REVIEW ARTICLE

The Impact of 5-HT$_3$RA Use on Cost and Utilization in Patients with Chemotherapy-Induced Nausea and Vomiting: Systematic Review of the Literature

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Background: Individual studies have assessed the impact of standard prophylactic therapy with 5-hydroxytryptamine receptor antagonists (5-HT$_3$RAs) for chemotherapy-induced nausea and vomiting (CINV) on cost and utilization, but no synthesis of the findings exists.

Objective: To systematically review published literature on costs and utilization associated with CINV prophylaxis with palonosetron and other 5-HT$_3$RAs.

Methods: PubMed and the National Institute for Health Research Centre for Reviews and Dissemination databases, conferences of 4 organizations (ie, Academy of Managed Care Pharmacy, American Society of Clinical Oncology, International Society for Pharmacoeconomics and Outcomes Research, and Multinational Association of Supportive Care in Cancer), and the bibliographies of relevant articles were queried for the medical subject headings and key terms of "ondansetron," "granisetron," "palonosetron," "dolasetron mesylate," "costs," "cost analysis," and "economics." We included records published (full-length articles after 1997 and conference presentations after 2010) in English and with human patients, reporting data on cost and utilization (rescue medication, outpatient and inpatient services) associated with the use of 5-HT$_3$RAs for the treatment or prevention of CINV.

Results: Of the 434 identified studies, 32 are included in the current analysis: 7 studies report costs, 18 report utilization, and 7 studies report both. The costs are reported in US dollars (7 studies), in Euros (5 studies), and in Canadian dollars (2 studies). The studies vary in designs, patients, 5-HT$_3$RA regimens, and the definition of outcomes. The US studies report higher drug costs for CINV prophylaxis with palonosetron compared with ondansetron, lower medical outpatient and inpatient costs for palonosetron versus other 5-HT$_3$RAs, and higher acquisition costs for palonosetron versus ondansetron or other 5-HT$_3$RAs. Fewer patients receiving palonosetron versus with ondansetron or other 5-HT$_3$RAs required rescue medication or used outpatient or inpatient care. In Europe and in Canada, the total pharmacy costs and use of rescue medications reported are lower for patients receiving prophylaxis with palonosetron.

Conclusions: This analysis shows that prophylaxis with palonosetron for the treatment of CINV is associated with higher acquisition treatment costs, but also with lower use of rescue medications and outpatient and inpatient services compared with ondansetron or other 5-HT$_3$RAs in the United States. Therefore, the use of palonosetron as a standard treatment may lead to reduced service utilization for CINV.

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Chemotherapy-induced nausea and vomiting (CINV) is an adverse effect of cancer treatment. It may occur within a few minutes of or up to 24 hours after the administration of chemotherapy (ie, acute CINV), or it may occur more than 24 hours after treatment (ie, delayed CINV). CINV may last up to 7 days.[1-7] Although there are several patient-specific factors that place patients at an increased risk for developing CINV (eg, female sex, low consumption of alcohol, history of motion or morning sickness, age under 50 years, previous CINV), the most contributory risk factor is the emetogenic potential of the chemotherapy regimen itself.[8]

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KEY POINTS

- Poorly controlled CINV may lead to nutrient depletion, reduced functional ability, diminished quality of life, or the premature discontinuation of chemotherapy.
- Previous studies have examined the impact of CINV prophylaxis with palonosetron and other 5-HT_3RAs on cost and utilization, but this is the first systematic review of the published literature on this topic.
- A total of 32 studies were included in this systematic literature review, of which 14 studies report costs and 25 reported utilization.
- This review indicates that palonosetron is associated with higher treatment costs but also with lower rescue medication use and outpatient and inpatient services use compared with other 5-HT_3RAs.
- Based on this analysis, the use of palonosetron as a standard treatment may lead to reduced service utilization for CINV.

More than 90% of patients undergoing highly emetogenic chemotherapy (HEC) will experience emesis without antiemetic prophylaxis, and 30% to 90% of those undergoing moderately emetogenic chemotherapy (MEC) will vomit without the prophylactic administration of antiemetics.[8] From 10% to 30% of the patients receiving low emetogenic risk chemotherapy (LEC), and <10% of patients receiving minimal emetogenic risk chemotherapy (MinEC), will experience emesis without the administration of antiemetics.[3,6,7,9] The dose, frequency, and length of administration, as well as the combination of agents may impact the emetogenicity of the chemotherapy.[7]

Poorly controlled CINV may lead to nutrient depletion, reduced functional ability, diminished quality of life, or the premature discontinuation of chemotherapy.[1-4,6,7,9] The use of prophylactic antiemetic medications in patients undergoing HEC may reduce the incidence of CINV to as low as 30%.[7] A multidrug regimen containing a 5-hydroxytryptamine receptor antagonist (5-HT_3RA) is the standard approach for CINV prophylaxis.[7] Drugs in this category include dolasetron mesylate, granisetron, ondansetron, palonosetron, and tropisetron, with palonosetron recommended as the preferred 5-HT_3RA for CINV prophylaxis with MEC by the guidelines of the National Comprehensive Cancer Network (NCCN), the Multinational Association of Supportive Care in Cancer/Economic Society for Medical Oncology (MASCC/ESMO), and the American Society of Clinical Oncology (ASCO).[5,7,10]

Secondary rescue medications are used to treat breakthrough CINV among patients who have received prophylaxis.[7] These medications may include metoclopramide, lorazepam, diphenhydramine, olanzapine, prochlorperazine, or dexamethasone.

CINV increases direct costs (eg, medication, office visits, or hospitalizations) and indirect costs (eg, missed work).[3,4,9] The effective prevention of CINV may reduce these costs. The clinical and economic impact of CINV underscore the importance of achieving CINV prophylaxis.[3,4,9] Palonosetron—which has greater binding affinity and a longer half-life than the other 5-HT_3RAs, binds allosterically, stimulates receptor internalization, demonstrates positive cooperativity, and cross talks with the neurokinin (NK)-1 signaling pathway—prevents both acute and delayed CINV more effectively than the other 5-HT_3RAs.[7,11-14]

