Original Article

Adherence to National Guidelines for Antiemesis Prophylaxis in Patients Undergoing Chemotherapy for Lung Cancer

A Population-Based Study

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BACKGROUND: Nausea and vomiting (N/V) during chemotherapy can have profound clinical and economic consequences. Effective antiemetic agents are available for prophylaxis, but barriers may prevent their use. For this population-based study, the authors assessed the rates of antiemetic prophylaxis use, and predictors of such use, among patients who were receiving platinum-based chemotherapy for lung cancer between 2001 and 2007. **METHODS:** The authors searched the Texas Cancer Registry–Medicare-linked database for individuals aged >65 years who received platinum-based chemotherapy within 12 months after a first diagnosis of lung cancer from 2001 to 2007; and all patients had continuous Medicare Part A and Part B coverage for the same period. Adherence to recommended regimens for N/V prophylaxis (established by the National Comprehensive Cancer Network) was scored as a binary variable (adherent vs nonadherent) and was calculated as the percentages of treated patients receiving each recommended agent within 1 day of beginning chemotherapy. Logistic regression with stepwise selection was used to examine whether patient characteristics influenced adherence. **RESULTS:** Of 4566 selected patients, adherence rates for the receipt of serotonin antagonists (eg, ondansetron) with dexamethasone were 60% to 90% regardless of whether the chemotherapy agent was considered moderately or highly emetogenic. The receipt of substance-P antagonists was much less common (<10%) during any period. On multivariate logistic regression modeling, variables that predicted adherence were older age, white race, higher median income, and concurrent radiation therapy. **CONCLUSIONS:** Recommended use of antiemetics for prophylaxis, especially substance-P antagonists, during chemotherapy for lung cancer is suboptimal. Factors that were correlated with adherence suggest socioeconomic barriers in the community. ***Cancer*** **2013;119:1428-36.** © *2012 American Cancer Society.*

KEYWORDS: 5-hydroxytryptamine-3 antagonists, antiemetogenic prophylaxis, National Comprehensive Cancer Care guidelines, Medicare.

INTRODUCTION

Nausea and vomiting during chemotherapy can have profound clinical and economic consequences, including malaise, dehydration, electrolyte abnormalities, weight loss, feeding tube placement, hospitalization, and death. These symptoms also can lead to decreased treatment adherence and, hence, inadequate therapy. In 1 population-based analysis, Burke et al studied the clinical impact of chemotherapy-induced nausea and vomiting (CINV) from agents considered at high or moderate risk of inducing emesis and observed that, after the first cycle of chemotherapy, the risk of resultant inpatient admissions, emergency room visits, or outpatient hospital visits was 18%. Those authors also observed that the cost of treating patients who experienced CINV after the first cycle could reach $9578 per patient. They concluded that visits for CINV during the first cycle of chemotherapy were both common and costly and that strategies to reduce the incidence of CINV could reduce health care use and cost.[1]

Effective antiemetics do exist in the form of serotonin receptor (5-hydroxytryptamine-3 [5-HT_3]) antagonists and substance P antagonists (SPAs), and several studies have supported their effectiveness for this purpose. For instance, investigators from France compared the use of the 5-HT_3 antagonist ondansetron with high-dose metoclopramide for CINV and observed a significant patient preference for ondansetron (63% vs 26%).[2] The superior effectiveness suggested by this

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preference was then demonstrated in a comparison by Hainsworth et al of patients receiving high-dose cisplatin chemotherapy, in which they observed that ondansetron was more effective, produced fewer adverse events, and was easier to administer than intravenous metoclopramide.[3] More recent randomized controlled trials have demonstrated the superiority of regimens that include SPAs over those with 5-HT_3 antagonists alone. Those studies evaluated patients who were receiving chemotherapy for breast cancer, lung cancer, ovarian cancer, and head and neck cancer.[4-7] The National Comprehensive Cancer Network (NCCN) guidelines for antiemesis prophylaxis currently include the use of both a 5-HT_3 antagonist for high-emetogenic-risk (HER) regimens and an SPA for moderate-emetogenic-risk (MER) regimens.[8]

