & Busulfan \textgreater= 4 mg/d & \\
\hline
\end{tabular}
\caption{Moderately and highly emetogenic chemotherapy}
\end{table}
likelihood of CINV on subsequent chemotherapy cycles. These aspects preclude the use of traditional per member per month methods of analysis. Rather a patient-centric analysis method is required.

Patient demographics, cancer diagnosis, and chemotherapy regimen attributes were compared between the individual 5HT3 groups. These analyses were conducted using traditional univariate and categorical methods. Repeated measures analyses of total direct costs and costs for the 5-HT3 and non-5HT3 were conducted using a general linear regression model with independent variables of cancer type, prior uncontrolled CINV, emetogenicity of chemotherapy (high vs. moderate), chemotherapy cycle, previous 5-HT3 agent received and current 5-HT3 received for that cycle. Also a patient within 5-HT3 regimen was incorporated to control for patient-oriented risk and previous CINV outcomes. Age and gender were considered but were found to add no explanatory value to the regression model and thus, removed from the model. The use of individual 5-HT3 agents was significantly different across chemotherapy cycle lengths (p<0.02). As defined, fully 41% of chemotherapy cycles were less than 7 days or greater than 28 days in length. It was determined that this variation would impact the cost analysis. Thus, this analysis was restricted to only the chemotherapy regimens of 14, 21, and 28 days in length. Differences with p<0.05 were deemed significant.

Results
For this analysis, 652,337 medical and 269,932 pharmacy claims were evaluated. In terms of those patients fitting the inclusion criteria of the study as well as the limited chemotherapy regimen criteria, 837 individuals received 3532 rounds of chemotherapy. The mean age (SD) of the analyzed group was 63.5 (11.2) years and 34% were male, although there were significant differences among the various cancers. Twenty-six percent had lung cancer, 28% had breast cancer, 28% colon cancer, 11% lymphomas, and 7% had ovarian cancer. Overall, 8% had a history of prior CINV and 5% received highly emetogenic chemotherapy, which also varied by cancer type.

Based upon the repeated measures general linear model with control variables described previously, when considering average drug costs per cycle, no significant differences were identified between the 5-HT3 agents (Figure 1). On average, the additional cost for non-5-HT3 antiemetics ranged between $8.33 and $16.25 per cycle, depending upon the 5-HT3 agent used (p>0.05). (Figure 2)

More patients with previous CINV received palonosetron. Palonosetron had an 11% rate of uncontrolled CINV events during the first observed cycle, which was higher than the first-generation 5-HT3s. However the rate of uncontrolled CINV events for these agents was approximately half of the published rates. Once again, based on the repeated measures general linear model analysis, no significant

<table>
<thead>
<tr>
<th>Table 2. Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
</tr>
<tr>
<td>Uncontrolled CINV</td>
</tr>
<tr>
<td>Controlled CINV</td>
</tr>
<tr>
<td>Highly emetogenic chemo</td>
</tr>
<tr>
<td>Moderately emetogenic chemo</td>
</tr>
<tr>
<td>Eligible patient</td>
</tr>
<tr>
<td>First dose of chemo</td>
</tr>
<tr>
<td>Chemotherapy cycle</td>
</tr>
</tbody>
</table>

Figure 1. Average costs per cycle for 5-HT3 antiemetic agents.
difference in average treatment costs for these events were found between the 5-HT3 groups. Most patients with treatment failures were switched to another 5-HT3, including palonosetron, while 95% patients remained on palonosetron when they had an uncontrolled CINV event.

Overall no significant differences in total antiemetic cost of care were found when comparing the individual 5-HT3 agents in the repeated measures general linear model analysis ($p=0.22$; Figure 3). This can be attributed to the wide variation in costs, i.e. reimbursement, and quantity of drug used throughout the chemotherapy cycle.

**Discussion**

The findings of a retrospective claims analysis can be helpful in providing guidance about the impact of new agents on the overall cost of care. When applying this to the 5-HT3 class, key patient and chemotherapy attributes play a significant role in drug selection and are not often available to the payer. This creates a heterogeneous sample, which increases the variability in effectiveness and costs. Thus, it may be necessary to control the variation directly associated with the patient.

Taking these factors into account, this analysis demonstrated that palonosetron was typically used in higher risk patients, especially those that had previous CINV.

Exercising chemotherapy regimens of 14-28 days in length resulted in no significant differences in average drug costs between the 5-HT3s or average costs for additional non-5HT3 antiemetics. Though palonosetron had more uncontrolled CINV events, the total antiemetic costs of care did not differ between the 5-HT3 treatment groups. Thus, the use of palonosetron was not associated with an overall increase in cost to the payer.

**Editor’s Note:**

In December of last year, Zofran became generic. While this changes the cost-profiles and results of this study for those payors utilizing an ASP-based reimbursement, today approximately 14% of U.S. commercial managed lives use such reimbursement methodologies. For health plans that continue to use ASP-based reimbursement methods, the relative cost comparisons presented in this study continue to hold true and absolute costs depend upon the actual discounts off AWP pricing. The cost comparisons hold true since several manufacturers of Zofran continue to post undiscounted AWP prices. 

Dr. Force is Professor of Pharmacy Practice, Professor of Family Medicine at Idaho State University, and Partner, improveRX, LLC, Medication Management Consulting. Dr. Chitwood is Vice President of Pharmacy Services at Great-West Healthcare. Mr. Gill is Manager, Specialty Pharmacy and Dr. Valderrama is a Clinical Pharmacist; both are with Horizon Blue Cross Blue Shield of New Jersey’s Pharmacy Management Program. Ms. Weidner is Senior Director, Health Outcomes, Pharmacoeconomics and Post-Market Research, MGI Pharma, Inc. Dr. Hill is Associate Professor of Economics, Idaho State University.

**References**

1. Horizon Blue Cross Blue Shield is an independent licensee of the Blue Cross and Blue Shield Association.