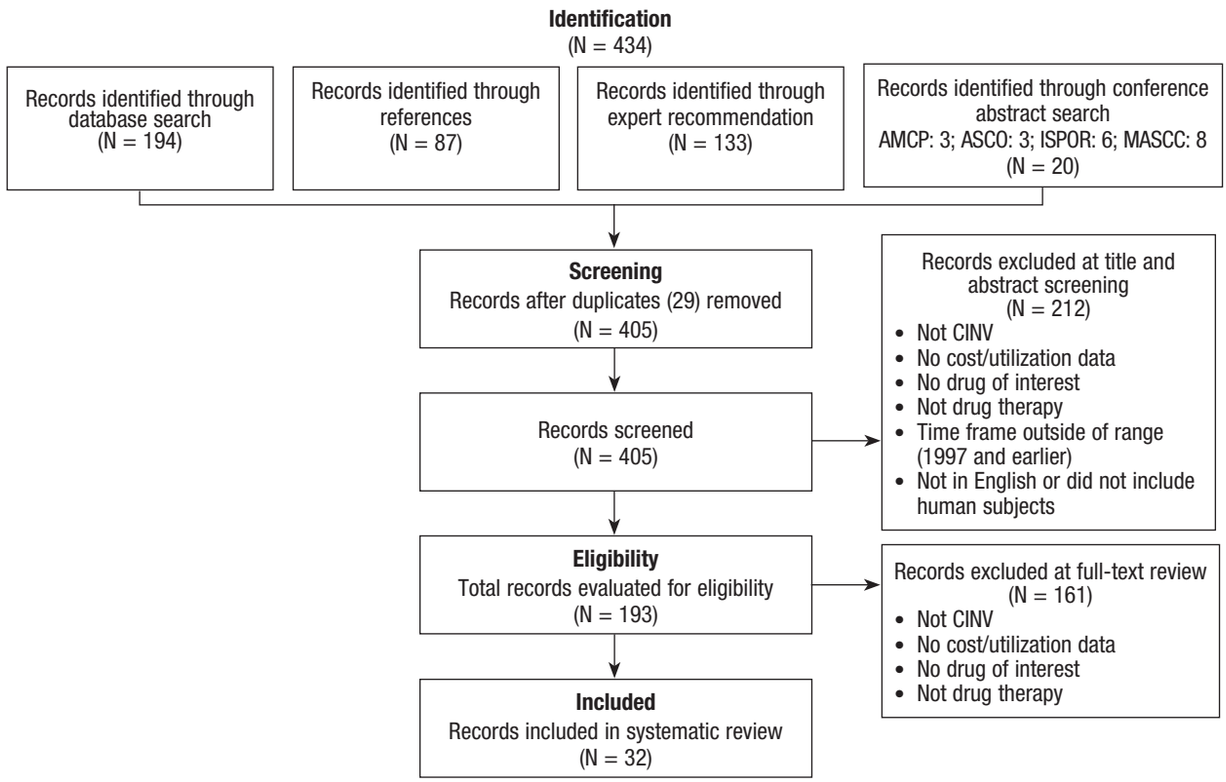
The extent to which the clinical benefit of 5-HT_3RAs translates into reduced costs or utilization of healthcare services among patients with CINV has been shown in individual studies for subsets of outcomes,[3,15] but no summary of the literature exists. We conducted a systematic literature review of published research on the healthcare costs and utilization associated with the use of 5-HT_3RAs for the prevention of CINV in patients receiving chemotherapy, with the goal of comparing palonosetron with the other 5-HT_3RAs.

Methods

This systematic review of the literature was conducted according to the Cochrane Collaboration model.[16,17] The searches were done in PubMed and in 3 additional databases of the National Institute for Health Research Centre for Reviews and Dissemination (NIHRCRD), including the Database of Abstracts of Reviews of Effects, the National Health Service Economic Evaluation Database, and the Health Technology Assessment Database. We also searched conference abstracts that were presented at meetings of the Academy of Managed Care Pharmacy, ASCO, International Society for Pharmacoeconomics and Outcomes Research, and MASCC. Searches for articles were conducted on July 12, 2012 (PubMed) and July 5, 2012 (NIHRCRD). The searches of conferences covered the years 2010, 2011, and 2012. The searched terms included the medical subject headings, subheadings, and key words "5-HT_3RAs," "dolasetron mesylate," "granisetron," "ondansetron," "palonosetron," "tropisetron," "Anzemet," "Kytril," "Zofran," "Aloxi," "Navoban," "cost," "cost analysis," "economics," "utilization," "CINV," "emesis," "nausea," and "vomiting."

We excluded full-length articles that were published before 1997 and were not in the English language, or those that did not report data on human subjects,

Figure Flow Chart of Review Process



AMCP indicates Academy of Managed Care Pharmacy; ASCO, American Society of Clinical Oncology; CINV, chemotherapy-induced nausea and vomiting; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; MASCC, Multinational Association of Supportive Care in Cancer.

CINV, 5-HT$_3$RAs, pharmacologic treatment, or cost and utilization. If a study was duplicated as a full-length article and a conference abstract, only the article was retained for review.

Data abstracted from accepted articles included study metadata, design, patients, treatments, and healthcare cost and utilization. The cost data included pharmacy costs (eg, acquisition/administration of 5-HT$_3$RAs, acquisition/administration of rescue medication), medical costs (eg, outpatient, inpatient), total healthcare costs (eg, total pharmacy, total medical). The utilization data included the rates of rescue medication use, outpatient service use, inpatient service use, and any healthcare resource use (eg, medication, outpatient, or inpatient use).

A single reviewer abstracted the articles. As part of the quality assurance process, all data were independently reabstracted, all inconsistencies were discussed, and final determinations were recorded in the review. The Oxford Centre for Evidence-Based Medicine's (OCEBM) level of evidence scale was used to assess quality of evidence and to assign a grade of 1 to 5 to each of the included studies, where 1 indicated a study with the strongest scientific basis for support of conclusions and 5 the weakest (eg, expert opinion).[18]

Randomized controlled trials (RCTs) were assigned a quality score using the Jadad scale, which assigns points on a scale of 0 to 5 based on a study's use of randomization, and blinding and on its description of withdrawals and dropouts from participation.[19] The costs were directly abstracted from studies, and no currency conversions or inflation adjustments were applied in this review.

Results

The initial search identified 434 studies, including 414 journal articles and 20 conference abstracts (**Figure**). Of these, 29 were duplicates, 212 were ineligible after screening titles and abstracts, and 161 were ineligible after screening the full articles. A total of 32 studies were included in this review, of which 21 were full-length articles and 11 were conference abstracts.

The 32 studies were published between 1998 and 2012 and reported data from 1995 to 2011 (**Appendix A**).[1,3,4,6,9,15,20-45] Of the 32 studies, 19 were conducted in the United States. A total of 7 studies were RCTs; 8 were nonrandomized, prospective studies; 14 were retrospective cohort analyses; and 3 were cost-efficacy analyses. Sample sizes ranged from 36 patients[43] to 11,974 patients.[30] The OCEBM levels of evidence ranged from 1b to 3b for all reviewed studies, and Jadad scores ranged from 2 to 5 for the 7 RCTs.

Description of Included Studies

A variety of indications for chemotherapy were represented in the studies, including breast, lung, head, neck, ovarian, gastrointestinal, colorectal, urogenital cancers, lymphoma, leukemia, and bone marrow transplant (Appendix A). Two studies included only patients with breast cancer,[21,37] and in 7 other studies, the majority (≥50%) of patients had breast cancer.[1,6,22,28,31,32,38] Chemotherapy treatment protocols (single or multiday) ranged from 1 to 5 days. A total of 9 studies included solely HEC regimens, 9 included only MEC regimens, and 13 included some combination of chemotherapy (eg, HEC, MEC, LEC, and MinEC).

The studies examined single and multiple 5-HT_3RAs, alone and in combination with other medications. Of the 32 studies, 25 included palonosetron. Dosing schedules ranged from a single intravenous (IV) administration of a 5-HT_3RA to courses of IV and oral formulations given over several days. CINV prophylaxis was administered with and without adjunctive aprepitant and dexamethasone. Rescue medications included metoclopramide, lorazepam, diphenhydramine, prochlorperazine, and dexamethasone.