However, barriers to effective antiemesis prophylaxis have been noted, the most significant of which may be cost. The 5-HT_3 antagonists typically cost $5 to $10 per tablet, and SPAs can cost $500 to $600 for a 3-day course. Given the established clinical and economic benefit of antiemetic prophylaxis, the purpose of our current population-based study was 2-fold. First, we assessed the rate of adherence to national guidelines regarding the use of antiemetic agents as prophylaxis for patients receiving platinum-based chemotherapy regimens for lung cancer. Second, we attempted to identify factors that correlated with adherence to these guidelines in an attempt to better comprehend characteristics that could improve the use of prophylaxis in this setting. Our overall objectives were to provide provocative information regarding the use of antiemetic prophylaxis for patients with lung cancer, to determine whether the current guidelines reflect clinical practice, and to explore ways of increasing the use of these drugs if their use does not follow these guidelines.

MATERIALS AND METHODS

Data Source and Patient Population

The institutional review boards at the University of Texas Medical Branch at Galveston, The University of Texas MD Anderson Cancer Center, and the Texas Department of State Health Services approved this study, as did the Privacy Review Board of the Centers for Medicare and Medicaid Services. We used the Comparative Effectiveness Research on Cancer in Texas/Texas Cancer Registry (TCR)-Medicare linked database for this study. This database contains 2 large population-based data sources, which were linked under the guidance of the National Cancer Institute, the TCR, and the Centers for Medicare and Medicaid Services. This data set provides detailed information about elderly adults with cancer in Texas. Approximately 98% of all individuals aged $\geq$65 years in the TCR are matched with Medicare enrollment and claims files. The TCR collects and provides information on demographics, cancer incidence and prevalence, disease stage at diagnosis, first course of treatment, and survival outcomes. The Medicare claims data include information on hospital stays, physician services, and outpatient hospital visits. Data use agreements have been signed with both data providers.

Our study population was patients aged >65 years (eg, the age cutoff for receiving Medicare) who received platinum-based chemotherapy for a first diagnosis of lung cancer from 2001 to 2007. All patients were treated within 12 months of diagnosis and had continuous Medicare Part A and Part B coverage for the same period. Medicare Part A covers inpatient hospital stays, care with a skilled nursing facility, hospice, and some home health care; whereas Part B covers a portion of physician services, outpatient care, preventative care, and medical supplies (available at: www.medicare.gov; accessed June 1, 2012). Because the current antiemesis guidelines do not differ according to disease characteristics, patients with any stage and or histology of lung cancer were included in the analysis. In total, 4566 individuals were selected along with their Medicare claims during the first 12 months after the diagnosis of lung cancer.

National Comprehensive Cancer Care Guidelines for Antiemesis Prophylaxis

Recommendations for CINV prophylaxis were extracted from guidelines published by the NCCN during the period from 2001 to 2007.[8] These recommendations differ according to the emetogenicity of the chemotherapy agents, with cisplatin doses $\geq$50 mg/m^2 classified as HER and cisplatin doses <50 mg/m^2 or carboplatin at any dose classified as MER. It is noteworthy that doses of platinum compounds cannot be assessed directly through the population database. However, because patients with lung cancer (small cell or nonsmall cell) typically receive cisplatin doses $\geq$50 mg/m^2, for the purposes of the current study, we assumed that any patient receiving cisplatin was given an HER regimen, whereas carboplatin use represented an MER regimen. We acknowledge that most of the patients who received platinum agents for lung cancer also received other agents. However, our assumption holds, because other agents in the HER category (eg, doxorubicin, cyclophosphamide, dacarbazine, epirubicin, ifosfamide, mechlorethamine, and streptozocin) are rarely if ever used for lung cancer. Therefore, the risk category was driven by the type of platinum used.

