OPTIMIZING ANTIEMETIC USE IN PATIENTS INITIATING HIGHLY EMETOGENIC INTRAVENOUS CHEMOTHERAPY: LESSONS LEARNED FROM BIG DATA AND MODELING

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ABSTRACT

Nirosha Mahendraratnam Lederer: Optimizing Antiemetic Use in Patients Initiating Highly Emetogenic Intravenous Chemotherapy: Lessons Learned from Big Data and Modeling
(Under the direction of Stacie B. Dusetzina)

Patients initiating highly emetic chemotherapy are at a 90% risk of chemotherapy-induced nausea and vomiting (CINV). Antiemetic drugs are highly effective in preventing CINV and thus improve quality of life and generate cost savings by reducing the need for CINV-related health services. Despite guideline-concordant antiemetic prescribing preventing CINV in up to 80% of patients, evidence suggests that use of ASCO and NCCN guideline-concordant antiemetic regimens by patients initiating highly emetogenic chemotherapy is low. Furthermore, of the multiple CINV preventative treatment regimens that are considered guideline concordant, there is no clear clinical preference and costs vary widely. The purposes of this dissertation were to characterize antiemetic use; identify predictors of antiemetic under-use; and evaluate the trade-offs in cost, clinical, and quality of life outcomes across the guideline-concordant recommendations in patients initiating intravenous highly emetogenic chemotherapy. Aim 1 used descriptive statistics to describe antiemetic prescribing patterns, including antiemetic under-use, in patients with cancer initiating highly emetic chemotherapy using the IBM Watson's/Truven's MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits data. Aim 2 used a modified Poisson regression to identify factors associated with antiemetic under-use (i.e., environmental, predisposing, enabling, and need) in these same data. Aim 3 assessed the health and economic impacts of guideline-concordant antiemetic strategies through a cost-utility analysis in order to prioritize them. Alarmingly, under-use of guideline-concordant antiemetic fills is high, at 49% and 68% in the commercial claims and Medicare supplement populations, respectively (Aim 1). While more than 75% of patients are filling 5HT3As and dexamethasone, NK1 product fills were low and olanzapine fills were negligible. Site of chemotherapy setting was among the greatest predictors of antiemetic use, with

patients receiving chemotherapy in an outpatient hospital setting at a 1.28 ($p<0.0001$) and 1.48 ($p<0.0001$) times higher risk of under-use compared to outpatient physician setting in the CCAE and Medicare Supplement populations, respectively (Aim 2). Medical benefit generosity and prescription drug generosity has limited impact on under-use in both populations. Olanzapine + fosaprepitant + 5HT3A + dexamethasone dominates all other strategies; however, after excluding olanzapine-based strategies fosaprepitant + 5HT3A + dexamethasone was the most efficient strategy (Aim 3). Given the limited incremental benefits across strategies, treatment acquisition costs should be considered when deciding on an antiemetic strategy, thus prioritizing first-generation 5HT3As and intravenously administered products.

To my mother. Thank you for always being my greatest advocate and inspiring me.

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LIST OF ABBREVIATIONS

APR	Aprepitant
ASCO	American Society of Clinical Oncology
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CINV	Chemotherapy Induced Nausea and Vomiting
CMS	Centers for Medicare and Medicaid Services
CR	Complete Response
CP	Complete Protection
DEX	Dexamethasone
FOS	Fosaprepitant
DOL	Dolasetron
FDA	Food and Drug Administration
GRAN	Granisetron
HEC	Highly Emetogenic Chemotherapy
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IR	Incomplete Response
IV	Intravenous
NCCN	National Comprehensive Cancer Network
NDC	National Drug Code
NEPA	Netupitant Palonosetron Combination