A total of 14 studies reported cost data, and 25 reported data on utilization (Appendix A). Costs were reported in US dollars (7 studies), Euros (5 studies), and Canadian dollars (2 studies), based on a variety of sources and in several ways. The medication acquisition costs were from government schedules, prices paid by other payers, or from average wholesale prices. Medical costs were reported by treatment setting (outpatient, inpatient, or in aggregate) and in a variety of ways, such as mean cost per office visit and cost per cycle. The inpatient costs, either hospital admissions or emergency department visits, were stated per event (eg, per admission), per chemotherapy cycle, and per patient.

Healthcare Costs Associated with 5-HT_3RA Use in the United States

A total of 7 US studies reported costs associated with the use of 5-HT_3RAs for CINV, although only 4 studies compared the costs associated with the use of palonosetron and other drugs of this class (**Table 1**). Two studies reported the cost of 5-HT_3RA prophylaxis acquisition and rescue medication, 3 studies reported the cost of outpatient or inpatient medical services, and 6 studies reported the total pharmacy or total treatment costs.

Avritscher and colleagues reported the 5-HT_3RA prophylaxis acquisition costs of $49.74 per cycle for ondansetron alone, $207.20 for palonosetron alone, $324.51 for ondansetron when administered with aprepitant, and $482.46 for palonosetron when administered with aprepitant.[21] Another study reported the cost of acquisition for ondansetron, which was $1651 for the IV formulation and $539 for the oral formulation compared with $684 for oral granisetron.[25] Avritscher and colleagues reported the cost of rescue medications as $35.25, regardless of the specific 5-HT_3RA used.[21] The previous study also reported a rescue medication cost of $102 among patients receiving oral ondansetron, $96 for IV ondansetron, and $86 for patients receiving oral granisetron.[25]

A retrospective study of patients receiving HEC reported daily outpatient costs for CINV events of $1216 per cycle in patients receiving palonosetron compared with $1356 for patients taking other 5-HT_3RAs.[15] A more recent retrospective study reported daily outpatient costs for CINV events for patients receiving palonosetron prophylaxis were approximately $1048 compared with $1339 when taking other 5-HT_3RAs.[24] Balu and colleagues also reported mean emergency department service costs for CINV events of $1664 for patients receiving palonosetron compared with $1890 for patients receiving other 5-HT_3RAs, and mean inpatient costs of $2581 for the palonosetron cohort compared with $2671 for other 5-$HT_3$RAs.[15] For patients receiving any 5-HT_3RA, Avritscher and colleagues reported a mean cost of $60.30 per clinic office visit for a CINV event and $5237 per hospitalization.[21]

Fox-Geiman and colleagues reported the total pharmacy cost, including prophylaxis, rescue medication, and drug administration, to be $641 per cycle for patients receiving oral prophylaxis with ondansetron, $1747 for IV ondansetron, and $770 for oral granisetron.[25] A recent study reported a mean total pharmacy cost of $2129 in patients with CINV taking one of several 5-HT_3RAs.[31]

The total treatment costs, including all healthcare charges for prophylaxis and the treatment of CINV events, were reported in 5 studies.[15,21,31,33,34] Two studies reported that palonosetron when used alone was less costly than any other 5-HT_3RAs.[15,33] Avritscher and colleagues modeled the direct medical costs of ondansetron-based multiple drug therapies and palonosetron-based multiple drug therapies over 4 cycles of chemotherapy and reported that treatment costs with palonosetron-based regimens were higher compared with

Table 1 Cost of CINV Treatment in the United States, by 5-HT$_3$RA[a]

Study	Ondansetron, $	Palonosetron, $	Granisetron, $	Multiple 5-HT$_3$RAs[b], $	Notes
Acquisition cost of 5-HT$_3$RA prophylaxis[c]					
Avritscher, 2010[21]	49.74[d]	207.20[d]			IV and oral formulations
Avritscher, 2010[21]	324.51[d]	482.46[d]			IV and oral formulations with aprepitant
Fox-Geiman, 2001[25]	539.00		684.00		Oral formulation
Fox-Geiman, 2001[25]	1651.00				IV formulation
Acquisition cost of rescue medication[c]					
Avritscher, 2010[21]				35.25[d]	
Fox-Geiman, 2001[25]	102.00		86.00		Cost related to oral prophylaxis
Fox-Geiman, 2001[25]	96.00				Cost related to IV prophylaxis
Outpatient medical costs for CINV treatment with 5-HT$_3$RA					
Avritscher, 2010[21]				60.30[d]	Cost per office visit
Balu, 2010[15]		1216.00		1356.00	Mean daily cost of outpatient services for CINV-related events in patients with HEC
Craver, 2011[24]		1048.00		1339.00	Mean daily hospital outpatient costs
Inpatient medical costs for CINV treatment with 5-HT$_3$RA					
Avritscher, 2010[21]				5237.00[d]	Mean cost per hospitalization
Balu, 2010[15]		2581.00		2671.00	Mean daily cost of inpatient services for CINV-related events in patients with HEC
Balu, 2010[15]		1664.00		1890.00	Mean daily cost of emergency department services for CINV-related events in patients with HEC
Total pharmacy cost[c]					
Fox-Geiman, 2001[25]	641.00		770.00		Mean cost of treatment with oral medication, including scheduled 5-HT$_3$RA and rescue medication cost
Fox-Geiman, 2001[25]	1747.00				Mean cost of treatment with IV medication, including scheduled 5-HT$_3$RA and rescue medication cost
Knoth, 2011[31]				2129.00	Among patients with CINV
Total treatment cost					
Avritscher, 2010[21]	269.00	858.00			Mean cost for 4 cycles (84 days) of 5-HT$_3$RA and dexamethasone (prophylaxis)
Avritscher, 2010[21]	635.00	1177.00			Mean cost for 4 cycles (84 days) of 5-HT$_3$RA, dexamethasone (prophylaxis), and aprepitant (after emesis)
Avritscher, 2010[21]	1336.00	1939.00			Mean cost for 4 cycles (84 days) of 5-HT$_3$RA, dexamethasone, and aprepitant (prophylaxis)
Balu, 2010[15]		2004.00		2039.00	Mean daily total medical cost associated with CINV events including inpatient, outpatient, and emergency department visits
Balu, 2010[15]		2056.00		2268.00	Mean daily total medical cost associated with CINV events, including inpatient, outpatient, and emergency department visits for patients with HEC treatment
Knoth, 2011[31]				4816.00	Total costs are the sum of medical and pharmaceutical claims in patients with CINV
Knoth, 2011[33]		1127.00		1223.00	Adjusted mean costs for CINV-related events (medical and pharmaceutical claims) in patients receiving MEC
Knoth, 2011[34]				1604.00	Mean total cost per cycle per patient experiencing a CINV event (5-HT$_3$RA infusion or medical claims with CINV diagnosis); group primarily treated with palonosetron (72%) for CINV

[a]Cost per cycle unless indicated otherwise; currency is US dollars.
[b]Data included some combination of the indicated 5-HT$_3$RAs (specific breakdown was not provided by given article), unless otherwise noted.
[c]Medication cost assumption: IV regimens administered with dexamethasone unless noted.
[d]Number represents a model input used by author.
5-HT$_3$RA indicates 5-hydroxytryptamine receptor antagonist; CINV, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; IV, intravenous; MEC, moderately emetogenic chemotherapy.