TABLE 1. National Comprehensive Cancer Network Guidelines for the Use of Antiemetics in Combination With Emetogenic Platin-Based Chemotherapy Agents

Chemotherapy Agent	Antiemetic Agent		
	5-HT_3 Antagonists[a]	Dexamethasone[b]	Neurokinin-1 Antagonists[c]
Carboplatin			
2001-2005	X	X	
2006-2007	X	X	X
Cisplatin			
2001-2003	X	X	
2004-2007	X	X	X

Abbreviations: 5-HT_3, 5-hydroxytryptamine-3 (serotonin).
[a] For 5-HT_3 antagonists, the Healthcare Common Procedure Coding System (HCPCS) codes are J2405 (injection) and Q0179 or S0181 (oral) for ondansetron, J1626 (injection) and S0091 or Q0166 (oral) for granisetron, J1260 (injection) and Q0180 or S0174 (oral) for dolasetron, and J2469 for palonosetron (injection; 2004 and later).
[b] For dexamethasone, the HCPCS codes are J1094 or J1100 (injection) and J8540 or S0173 (oral).
[c] For neurokinin-1 antagonists (aprepitant or fosaprepitant), the HCPCS codes are J1453 (injection) or J8501 (oral).

Before the guidelines could be analyzed, it was necessary to identify appropriate Healthcare Common Procedure Coding System codes (also known as J codes) for both the platinum agents and the antiemetic regimens. The codes for cisplatin were J9060 and J9062; and the code for carboplatin was J9045. Codes for the relevant antiemetic medications (four 5-HT_3 antagonists, aprepitant or fosaprepitant, and dexamethasone) are listed in Table 1.

Because the NCCN recommendations for antiemesis prophylaxis changed during the study period (Table 1), we determined adherence in terms of the recommendation for the same year. That is, adherence for a patient who received treatment in 2001 would be analyzed according to the 2001 NCCN guidelines, and so on. Briefly, during 2001 to 2003, only a 5-HT_3 antagonist and dexamethasone were recommended for prophylaxis. From 2004 to 2005, aprepitant was added for patients who were receiving HER (ie, cisplatin-containing) regimens. From 2006 to 2007, this recommendation was expanded to patients who were receiving MER (ie, carboplatin) regimens.

Definition of Adherence

Adherence to guidelines regarding prophylaxis was scored as a binary variable (ie, adherent or nonadherent), and adherent was defined as delivery of the antiemetic agent within 24 hours of the first day of the first cycle of chemotherapy. This definition was selected because of its directness and objectivity and because it is not influenced by a patient's prior experience with CINV.

Our original plan was to identify factors that were correlated with adherence to use of all of the agents specified in the NCCN guidelines. However, when we discovered the very low rate aprepitant use (<10%), we analyzed correlative factors only with the other remaining agents (ie, 5-HT_3 blockers and dexamethasone) to ensure adequate sample sizes for statistical analysis.

Statistical Methods

To assess the appropriateness of the timing of antiemetic agent use (the objective being within 1 day of the first day of the first cycle of chemotherapy), we evaluated Medicare Part B claims with the Healthcare Common Procedure Coding System codes for platinum-based chemotherapy and antiemetic agents for each selected patient from 2001 to 2007. We anticipated that all codes for the agents being studied would be present in the national claims history and outpatient claims within 12 months after the diagnosis date.[9,10] We then estimated the percentage of patients (with 95% confidence intervals [CIs]) who received care as defined in the guideline for each antiemetic agent.

Logistic regression with stepwise selection was used to examine whether patient and provider characteristics influenced the rate of adherence to antiemetic prophylaxis. Factors with $\alpha < .05$ were retained in the multivariate logistic regression model. Because the numbers of Medicare claims for aprepitant/fosaprepitant were so low, the independent variable was the combination of both 5-HT_3 antagonists and dexamethasone claims within 1 day of the first chemotherapy date. Candidate variables that were included in this model (Table 2) were chosen based on a combination of their availability in the database and their potential clinical or socioeconomic significance. We also determined adherence rates across each year of the analysis to determine whether the time at which the guidelines were implemented influenced the level of compliance. Adjusted odds ratio (OR) values and 95% CIs were calculated for each significant variable in the logistic regression model.