OND	Ondansetron
OLANZ	Olanzapine
ROL	Rolapitant

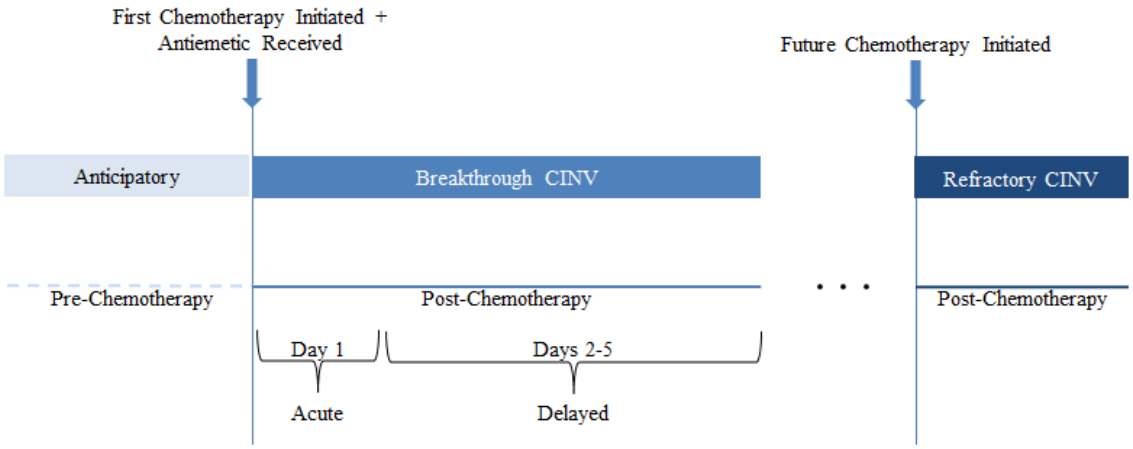
CHAPTER 1: INTRODUCTION

1.1 Background

Cancer is among the leading causes of mortality in the US, with incidence rates increasing in certain cancer types.(5) Managing cancer is challenging given the need to balance high costs and varied patient preferences regarding quality of life (e.g., side-effects) with survival. Furthermore, cancer treatment is highly heterogeneous even within cancer type. Chemotherapy is one type of cancer treatment that uses chemical anti-cancer drugs systemically. While chemotherapy can be life-saving and life-prolonging, certain types include the risk of significant side-effects including severe nausea and vomiting.

Uncontrolled, severe chemotherapy-induced nausea and vomiting (CINV) is among the most feared treatment side effects by patients and reduces patient quality of life.(6) CINV can occur in the acute (i.e., within 24 hours / day 1) or delayed (i.e., 24-120 hours / days 2-5) phases after chemotherapy administration.(1) Patients with breakthrough CINV are those that experience it despite receiving appropriate prophylactic antiemetics. Additionally, patients who experience CINV in anticipation of future chemotherapy cycles are defined as anticipatory, while those who experience CINV following future chemotherapy treatments are classified as refractory.(7) Figure 1.1 depicts CINV types.

Figure 1.1 Types of CINV



CINV leads to significant clinical issues including, but not limited to dehydration, fatigue, and slow wound healing, as well as utilizing significant healthcare resources, including additional hospital and physician visits.(3) Preventing CINV has been shown to reduce downstream costs and improve quality of life. Estimates on average CINV-related monthly costs range from $1,280 to $5,386.(8-10) CINV may also prevent patients from adhering to chemotherapy treatments.(1, 4, 11-13) In addition to patient history, evidence has overwhelmingly demonstrated that the type of chemotherapy initiated is the best predictor of CINV risk.(14)