Table 2 Utilization Associated with CINV Treatment in the United States, by 5-HT_3RA[a]

Study	Ondansetron, %	Palonosetron, %	Granisetron, %	Dolasetron, %	Multiple 5-HT_3RAs[b], %	Notes
Rescue medication						
Avritscher, 2010[21]	61[c]	56[c]				IV[b] and oral regimens (patients with emesis)
Feinberg, 2009[3]	67	24				Prescribed as follow-up therapy on days 2-5
Feinberg, 2012[4]	83	28				From day 2 to 7 days after last round of chemotherapy
Fox-Geiman, 2001[25]	91		85			Oral regimen
Fox-Geiman, 2001[25]	79					IV regimen
Gralla, 1998[27]	25		31			IV and oral regimens (day 1)
Grote, 2006[29]		7				IV regimen (day 1); at least 1 dose of aprepitant and dexamethasone
Grote, 2006[29]		21				Days 1-5; at least 1 dose of aprepitant and dexamethasone
Knoth, 2011[32]		7			12	Within first cycle of chemotherapy
Knoth, 2011[33]		16			30	Within first cycle of chemotherapy
Knoth, 2012[35]	11	8	20	20		Prescribed as follow-up therapy on days 2-5
Knoth, 2012[36]	24	14	27	31		Within 1 cycle of chemotherapy
Mattiuzzi, 2010[41]	11	6				Day 1: 5-HT_3RA on days 1-5
Mattiuzzi, 2010[41]		10				Day 1: palonosetron on days 1, 3, 5
Schwartzberg, 2011[6]		35			35	Prescribed as follow-up therapy on days 2-5
Outpatient						
Avritscher, 2010[21]	10[c]	5[c]				Office visit (patients with emesis)
Yeh, 2011[45]	10	8				Outpatient, related to CINV
Inpatient						
Avritscher, 2010[21]	0.4[c]	0.2[c]				Hospitalization (patients with emesis)
Feinberg, 2012[4]	1	1				Hospital readmission related to CINV from day 1 to 7 days after last round of chemotherapy
Hatoum, 2012[30]		4			6	Hospitalization (breast cancer group)
Hatoum, 2012[30]		10			14	Hospitalization (lung cancer: carboplatin group)
Hatoum, 2012[30]		16			23	Hospitalization (lung cancer: cisplatin group)
Knoth, 2012[35]					6	Hospitalization among patients with CINV
Knoth, 2012[35]					1	Emergency department visit related to CINV for patients with CINV
Lin, 2011[39]		7			10	Emergency department/hospital admission events
Yeh, 2011[45]	5	0				Hospital readmission related to CINV from day 1 to 7 days after last round of chemotherapy
Yeh, 2011[45]	0	0				Emergency department visit related to CINV for patients with CINV

[a]Rate per cycle for all patients unless indicated otherwise.
[b]Data included some combination of the indicated 5-HT_3RAs (specific breakdown was not provided by given article), unless otherwise noted.
[c]Represents a model input used by author.
5-HT_3RA indicates 5-hydroxytryptamine receptor antagonist; CINV, chemotherapy-induced nausea and vomiting; IV, intravenous.

ondansetron-based regimens.[21] A recent study of patients undergoing HEC or MEC and using 5-HT$_3$RAs reported total CINV-related treatment costs (ie, medical and pharmaceutical claims) of $4816, although the costs for palonosetron alone were not reported.[31] A study of commercially insured patients who were primarily treated with palonosetron (72%) reported a treatment cost of $1604 per cycle for a patient experiencing a CINV event (ie, 5-HT$_3$RA infusion or medical claims with CINV diagnosis), but the study did not report costs for palonosetron alone.[34]

Healthcare Utilization Associated with 5-HT$_3$RA Use in the United States

In all, 16 studies reported data on healthcare utilization related to the use of 5-HT$_3$RAs for CINV in the United States, of these 12 reported rescue medication use, 2 reported outpatient medical service use, and 6 reported inpatient service use (**Table 2**).

Of the 12 studies, 10 that reported the frequency of rescue medication use in the United States specifically presented comparative results between patients receiving palonosetron and patients receiving other 5-HT$_3$RAs. Of these 10 studies, 8 found lower rescue medication use among patients receiving palonosetron. One RCT reported lower rescue medication use in patients receiving palonosetron compared with patients receiving ondansetron (6% vs 11%, respectively).[41] Four retrospective studies also reported lower rescue medication utilization rates in those treated with palonosetron compared with ondansetron (24% vs 67%, respectively[3]; 28% vs 83%, respectively[4]; 8% vs 11%, respectively[35]; and 14% vs 24%, respectively[36]). Knoth and colleagues also reported higher rescue antiemetic rates in Medicaid patients with cancer who received granisetron (20%) and dolasetron (20%) compared with palonosetron (8%).[35] Another retrospective study of commercially insured patients also reported higher rescue medication needs in patients given granisetron (27%) and dolasetron (31%) compared with palonosetron (14%).[36] Three other retrospective studies reported rescue medication needs in patients treated with palonosetron versus with multiple 5-HT$_3$RAs (7% vs 12%, respectively,[32] 16% vs 30%, respectively,[33] and 35% vs 35%, respectively[6]). The rates of rescue medication use were 61% in patients receiving ondansetron and 56% in patients receiving palonosetron in one cost-efficacy analysis study.[21]

Of 10 outpatient or inpatient utilization rate comparisons reported in 6 studies, 8 comparisons were lower among patients receiving palonosetron prophylaxis than in patients receiving other 5-HT$_3$RAs, and 2 comparisons had equivalent rates between the palonosetron and other 5-HT$_3$RA cohorts (Table 2). Two studies reported lower rates of physician office visits (5% vs 10%, respectively) and outpatient service use (8% vs 10%, respectively) related to CINV among patients receiving palonosetron compared with patients receiving ondansetron.[21,45]

Patients receiving palonosetron had lower or equivalent rates of outpatient service use compared with patients treated with ondansetron: the rates of hospitalization were approximately 0.2% versus approximately 0.4%, respectively,[21] whereas the rates of hospital readmission (which are related to CINV from days 1-7 after the last round of chemotherapy) were 1% versus 1%, respectively,[4] and 0% versus 5%, respectively.[45] Yeh and colleagues reported the same rate (0%) of emergency department visits related to CINV in patients receiving palonosetron and in patients receiving ondansetron.[45] In comparing patients treated with palonosetron with patients treated with any other 5-HT$_3$RA, fewer patients in the palonosetron group had hospitalizations (4% vs 6%, respectively; 10% vs 14%, respectively; and 16% vs 23%, respectively[30]) and emergency department or hospital admission events (7% vs 10%, respectively[39]).

Healthcare Cost Associated with 5-HT$_3$RA Use in Europe and Canada

A total of 7 studies reported the costs associated with the use of 5-HT$_3$RAs for CINV in Europe and Canada. Of these studies, 6 reported the cost of 5-HT$_3$RA acquisition, 5-HT$_3$RA administration, or rescue medication; 3 studies reported the cost of outpatient or inpatient medical services; and 5 studies reported the total pharmacy or total treatment costs (**Appendix B**).