RESULTS

Patient Demographics

Of the 4566 selected patients, 57% were men, 87% were white, and the average age at diagnosis was 73.5 years (range, 66-93 years) (Table 2). Most patients had non-small cell lung cancer, and approximately the same proportion of patients had a score of zero on the Charlson Comorbidity Index (obtained 6 months before the

TABLE 2. Patient Characteristics, N = 4566

Characteristic	No. of Patients (%)
Age at diagnosis, y	
Mean±SD [range], y	73.5±5.13 [66-93]
Sex	
Men	2580 (56.5)
Women	1986 (43.5)
Race	
White	3972 (87.0)
Black	383 (8.4)
Hispanic	147 (3.2)
Other	64 (1.4)
Residency	
Urban	3392 (74.3)
Rural	1174 (25.7)
Median income quartile	
Q_1 $0-$29,621	1124 (24.6)
Q_2: $29,621-$36,272	1146 (25.1)
Q_3: $36,272-$47,260	1155 (25.3)
Q_4: $47,260-$200,008	1141 (25)
Education quartile: % <12 y	
Q_1:0%-14.4%)	1132 (24.8)
Q_2:14.4%-24.4%)	1133 (24.8)
Q_3:24.4%-32.1%)	1155 (25.3)
Q_4: 32.1%-75%)	1146 (25.1)
Year of diagnosis	
2001	552 (12.1)
2002	595 (13)
2003	698 (15.3)
2004	692 (15.2)
2005	678 (14.8)
2006	715 (15.7)
2007	636 (13.9)
Tumor type	
Small cell	1024 (22.4)
Nonsmall cell	3542 (77.6)
Charlson Comorbidity Index	
0	3567 (78.1)
>1	999 (21.9)
Chemotherapy regimen	
Carboplatin	3869 (84.7)
Cisplatin	697 (15.3)
Radiation	
Yes	1839 (40.3)
No	2727 (59.7)

diagnosis date). Most patients (85%) also received MER regimens.

Rates of Adherence to Guidelines on Antiemetic Prophylaxis

Rates of adherence to antiemetic prophylaxis for MER (eg, carboplatin) regimens and HER (eg, cisplatin) regimens from 2001 to 2007 are provided in Table 3. Several points can be made about these adherence rates. First, 5-HT_3 antagonists with dexamethasone were received by approximately 60% to 90% of patients regardless of whether they received HER or MER chemotherapy. Second, adherence to guidelines regarding SPAs was much lower at <10% for all periods studied (sample sizes of <11 patients were suppressed according to the data user agreement). Third, although fluctuations were apparent across periods, adherence rates tended to increase over time, including use of SPAs. For instance, from 2001 to 2007, use of 5-HT_3 antagonists for MER regimens increased from 84.7% in 2001 to 89% in 2007; the corresponding percentages for dexamethasone were 53.5% and 74.2% ($P < .001$; Cochran-Armitage test). The overall trends in use of 5-HT_3 antagonists and dexamethasone are illustrated in Figure 1.

Because the rate of adherence to recommendations regarding antiemetic agents was lower than expected, we performed a supplemental sensitivity analysis to determine whether expanding the timeframe for "adherence" from 1 day to up to 5 days after the start of chemotherapy would improve the compliance rate (keeping in mind that antiemetics administered on later days may have been given for nausea rather than for the prevention of it). Regardless, we observed that increasing the timeframe for adherence did not significantly affect adherence rates (Table 4).

Factors Affecting Adherence Rates to Antiemetic Prophylaxis

Because compliance rates regarding the use of aprepitant or other SPAs were ≥10% for all years studied, our analysis of predictive factors for use of the recommended prophylaxis was restricted to 5-HT_3 antagonists and dexamethasone (which had been part of the recommendation during all years for both HER and MER regimens). That analysis revealed that patients who received treatment in the later years were more likely to have received antiemetic prophylaxis than patients who received treatment in 2001, with an overall adherence rate of 50.7% in 2001 and 70.9% in 2007 ($P < .001$; Cochran-Armitage trend test) (Fig. 1).