Antiemetic drugs are a highly effective prophylaxis to prevent CINV and the evidence base to support these products' ability to prevent and reduce CINV, improve quality of life, and generate cost savings is robust. (1-4) Conventional antiemetic drugs used to prevent acute and delayed CINV, in order of least to most potent, are glucocorticoids (i.e., dexamethasone), 5-HT3 receptor antagonists (5HT3A) (e.g., ondansetron), and NK1 receptor antagonists (e.g., aprepitant and fosaprepitant).(15) Notably, these conventional antiemetics used to prevent CINV are generally not effective in treating CINV.(7, 16, 17) As such, non-traditional antiemetics may be used as rescue therapies to treat CINV in patients who failed conventional prophylactic therapy and experienced breakthrough CINV, as well as those experiencing anticipatory, or refractory CINV.(18-20) Specifically, non-traditional antiemetics for CINV-treatment include: antipsychotics (i.e., olanzapine), benzodiazepines (e.g., lorazepam), cannabinoids (e.g., nabilone), and phenothiazines (e.g., prochlorperazine), among others (e.g., haloperidol, metoclopramide, and scopolamine). (While they lack a strong evidence base, 5HT3As and corticosteroids are also used to treat breakthrough therapy.) Leveraging rigorous evidence reviews, US-based guidelines developed by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) offer recommendations on the appropriate use of antiemetic drugs to prevent acute and delayed CINV based on the classification of the likelihood of emesis of the chemotherapy regimen (i.e., emetogenicity), which include high, moderate, low, and minimal (Table 1.1).(15, 18-21) This dissertation focuses on patients with cancer who are newly initiating highly emetogenic chemotherapy, who are at a 90% risk of having a CINV event. For this population, both ASCO and NCCN guidelines

recommend that patients receive a triple therapy combination of an NK1, 5HT3A, and glucocorticoids for CINV prevention. Additionally, more recently, NCCN and ASCO guidelines recommend the use of olanzapine for CINV prevention, though they differ in the recommended olanzapine strategies (Table 1.1). Notably, there are many prophylactic treatment regimens that are considered guideline-concordant for patients initiating highly emetogenic chemotherapy with varying costs, and there is no preferred option. Recommendations on treating breakthrough CINV are sparse given the limited evidence on treating CINV, but those that exist center on adding a product that is from a different drug class than the current treatment.

Table 1.1 2017 ASCO and 2017 NCCN Prophylactic Antiemesis Guideline Recommendations in Patients Initiating Highly Emetogenic Chemotherapy Intravenously*(18, 20)

	ASCO	NCCN
Day 1 (Acute)	• NK1, 5-HT3A, and corticosteroid • NEPA and corticosteroid • Olanzapine+aprepitant+5HT3A+ corticosteroid**	• NK1, 5-HT3A, and corticosteroid • NEPA and corticosteroid • Olanzapine, palonosetron, and corticosteroid** • Olanzapine+aprepitant+5HT3A+ corticosteroid***
Days 2-5 (Delayed)	• Aprepitant on days 2-3 (if aprepitant on day 1) • Corticosteroid days 2-4 • Olanzapine days 2-4 (if olanzapine on day 1)	• Aprepitant on days 2-3 (if aprepitant on day 1) • Corticosteroid days 2-4 • Olanzapine days 2-4 (if olanzapine on day 1)

*Corticosteroid: Dexamethasone; 5-HT3A: Granisetron, Ondansetron, Palonosetron, Dolasetron; NK1s: Aprepitant, Fosaprepitant, Rolapitant
**This strategy is only recommended in NCCN guidelines
***2017 NCCN and ASCO guidelines newly recommend olanzapine + aprepitant + 5HT3A + dexamethasone

The purposes of this dissertation were to characterize antiemetic use; identify predictors of antiemetic under-use; and evaluate the trade-offs in cost, clinical, and quality of life outcomes across the guideline-concordant recommendations in patients who initiate highly emetogenic chemotherapy.

1.2 Specific Aims

1.2.1 Aim 1: To characterize antiemetic use (including types and regimens) in patients who were diagnosed with cancer and newly initiated highly emetogenic, intravenous chemotherapy for the first time from 2013-2015.