Only 1 study reported costs for the use of palonosetron.[26] The acquisition costs of 5-HT$_3$RAs and rescue medication costs varied by study. For example, 1 study reported the acquisition cost of ondansetron ranged from €17.90 to €57.75, tropisetron from €14.80 to €23.59, and granisetron from €26.16 to €41.60,[22] whereas another study reported the costs for rescue medication ranged from €7.22 for all cycles to €11.20 for cycles with CINV per treatment cycle per patient.[9] The outpatient and inpatient medical costs varied across the studies. For example, the outpatient medical costs for CINV treatment ranged from €0.23 for medical consultation in patients treated with tropisetron[22] to €9.28 for outpatient care in patients treated with ondansetron.[40] The inpatient medical costs varied from €0.43 for emergency department admission per cycle[22] to €151.86 per patient for hospitalization.[40] Of the 5 studies that reported the total costs, only 1 study reported the costs associated with the use of palonosetron.[26] There were substantially lower total pharmacy costs related to prophylaxis with palonosetron compared with tropisetron: €107.25 versus €410.50, respectively.[26]

Table 3 Utilization Rates Associated with CINV Treatment in Europe and Canada, by 5-HT_3RA[a]

Study	Rescue medication					Notes
	Ondansetron, %	Palonosetron, %	Tropisetron, %	Granisetron, %	Multiple 5-HT_3RAs[b], %	
Aapro, 2006[20]	23	20				Day 1 IV palonosetron 0.25 mg
Aapro, 2006[20]		17				Day 1 with IV palonosetron 0.75 mg
Barrajon, 2000[22c]	5		5	3		
Celio, 2011[23]		9				Day 1 with palonosetron and 1-day Dexa
Celio, 2011[23]		27				Days 2-5 with palonosetron and 1-day Dexa
Celio, 2011[23]		29				Days 1-5 with palonosetron and 1-day Dexa
Celio, 2011[23]		11				Day 1 with palonosetron and 3-day Dexa
Celio, 2011[23]		17				Days 2-5 with palonosetron and 3-day Dexa
Celio, 2011[23]		20				Days 1-5 with palonosetron and 3-day Dexa
Giordano, 2011[26]		9	12			All cycles
Gralla, 2003[28]	24	16				Days 2-5 with palonosetron 0.25 mg
Gralla, 2003[28]		23				Days 2-5 with palonosetron 0.75 mg
Gralla, 2003[28]	27	19				Days 1-5 with palonosetron 0.25 mg
Gralla, 2003[28]		24				Days 1-5 with palonosetron 0.75 mg
Ihbe-Heffinger, 2004[9]					6	IV regimen
Ihbe-Heffinger, 2004[9]					10	Oral or rectal regimens
Musso, 2009[42]	40	20				Days 1-5 after the end of treatment
Rigacci, 2012[43]		8				Day 1, after first chemotherapy administration on day 1
Rigacci, 2012[43]		39				Days 1-5, after first chemotherapy administration on day 1
Rigacci, 2012[43]		4				Day 1, after second chemotherapy administration on day 15
Rigacci, 2012[43]		11				Days 1-5, after second chemotherapy administration on day 15
Schroeder, 2011[44]		9				Day 1
Schroeder, 2011[44]		34				Days 2-3
Outpatient						
Barrajon, 2000[22c]	4		2	5		Medical consultation
Ihbe-Heffinger, 2004[9]					11	Medical consultation
Ihbe-Heffinger, 2004[9]					3	Outpatient hospital visit
Inpatient						
Barrajon, 2000[22c]	0		1	0		Emergency department visit
Barrajon, 2000[22c]	1		1	1		Hospitalization
Ihbe-Heffinger, 2004[9]					1	Hospitalization
Any healthcare resource						
Ihbe-Heffinger, 2004[9]					33	Any medication, outpatient or inpatient use

[a]Rate per cycle for all patients unless indicated otherwise.
[b]Data included some combination of the indicated 5-HT_3RAs (specific breakdown was not provided by given article), unless otherwise noted.
[c]This was calculated by dividing the number of events for each 5-HT_3RA by 120 (ie, the number of chemotherapy cycles).
5-HT_3RA indicates 5-hydroxytryptamine receptor antagonist; CINV, chemotherapy-induced nausea and vomiting; Dexa, dexamethasone; IV, intravenous.

Healthcare Utilization Associated with 5-HT$_3$RA Use in Europe and Canada

A total of 9 studies reported data on healthcare utilization related to the use of 5-HT$_3$RAs for CINV in Europe or in Canada, and, of these, 8 studies reported utilization associated with the use of palonosetron (**Table 3**). The use of rescue medication varied widely (3%-40% of patients), considering which 5-HT$_3$RA was used, treatment time relative to chemotherapy, and treatment duration, dosage, and administration route.

Similar to US studies, the rates of rescue medication use were lower for palonosetron versus for other 5-HT$_3$RAs: 20% vs 23%, respectively[20]; 9% vs 12%, respectively[26]; 16% vs 24% or 19% vs 27%, respectively[28]; and 20% vs 40%, respectively.[42] The use of outpatient services, including medical consultations and hospital visits, ranged from 2% (tropisetron) to 11% (multiple 5-HT$_3$RAs) and the use of inpatient services, including emergency department visits and hospitalizations, ranged from 0% (ondansetron or granisetron) to 1% (ondansetron, tropisetron, granisetron, or multiple 5-HT$_3$RAs), but no rates were reported for palonosetron in these studies.[9,22]

Discussion

Our literature review shows that CINV prophylaxis with palonosetron compared with ondansetron is generally associated with higher acquisition costs, a finding supported by the ASCO guidelines that reported a higher total cost per treatment cycle for palonosetron than for granisetron, ondansetron, and dolasetron.[10] However, palonosetron is generally associated with lower use of rescue medications and outpatient and inpatient services compared with ondansetron or other 5-HT$_3$RAs.

In Europe and in Canada, the total pharmacy costs and rescue medication use are lower for patients treated with palonosetron. Overall, the healthcare utilization results from Europe and Canada are consistent with results from the United States. This study highlights the use of palonosetron as a standard treatment, which may lead to the reduced utilization of rescue medications and healthcare services for CINV, and possibly result in subsequent cost-savings related to medical outpatient and inpatient services.

A recent comprehensive review of efficacy data suggests that patients who receive palonosetron experience less nausea, both acute (relative risk [RR], 0.86; 95% confidence interval [CI], 0.76-0.96; P = .007) and delayed (RR, 0.82; 95% CI, 0.75-0.89; P <.001), and less acute vomiting (RR, 0.76; 95% CI, 0.66-0.88; P = .002) and delayed vomiting (RR, 0.76; 95% CI, 0.68-0.85; P <.001).[11]

The NCCN recommends palonosetron as the preferred 5-HT$_3$RA for patients undergoing HEC.[7] Palonosetron is also recommended by the NCCN, MASCC/ESMO, and ASCO guidelines as the preferred 5-HT$_3$RA for CINV prophylaxis with MEC,[5,7,10] and is the preferred 5-HT$_3$RA according to the MASCC/ESMO guidelines for anthracycline combined with cyclophosphamide chemotherapy when an NK$_1$ receptor antagonist is not available.[5]

The utilization data evaluated in the reviewed studies support the hypothesis that patients managed with palonosetron use fewer outpatient, emergency department, and inpatient care services than patients who receive other 5-HT$_3$RA agents. The utilization of medical services related to CINV may have a role as an important metric for plans, providers, and patients in identifying the appropriate therapy for CINV prophylaxis.