Of all the variables that we tested for correlation with adherence to antiemetics (see Table 2), only a subset of these variables was statistically significantly associated with this endpoint. All variable categories are listed in Table 5 along with their P values and 95% CIs from univariate (unadjusted) and multivariate (adjusted) analyses. Multivariate analysis was performed only on those variable categories that were significant in univariate analysis. For instance, because white race was associated with adherence, the category of race was included in both univariate and multivariate logistic regression. Specifically, using this method on multivariate logistic regression modeling, variables that predicted adherence (adjusted ORs with 95% CIs) were older age (OR, 1.013; 95% CI, 1.001-1.026), treatment year (2007 vs 2001: OR, 2.444; 95%

TABLE 3. Adherence to Recommended Antiemetic Prophylactic Regimens by Year

Drug and Year[a]	Total No. of Patients	No. of Patients (%)		
		5-HT_3 Antagonist	Dexamethasone	Aprepitant
Carboplatin				
2001	458	388 (84.7)	245 (53.5)	NA
2002	520	430 (82.7)	318 (61.2)	NA
2003	589	491 (83.4)	380 (64.5)	NA
2004	578	407 (70.4)	390 (67.5)	NA
2005	575	482 (83.8)	380 (66.1)	NA
2006	614	544 (88.6)	447 (72.8)	<11 (DNR)[a]
2007	535	476 (89)	397 (74.2)	<11 (DNR)[a]
Total	3869	3218 (83.2)	2557 (66.1)	DNR (DNR)[a]
Cisplatin: HER				
2001	94	73 (77.7)	42 (44.7)	NA
2002	75	58 (77.3)	44 (58.7)	NA
2003	109	94 (86.2)	85 (78)	NA
2004	114	63 (55.3)	71 (62.3)	<11 (DNR)[a]
2005	103	87 (84.5)	78 (75.7)	<11 (DNR)[a]
2006	101	91 (90.1)	72 (71.3)	<11 (DNR)[a]
2007	101	79 (78.2)	62 (61.4)	<11 (DNR)[a]
Total	697	545 (78.2)	454 (65.1)	DNR (DNR)[a]

Abbreviations: 5-HT_3, 5-hydroxytryptamine-3 (serotonin); HER, high emetogenic risk; NA, not applicable; DNR, data not reported (because cell sizes less than 11 patients were suppressed according to the data user's agreement); NR, not applicable; SD, standard deviation.

[a] Carboplatin was considered a moderate emetogenic risk, and cisplatin was a considered a high emetogenic risk.

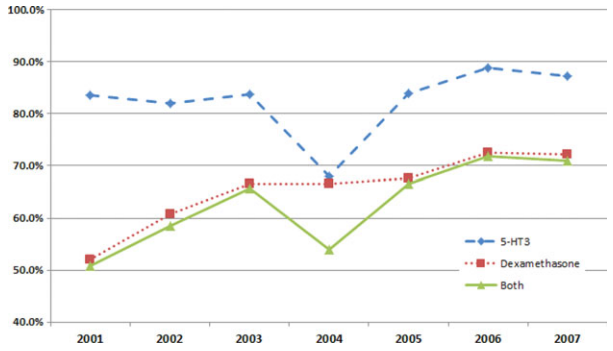

Figure 1. Overall rates of adherence to the use of 5-HT_3 (5-hydroxytryptamine-3 [serotonin]) antagonists and dexamethasone for antiemetic prophylaxis during the study period is illustrated for both high-emetogenic-risk and moderate-emetogenic-risk regimens.

CI, 1.916-3.117), race (black vs white: OR, 0.672; 95% CI, 0.538-0.839), higher median income (highest vs lowest quartile: OR, 1.472; 95% CI, 1.227-1.766; third vs lowest quartile: OR, 1.283; 95% CI, 1.075-1.532; second vs lowest quartile: OR, 1.379; 95% CI, 1.157-1.645), Charlson Comorbidity Index (>1 vs 0: OR, 0.612; 95% CI, 0.528-0.709), and concurrent radiotherapy (yes vs no: OR, 1.360; 95% CI, 1.198-1.544; $P = .9203$; Hosmer and Lemeshow goodness-of-fit test) (Table 5).

We observed no evidence that rare events like clinic or emergency room visits were more common among the patients who did not receive the recommended prophylaxis (data not shown). Unfortunately, the claims data did not allow an analysis of more common adverse events, such as breakthrough nausea (which was managed over the telephone).

DISCUSSION

This population-based study of rates of adherence to recommended antiemetic regimens for patients with lung cancer receiving platinum-based chemotherapy revealed that those rates were suboptimal, particularly with regard to SPAs (eg, aprepitant). We also observed that the rate of adherence increased over time, suggesting the existence of a time lag with regard to physicians incorporating the use of guidelines after they are published. Finally, several clinical factors were associated with improved use of antiemetic prophylaxis, including white race, higher income levels, and the receipt of concurrent radiation, suggesting that multiple components factor into a physician's decision to implement these national standards for individual patients.

Several studies have described the effects of CINV on quality of life. For example, Fernandez-Ortega et al assessed quality-of-life scores prospectively in patients from 9 hospitals who received chemotherapy and who kept diaries for 5 days after the receipt of systemic treatment. Those authors observed that 40% to 45% of patients experienced CINV that significantly affected their quality of life, as estimated by a functional living index-emesis questionnaire, and that those who experienced significant nausea did so in 90% of chemotherapy cycles.[11] In another study of quality of life in a community

TABLE 4. Findings From Sensitivity Analysis of Adherence Rates During the First 5 Days After Beginning Chemotherapy

Drug and Year	No. of Patients Receiving Antiemetic Prophylaxis (%)					
	By 1 Day of Chemotherapy	By 2 Days of Chemotherapy	By 3 Days of Chemotherapy	By 4 Days of Chemotherapy	By 5 Days of Chemotherapy	Max Difference
5-HT_3 Antagonists						
2001	461 (83.5)	465 (84.2)	465 (84.2)	465 (84.2)	466 (84.4)	5
2002	488 (82)	488 (82)	489 (82.2)	490 (82.4)	490 (82.4)	2
2003	585 (83.8)	589 (84.4)	590 (84.5)	591 (84.7)	592 (84.8)	7
2004	470 (67.9)	471 (68.1)	472 (68.2)	472 (68.2)	472 (68.2)	2
2005	569 (83.9)	571 (84.2)	571 (84.2)	572 (84.4)	573 (84.5)	4
2006	635 (88.8)	636 (89)	636 (89)	636 (89)	636 (89)	1
2007	555 (87.3)	556 (87.4)	557 (87.6)	557 (87.6)	558 (87.7)	3
Dexamethasone						
2001	287 (52)	289 (52.4)	290 (52.5)	290 (52.5)	290 (52.5)	3
2002	362 (60.8)	362 (60.8)	363 (61)	363 (61)	363 (61)	1
2003	465 (66.6)	467 (66.9)	468 (67)	468 (67)	469 (67.2)	4
2004	461 (66.6)	462 (66.8)	462 (66.8)	462 (66.8)	462 (66.8)	1
2005	458 (67.6)	458 (67.6)	458 (67.6)	458 (67.6)	459 (67.7)	1
2006	519 (72.6)	520 (72.7)	520 (72.7)	520 (72.7)	520 (72.7)	1
2007	459 (72.2)	459 (72.2)	459 (72.2)	459 (72.2)	459 (72.2)	0

Abbreviations: 5-HT_3, 5-hydroxytryptamine-3 (serotonin); Max difference, the maximum absolute difference in adherent patients from increasing time window from 1 to 5 days.

hospital-based setting, approximately 33% of patients reported that CINV had a substantial impact on their daily lives. Both acute and delayed CINV affected quality of life, but only the presence of acute CINV influenced antiemetic treatment, suggesting that delayed effects are not being appropriately addressed.[12]