This review focused on 2 specific outcomes—medical costs and utilization—but the evidence we report has implications for patients in terms of quality of life, indirect costs, and treatment discontinuation resulting from CINV. Studies have shown that CINV adversely impacts quality of life of patients with cancer.[46] Patients with cancer have rated being free from CINV as one of the most favorable health states after perfect health and complete remission.[47] Less quantifiable but still important, indirect costs associated with CINV may include lost productivity and patient and family anxiety.

Studies have previously documented the impact of CINV on indirect costs in terms of reduced productivity or workdays lost.[9,48,49] A Canadian study found that indirect costs accounted for up to 66% of the total cost of CINV among 72 patients,[49] whereas a US study reported that 23% of their patients were not able to work as a result of emesis.[48] CINV prophylaxis may also be important in avoiding chemotherapy discontinuation as a result of CINV complications. The NCCN antiemesis guidelines cite research that suggests that compliance with therapy—in particular, infusion therapy appointments—is decreased in patients who experience nausea and vomiting.[7,50]

Several independent studies have demonstrated the benefits of compliance to antiemetic guidelines for CINV prophylaxis before single-day HEC or MEC.[51-53] A recent prospective observational study of oncology practices in the United States reported the incidence of no CINV was significantly higher in the guideline-consistent CINV prophylaxis (GCCP) cohort compared with the guideline-inconsistent CINV prophylaxis (GICP) cohort over 5 days postchemotherapy (53.4% vs 43.8%, respectively; P <.001).[52] The adjusted odds of no CINV in the GCCP group were 1.31 (95% CI, 1.07-1.69).[52]

An earlier prospective observational study, which was conducted in 8 European countries, reported a higher complete response (no emesis and no use of rescue therapy) rate in a GCCP cohort (59.9%) compared with in

a GICP cohort (50.7%; $P = .008$).[51] After controlling for a variety of confounding factors, patients in the GCCP cohort had 1.43 times the odds of complete response (95% CI, 1.04-1.97; $P = .027$) compared with patients in the GICP cohort.[51]

Despite the wide availability of guidelines on the prevention of CINV and the worldwide evidence of favorable outcomes with higher guideline compliance, adherence to and implementation of treatment recommendations in antiemetic guidelines on CINV are often suboptimal.[51-53] Studies indicate that more effective clinical uptake of guidelines, developed by consensus opinions of international experts published by the MASCC, ASCO, and the NCCN, for the prevention of CINV improve patient outcomes, including the reduced incidence of CINV and healthcare visits to manage CINV and improved quality of care and cost-savings.[51-53]

Strengths and Limitations

The strength of this research lies in its comprehensive review and in its synthesis of global literature that is published in peer-reviewed journals and is presented at professional congresses.

This study also has limitations. To conduct a comprehensive review, we did not exclude studies that used relevant outcomes of interest (eg, costs, utilization) as model inputs.[21,38,40]

The studies included in this review varied in designs, patients, 5-HT_3RA regimens, and definition of outcomes, and the data presented in this study, particularly regarding costs, were derived from a variety of sources, and were reported in several ways across the reviewed studies. Thus, the heterogeneity of these data prevented us from conducting a meta-analysis.

This literature review includes studies published between 1998 and 2012, many of which would not have reflected the dramatically lower cost of generic ondansetron, which became available in 2006. This may be a significant limitation in our assessment of drug costs, but it would not be expected to impact nondrug costs.

We were unable to examine the costs of managing CINV when the current prevention and treatment guidelines are being followed, because the guidelines are not organized in a way that would make it clear how to assess the costs associated with implementing various recommendations.

Future studies should develop models to compare the cost of care associated with compliant versus noncompliant treatment guideline recommendations in relation to CINV prophylaxis.

Conclusion

The use of palonosetron for CINV prophylaxis is associated with higher total acquisition costs, as well as with lower use of rescue medications and outpatient and inpatient services, compared with ondansetron or other 5-HT_3RAs in the United States. In Europe and in Canada, the total pharmacy costs and rescue medication use are lower for patients who receive palonosetron. This study supports the use of palonosetron as the preferred 5-HT_3RA, because it may lead to reduced service utilization for CINV. ■

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References

1. Abali H, Çelik I. Tropisetron, ondansetron, and granisetron for control of chemotherapy-induced emesis in Turkish cancer patients: a comparison of efficacy, side-effect profile, and cost. *Cancer Invest*. 2007;25:135-139.
2. Billio A, Morello E, Clarke MJ. Serotonin receptor antagonists for highly emetogenic chemotherapy in adults. *Cochrane Database Syst Rev*. Jan 2010:CD006272. Update in: *Cochrane Database Syst Rev*. 2013;12:CD006272.
3. Feinberg BA, Gilmore J, Haislip S, et al. Data-driven medical decision-making in managing chemotherapy-induced nausea and vomiting. *Community Oncol*. 2009;6:62-67.
4. Feinberg B, Gilmore J, Haislip S, et al. Impact of initiating antiemetic prophylaxis with palonosetron versus ondansetron on risk of uncontrolled chemotherapy-induced nausea and vomiting in patients with lung cancer receiving multi-day chemotherapy. *Support Care Cancer*. 2012;20:615-623.
5. Roila F, Herrstedt J, Aapro M, et al; for the ESMO/MASCC Guidelines Working Group. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol*. 2010;21(suppl 5):v232-v243.
6. Schwartzberg L, Jackson J, Jain G, et al. Impact of 5-HT_3 RA selection within triple antiemetic regimens on uncontrolled highly emetogenic chemotherapy-induced nausea/vomiting. *Expert Rev Pharmacoecon Outcomes Res*. 2011;11:481-488.
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): antiemesis. Version 2.2014. www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed May 6, 2014.
8. Wickham R. Best practice management of CINV in oncology patients: II. Antiemetic guidelines and rationale for use. *J Support Oncol*. 2010;8(2 suppl 1):10-15.
9. Ihbe-Heffinger A, Ehlken B, Bernard R, et al. The impact of delayed chemotherapy-induced nausea and vomiting on patients, health resource utilization and costs in German cancer centers. *Ann Oncol*. 2004;15:526-536.
10. Basch E, Prestrud AA, Hesketh PJ, et al; for the American Society of Clinical Oncology. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2011;29:4189-4198.
11. Botrel TE, Clark OA, Clark L, et al. Efficacy of palonosetron (PAL) compared to other serotonin inhibitors (5-HT_3R) in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic (MoHE) treatment: systematic review and meta-analysis. *Support Care Cancer*. 2011;19:823-832.
12. De Leon A. Palonosetron (Aloxi): a second-generation 5-HT_3 receptor antagonist for chemotherapy-induced nausea and vomiting. *Proc (Bayl Univ Med Cent)*. 2006;19:413-416.
13. Smith HS, Cox LR, Smith EJ. 5-HT3 receptor antagonists for the treatment of nausea/vomiting. *Ann Palliat Med*. 2012;1:115-120.
14. Rojas C, Li Y, Zhang J, et al. The antiemetic 5-HT3 receptor antagonist palonosetron inhibits substance P-mediated responses in vitro and in vivo. *J Pharmacol Exp Ther*. 2010;335:362-368.
15. Balu S, Craver C, Gayle J, Buchner D. Cost consequences of initiating palonosetron versus other 5-hydroxytryptamine 3 receptor antagonists for prevention of chemotherapy-induced nausea and vomiting among patients with cancer treated with highly emetogenic chemotherapy in a hospital outpatient setting. *J Support Oncol*. 2010;8. Abstract PA-2. Poster presented at the 6th Annual Chicago Supportive Oncology Conference; Chicago, IL; October 7-9, 2010. Poster PA-2.
16. Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. Cochrane Collaboration; 2011. Updated March 2011. www.cochrane-handbook.org. Accessed August 7, 2012.
17. Yoshii A, Plaut DA, McGraw KA, et al. Analysis of the reporting of search strategies in Cochrane systematic reviews. *J Med Libr Assoc*. 2009;97:21-29.
18. OCEBM Levels of Evidence Working Group. The Oxford 2011 levels of evidence. www.cebm.net/index.aspx?o=5653. Accessed May 6, 2014.

19. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1-12.
20. Aapro MS, Grunberg SM, Manikhas GM, et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. *Ann Oncol*. 2006;17:1441-1449.
21. Avritscher EB, Shih YC, Sun CC, et al. Cost-utility analysis of palonosetron-based therapy in preventing emesis among breast cancer patients. *J Support Oncol*. 2010;8:242-251.
22. Barrajon E, de las Peñas R. Randomised double blind crossover study comparing ondansetron, granisetron and tropisetron. A cost-benefit analysis. *Support Care Cancer*. 2000;8:323-333.
23. Celio L, Frustaci S, Denaro A, et al; for the Italian Trials in Medical Oncology Group. Palonosetron in combination with 1-day versus 3-day dexamethasone for prevention of nausea and vomiting following moderately emetogenic chemotherapy: a randomized, multicenter, phase III trial. *Support Care Cancer*. 2011;19:1217-1225.
24. Craver C, Gayle J, Balu S, Buchner D. Impact on hospital outpatient visit costs by initiating palonosetron versus other 5-hydroxytryptamine3 receptor antagonists for prevention of chemotherapy induced nausea and vomiting (CINV) among patients with cancer. *Value Health*. 2011;14. Abstract PCN48.
25. Fox-Geiman MP, Fisher SG, Kiley K, et al. Double-blind comparative trial of oral ondansetron versus oral granisetron versus IV ondansetron in the prevention of nausea and vomiting associated with highly emetogenic preparative regimens prior to stem cell transplantation. *Biol Blood Marrow Transplant*. 2001;7:596-603.
26. Giordano G, Tambaro R, Mondello P, et al. Chlorpromazine plus methoclopramide and prednisone is effective in late hemesis control of patients pretreated with palonosetron than with tropisetron. *Support Care Cancer*. 2011;19(suppl 2). Abstract 145.
27. Gralla RJ, Navari RM, Hesketh PJ, et al. Single-dose oral granisetron has equivalent antiemetic efficacy to intravenous ondansetron for highly emetogenic cisplatin-based chemotherapy. *J Clin Oncol*. 1998;16:1568-1573.
28. Gralla R, Lichinitser M, Van Der Vegt S, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann Oncol*. 2003;14:1570-1577.
29. Grote T, Hajdenberg J, Cartmell A, et al. Combination therapy for chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: palonosetron, dexamethasone, and aprepitant. *J Support Oncol*. 2006;4:403-408.
30. Hatoum HT, Lin SJ, Buchner D, Cox D. Comparative clinical effectiveness of various 5-HT$_3$ RA antiemetic regimens on chemotherapy-induced nausea and vomiting associated with hospital and emergency department visits in real world practice. *Support Care Cancer*. 2012;20:941-949.
31. Knoth RL, Chang E, Broder M, Powers A. Examining health care costs in chemotherapy-induced nausea and vomiting: a retrospective analysis. *J Manag Care Pharm*. 2011;17:250. Poster presented at the Academy of Managed Care Pharmacy's 23rd Annual Meeting and Showcase; Minneapolis, MN; April 27-29, 2011. Poster PRR-36.
32. Knoth RL, Chang E, Broder M, Powers A. Chemotherapy induced nausea and vomiting following prophylactic 5-HT$_3$-RA antiemetic treatment in highly emetogenic chemotherapy. *Support Care Cancer*. 2011;19(suppl 2). Abstract 471. Poster presented at the 2011 Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology International Symposium; Athens, Greece; July 23-25, 2011.
33. Knoth RL, Chang E, Broder M, Powers A. Chemotherapy induced nausea and vomiting following prophylactic 5-HT$_3$-RA antiemetic treatment in moderately emetogenic chemotherapy. *Support Care Cancer*. 2011;19(suppl 2). Abstract 468. Poster presented at the 2011 Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology International Symposium; Athens, Greece; July 23-25, 2011.
34. Knoth RL, Chang E, Broder M, Powers A. Health care costs in chemotherapy induced nausea and vomiting: a retrospective analysis of a commercially insured U.S. patient population. *Support Care Cancer*. 2011;19(suppl 2). Abstract 458. Healthcare costs related to chemotherapy-induced nausea and vomiting: a retrospective analysis in a U.S. commercially insured population. Poster presented at the 2011 Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology International Symposium; Athens, Greece; July 23-25, 2011.
35. Knoth RL, Faria C, Li X, Powers A. Examining the use of rescue antiemetic medication for chemotherapy-induced nausea and vomiting in a Medicaid population. *Support Care Cancer*. 2012;20(suppl 1). Abstract 722. Poster presented at the 2012 Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology International Symposium; New York, NY; June 28-30, 2012.
36. Knoth RL, Faria C, Chang E, Broder M. Examining the use of rescue antiemetic medication for chemotherapy induced nausea and vomiting in a commercial population. *Value Health*. 2012;15:Abstract PCN10. Poster presented at the International Society for Pharmacoeconomics and Outcomes Research 15th Annual European Congress; November 3-7, 2012; Berlin, Germany.
37. Lachaine J, Laurier C, Langleben A, Vaillant L. Cost-effectiveness and quality of life evaluation of ondansetron and metoclopramide for moderately emetogenic chemotherapy regimens in breast cancer. *Crit Rev Oncol Hematol*. 1999;32:105-112.
38. Lachaine J, Laurier C. Cost-efficacy analysis of ondansetron regimens for control of emesis induced by noncisplatin, moderately emetogenic chemotherapy. *Am J Health Syst Pharm*. 2002;59:1837-1846.
39. Lin S, Hatoum HT, Balu S. Effect of antiemetic prophylaxis against chemotherapy-induced nausea and vomiting with 5-HT3 receptor antagonists in patients with lymphoma. *Value Health*. 2011;14: Abstract PCN4. Poster presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 14th Annual European Congress; November 5-8, 2011; Madrid, Spain (poster title modified to: Effect of 5-HT$_3$ RA prophylaxis for chemotherapy induced nausea & vomiting in patients with lymphoma).
40. Lordick F, Ehlken B, Ihbe-Heffinger A, et al. Health outcomes and cost-effectiveness of aprepitant in outpatients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany. *Eur J Cancer*. 2007;43:299-307.
41. Mattiuzzi GN, Cortes JE, Blamble DA, et al. Daily palonosetron is superior to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients with acute myelogenous leukemia. *Cancer*. 2010;116:5659-5666.
42. Musso M, Scalone R, Bonanno V, et al. Palonosetron (Aloxi) and dexamethasone for the prevention of acute and delayed nausea and vomiting in patients receiving multiple-day chemotherapy. *Support Care Cancer*. 2009;17:205-209.
43. Rigacci L, Landi C, Caruso JP, et al. Single dose palonosetron and dexamethasone in preventing nausea and vomiting induced by high emetogenic ABVD regimen in Hodgkin lymphoma patients. *Leuk Res*. 2012;36:182-185.
44. Schroeder H, Nadaraja S, Rosthoej S, et al. Palonosetron in the prevention of chemotherapy-induced nausea and vomiting in children with acute lymphoblastic leukemia treated with high-dose methotrexate. *J Clin Oncol*. 2011;29(15 suppl). Abstract 9535.
45. Yeh YC, McDonnell A, Klinger E, et al. Comparison of healthcare resource use between patients receiving ondansetron or palonosetron as prophylaxis for chemotherapy-induced nausea and vomiting. *J Oncol Pharm Pract*. 2011;17:179-185.
46. Bloechl-Daum B, Deuson RR, Mavros P, et al. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. *J Clin Oncol*. 2006;24:4472-4478.
47. Sun CC, Bodurka DC, Weaver CB, et al. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. *Support Care Cancer*. 2005;13:219-227.
48. Lindley CM, Hirsch JD, O'Neill CV, et al. Quality of life consequences of chemotherapy-induced emesis. *Qual Life Res*. 1992;1:331-340.
49. O'Brien BJ, Rusthoven J, Rocchi A, et al. Impact of chemotherapy-associated nausea and vomiting on patients' functional status and on costs: survey of five Canadian centres. *CMAJ*. 1993;149:296-302.
50. Richardson JL, Marks G, Levine A. The influence of symptoms of disease and side effects of treatment on compliance with cancer therapy. *J Clin Oncol*. 1988;6:1746-1752.
51. Aapro M, Molassiotis A, Dicato M, et al; for the PEER investigators. The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). *Ann Oncol*. 2012;23:1986-1992.
52. Gilmore JW, Peacock NW, Gu A, et al. Antiemetic guideline consistency and incidence of chemotherapy-induced nausea and vomiting in US community oncology practice: INSPIRE study. *J Oncol Pract*. 2014;10:68-74.
53. Jordan K, Gralla R, Jahn F, Molassiotis A. International antiemetic guidelines on chemotherapy induced nausea and vomiting (CINV): content and implementation in daily routine practice. *Eur J Pharmacol*. 2014;722:197-202.

STAKEHOLDER PERSPECTIVE

The Value of Pharmaceuticals in the Prevention and Treatment of CINV

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PATIENTS: Chemotherapy-induced nausea and vomiting (CINV) is one of the most common adverse effects of cancer treatment.[1] Symptoms may range from slight nausea to persistent vomiting with dehydration, which can severely impact quality of life.[2] A better understanding of the etiology and pathophysiology of CINV has led to the approval of several effective targeted agents, including the serotonin receptor antagonists

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STAKEHOLDER PERSPECTIVE *Continued*

and neurokinin-1 (NK_1) receptor antagonists. Even with these advances, challenges remain regarding the prevention and management of CINV. Depending on the severity of their symptoms, patients may be hesitant to continue with potentially lifesaving therapy.

Although most CINV is observed with infused chemotherapy agents, it is also seen with some oral oncolytic therapies and can lead to lower adherence rates, even for the currently available oral oncolytic therapies.

PAYERS/PROVIDERS: The direct and indirect costs of CINV are also significant. These include costs related to the acquisition of antiemetic drugs, as well as expenses associated with unscheduled office or emergency department visits, hospitalization admissions, and loss of productivity for patients and their caregivers.[3]

Broder and colleagues conducted an extensive, systematic review of the published literature on the prevention and treatment of CINV between 1997 and 2010, and found that the patients receiving palonosetron had lower rescue medication use and less inpatient and outpatient services despite higher acquisition treatment costs. On the surface, a skeptic may think that the conclusions are biased toward a higher-cost therapy and may note that a study funded by the pharmaceutical manufacturer would also introduce bias. This could not be further from the truth.

The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) antiemesis guidelines were updated in 2011.[4,5] Both organizations recommend the use of a 5-hydroxytryptamine receptor antagonist ($5\text{-}HT_3RA$; preferably administered before the first dose of chemotherapy), dexamethasone, and an NK_1 receptor antagonist for the prevention of CINV in highly emetogenic chemotherapy (HEC). Aprepitant (oral) and fosaprepitant (intravenous [IV]), both NK_1 receptor antagonists, are considered equivalent. For moderately emetogenic chemotherapy, a $5\text{-}HT_3RA$ with dexamethasone is recommended. Both guidelines list palonosetron, a second-generation IV $5\text{-}HT_3RA$, as preferred on day 1, because of its efficacy for the prevention of acute and delayed CINV.[4,5] Simple enough? Not quite.

The complicating factors, as always, are in gaining broad acceptance of clinical guidelines, and the cost of new preferred therapies compared with previously accepted therapies. It is widely known that general acceptance of clinical practice guidelines is difficult because of a variety of documented reasons.[6] Although some barriers to physician acceptance of clinical practice guidelines are very difficult to change, such as a perceived lack of self-efficacy and a lack of physician agreement, one of the barriers can effectively be overcome: the lack of awareness. It is the responsibility of the healthcare community to ensure that we are all aware of the updated antiemetic guidelines that were published 3 years ago.[5,6]

Once awareness of the updated guidelines is achieved, additional questions must be addressed. Most of the questions arise as a result of the cost differences between brand and generic drugs, in addition to the route of administration of the antiemetic therapies. Should IV or oral therapies be used, especially when choosing $5\text{-}HT_3RAs$? Yes, palonosetron is preferred for the prevention of HEC, because of its efficacy in acute and delayed CINV. However, can acute and delayed CINV also effectively be treated with a lower-cost $5\text{-}HT_3RA$ with an effective regimen to prevent delayed CINV? When choosing between $5\text{-}HT_3RAs$ other than palonosetron, should oral drugs be given preference over IV therapies because of cost?

Finally, one of the most concerning issues regarding the use of antiemetics for payers is how long the medications should be used. The administration of CINV prophylaxis should only occur over a 3-day period, preferably beginning 1 day before the administration of chemotherapy, according to the NCCN and the ASCO guidelines.[4,5] Breakthrough treatment should occur over a longer period of time, and is highly dependent on the emetogenic potential of the chemotherapy regimen and the cycles of therapy.

Payers have historically been challenged with these issues regarding the cost-effective use of antiemetics for CINV. The use of the recently published guidelines, and a keen focus on the issues raised here, should help with achieving the goals of providing patients with value-based cancer care as it relates to the management of CINV. ■

1. Sun CC, Bodurka DC, Weaver CB, et al. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. *Support Care Cancer*. 2005;13:219-227.
2. Bliss JM, Robertson B, Selby PF. The effect of nausea and vomiting upon quality of life measures. *Br J Cancer*. 1992;66(suppl 19):14S-23S.
3. Haiderali A, Menditto L, Good M, et al. Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a US population. *Support Care Cancer*. 2011;19:843-851.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Antiemesis. Version 2.2014. www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed May 15, 2014.
5. Basch E, Prestrud AA, Hesketh PJ, et al; for the American Society of Clinical Oncology. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. April 13, 2011. www.asco.org/sites/www.asco.org/files/antiemetics_full_guideline_update_92211.pdf. Accessed May 15, 2014.
6. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA*. 1999;282:1458-1465.