Population-based data regarding the use of antiemetic prophylaxis are sparse, particularly during the past decade, and the small studies that have been done have reported conflicting results. For instance, investigators from Italy assessed the use of antiemetic regimens in controlled clinical trials and observed that 5-HT_3 antagonists, either alone or with a corticosteroid, have almost completely replaced other regimens for CINV and that virtually all patients received this regimen regardless of the type of systemic treatment being used.[13] In another study assessing the performance of a feedback system for improving the use of antiemetic prophylaxis, the overall rate of compliance for preventing acute CINV was high, but the vast majority of deficiencies in compliance reflected not preventing delayed CINV and not administering steroids after chemotherapy.[14] Finally, in a recent analysis of compliance with recommendations from the European Society of Medical Oncology, the authors studied 299 patients who received chemotherapy in 2008 and 2009. The overall rate of noncompliance in that study was 39%, and only 24% of patients who received an MER regimen received an SPA; moreover, male sex and hematologic malignancies were predictors of noncompliance.[15] A recent review outlined several obstacles to implementing antiemetic guidelines, including, but not limited to, cost, direct financial conflicts of interest, underestimation of the incidence of delayed emesis, and the belief that it has not been sufficiently demonstrated that antiemetic guidelines improve outcomes.[16]

To our knowledge, the experience we report here represents 1 of the largest to date that evaluates compliance with antiemetic guidelines in this context. Our reported rate of adherence to SPAs was even lower than in previous reports. We took several measures in an attempt to include all instances of antiemetic administration, including a full analysis of Medicare Part B claims for all observed years as well as exploration of Part D claims for 2006 and 2007 National Drug Codes. Although we confirmed the unexpectedly low rate of aprepitant use, ultimately, we did not use the Part D findings in our analysis, because Part D was initiated in 2006 (which reduced our confidence in the enrollment rate), and, by excluding those claims, we maintained consistency across years.

This low compliance has several potential explanations. First, the findings may be specific to the population included in this study, which was limited to individuals in Texas. Second, our definition of adherence was different from the definitions used in previous publications. For example, in the study of compliance with European Society of Medical Oncology recommendations and in the analysis by Mertens et al, adherence was defined as the presence of a prescription for the appropriate

TABLE 5. Variable Categories That Had a Statistically Significant Association With Adherence to Recommendations on the Use of 5-Hydroxytryptamine-3 Antagonists Combined With Dexamethasone for Antiemetic Prophylaxis in Patients Receiving Highly or Moderately Emetogenic Chemotherapy for Lung Cancer

	Unadjusted Univariate Analysis		Adjusted Multivariate Analysis	
Characteristic	OR (95% CI)[a]	*P*	OR (95% CI)[a]	*P*
Age at diagnosis	1.018 (1.006-1.030)	.003	1.013 (1.001-1.026)	.033
Concurrent radiation therapy				
No[b]				
Yes	1.350 (1.193-1.528)	< .001	1.360 (1.198-1.544)	< .001
Race				
White[b]				
Black	0.606 (0.491-0.748)	< .001	0.672 (0.538-0.839)	.001
Hispanic	1.054 (0.746-1.490)	.764	1.219 (0.848-1.752)	.284
Other	0.635 (0.387-1.042)	.072	0.632 (0.380-1.051)	.077
Charlson Comorbidity Index				
0[b]				
>1	0.631 (0.547-0.727)	< .001	0.612 (0.528-0.709)	< .001
Median income quartile				
Q_1: $0-$29,621[b]				
Q_2: $29,621-$36,272	1.424 (1.203-1.686)	< .001	1.379 (1.157-1.645)	< .001
Q_3: $36,272-$47,260	1.362 (1.151-1.611)	< .001	1.283 (1.075-1.532)	.006
Q_4: $47,260-$200,008	1.622 (1.367-1.924)	< .001	1.472 (1.227-1.766)	< .001
Treatment year				
2001[b]				
2002	1.369 (1.084-1.728)	.008	1.404 (1.108-1.779)	.005
2003	1.854 (1.475-2.330)	< .001	1.877 (1.488-2.366)	< .001
2004	1.136 (0.908-1.421)	.265	1.157 (0.921-1.453)	.210
2005	1.930 (1.532-2.431)	< .001	2.028 (1.603-2.566)	< .001
2006	2.484 (1.967-3.136)	< .001	2.606 (2.055-3.305)	< .001
2007	2.368 (1.865-3.007)	< .001	2.444 (1.916-3.117)	< .001
Sex				
Women[b]				
Men	0.914 (0.809-1.032)	.146	—	—
Residency				
Rural[b]				
Urban	1.062 (0.926-1.218)	.390	—	—
Education quartile: % <12 y				
Q_1: 0%-14.4%[b]				
Q_2: 14.4%-24.4%	1.087 (0.914-1.292)	.346	—	—
Q_3: 24.4%-32.1%	0.901 (0.760-1.069)	.232	—	—
Q_4: 32.1%-75%	0.792 (0.669-0.938)	.007	—	—
Tumor type				
Nonsmall cell[b]				
Small cell	1.086 (0.940-1.256)	.263	—	—
Chemotherapy regimen				
Carboplatin[b]				
Cisplatin	0.905 (0.767-1.068)	.237	—	—

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] An OR >1.00 indicates increased adherence to recommendations.
[b] Reference category.

antiemetic[14,15] as opposed to our definition of administration of the antiemetic within 24 hours of chemotherapy. Our definition, although narrow, is consistent with true prophylaxis, because it is documented that patients have taken the medication within a very narrow time before or after the administration of systemic therapy. However, we acknowledge that this stricter guideline may have underestimated the proportion of patients who had received a prior prescription for an antiemetic agent.

Our discovery that compliance with the prophylaxis guidelines was associated with race and income implies that socioeconomic factors may have a role in antiemesis prevention. Physicians also may perceive (and often rightfully so) that patients who are older or who are receiving concurrent radiation therapy are at a higher risk of CINV, and, as such, this subgroup would be more likely to receive interventions in this context. However, if this is true, then our finding that patients with more comorbid

conditions, as determined by the Charlson Comorbidity Index, were *less* likely to receive prophylactic intervention is inconsistent with these results. However, it is noteworthy that the cormorbidity index is not equivalent to performance status, which is often what is apparent to the treating physician and may be more influential in determining management.

Our interpretation of these results is subject to several constraints. First, claims data are inherently limited, because they are designed for billing, and not for clinical purposes. Claims are subject to biases caused by under coding of important events. However, we believe the likelihood of under coding is low in this case, because the drugs and outcomes of interest are both costly and fully reimbursable under Medicare and other insurance policies. Second, cancer registry data are subject to ascertainment biases, because patients diagnosed in the ambulatory care setting may not be included and because treatment information is limited to the first course delivered within the first 4 months after diagnosis. Linkage to claims data permits us to identify missed patients and subsequent treatment, thereby minimizing this problem. Third, Medicare claims provide information on relatively limited populations. Although there is no single source for all populations, including other claim types in addition to Medicare, such as those for Medicaid patients, will provide large samples of the elderly, poor, and working age cancer patients. Finally, we made assumptions about cisplatin doses, and we assumed that physicians who adhered to guidelines during the first cycle would continue to do so in future cycles. These assumptions are based on clinical data and logical reasoning, but they do highlight the finding that the results from this study represent our best estimation of trends in the population based on the only population-level data available. Furthermore, even if some patients on cisplatin received doses <50 mg/m^2, those patients should have received an MER antiemetic regimen, and we observed that the receipt of 5-HT$_3$ antagonists with dexamethasone (excluding aprepitant) also was suboptimal in all patients.

In conclusion, we used a Texas population-based cancer registry linked to Medicare claims to demonstrate that adherence to national guidelines for antiemesis prophylaxis in patients with lung cancer is suboptimal. Although the data provided have some limitations, we took several steps to exhaustively include all available administrations by using claims data and what we consider to be a narrow but appropriate definition of adherence. In this context, we observed that compliance with administration of SPAs was minimal when the recommendation was first implemented, but it may have increased steadily over time. Finally, we observed that socioeconomic, patient-related, and treatment-related factors influenced adherence, a result that is both indicative of treatment variations based on practice setting as well as hypothesis-generating for the further exploration of interventions that could improve compliance across populations.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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