Evidence demonstrates that antiemetic drugs are highly effective in preventing CINV, and thus improve quality of life, and generate cost savings. (1-4) However, use of antiemetics in the real world is suboptimal. (22, 23) In general, patients receive at least one type of antiemetic in the acute phase, but receipt of an antiemetic in the delayed phase is much lower. Understanding patterns of antiemetic prescribing in the United States (US) is important given the number of options that are considered guideline-concordant in patients initiating highly emetogenic chemotherapy. Of particular interest is the uptake of the highly promising and less expensive product, olanzapine, which is currently unknown.(1, 7, 24-29) Notably, patterns of antiemetic prescribing among patients initiating highly emetogenic chemotherapy has not been well studied in the United States, especially in recent history or in a large, nationally representative study.(22, 23, 30-37) Studies that have examined prophylactic antiemetic prescribing were not only in different healthcare systems than the US, but also in countries where antiemetic product availability is dissimilar. There is also much within-country heterogeneity in prescribing patterns, highlighting the inability to generalize one country's study findings to another.

The rate of guideline-discordant CINV-related antiemetic prescribing is high in patients initiating highly emetogenic chemotherapy, especially in the delayed phase.(22, 38-44) The primary reason for guideline-discordance for patients initiating highly emetogenic chemotherapy is under-prescribing, which is defined as prescribing a product that is less potent (including lower doses) than recommended or excluding drugs that should be included. Under-prescribing of antiemetic drugs leads to the occurrence of preventable CINV-related events, their associated resource use and costs as well as reductions in quality of life.(4) The most common occurrence of under-prescribing in this population is not receiving an NK1.(45) In fact, a prior study found that only 40% of white women and 30% of black women in the Medicare population initiating highly emetogenic anthracycline and cyclophosphamide received NK1s.(45, 46). Over-prescribing is defined as prescribing: 1) a more potent drug or 2) more complex drug

regimens than recommended. In general, over-prescribing of antiemetics is an important issue to address, as those drugs that are intended to treat high-risk CINV are more expensive than low-risk CINV drugs.(47) However, for highly emetogenic products, over-prescribing centers on using NK1s or 5HT3As beyond the days recommended (if the patient is not experiencing symptoms). While three US-based guideline concordance studies were identified, there are several gaps in the literature that this dissertation will fill.(22, 38, 45) Two of the three prior studies focused on discordant prescribing in general. Additionally, these studies had limited generalizability given that one was a small southeast practice with an EMR-based automated prescription system and the other used two large claims data sets, but only focused on breast cancer. The third study assessed over-prescribing in a large claims data set, but under-prescribing was not assessed.(38)

The primary purpose of Aim 1 is to describe what types of antiemetic regimens are being used and to assess the proportion of antiemetic use in patients with cancer who are initiating highly emetogenic, intravenous chemotherapy. These results will help payers and providers identify opportunities to increase appropriate antiemetic uptake. While there is value in examining both under-use and over-use in patients initiating highly emetogenic chemotherapy because of their different implications on the healthcare system (disparity versus cost), this dissertation focuses on under-use because the narrow definition of over-prescribing presents outcomes measurement challenges.(22, 45) Our study population includes patients who were newly initiating single-day highly emetogenic intravenous chemotherapy for cancer, who were not pregnant, and who did not have comorbid schizophrenia or bipolar disorder. Data for Aim 1 came from IBM Watson's/Truven's MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (MCOB) database from 2013-2015. The MarketScan CCAE database is composed of a nationally representative sample of people with employer-sponsored insurance in the US consisting of over 200,000 new initiators of chemotherapy in this time period. The MarketScan Medicare Supplement database represents Medicare patients who purchase employer-paid supplemental insurance and are retired. Medicare serves as the primary source of insurance for those who are retired.(48)

Descriptive statistics will be used to assess patterns of antiemetic drug use as well as guideline-concordance. Patterns that will be examined include types of antiemetics filled (i.e., product and class), number of antiemetic products filled, as well as regimens filled and their associated costs. To assess guideline concordance, the most recent antiemetic guidelines in 2015 were used given the time frame of interest. Antiemetics were identified using HCPCS codes for intravenously administered products and NDC codes for oral products. Analyses were run on the commercially insured and Medicare Supplement populations separately.

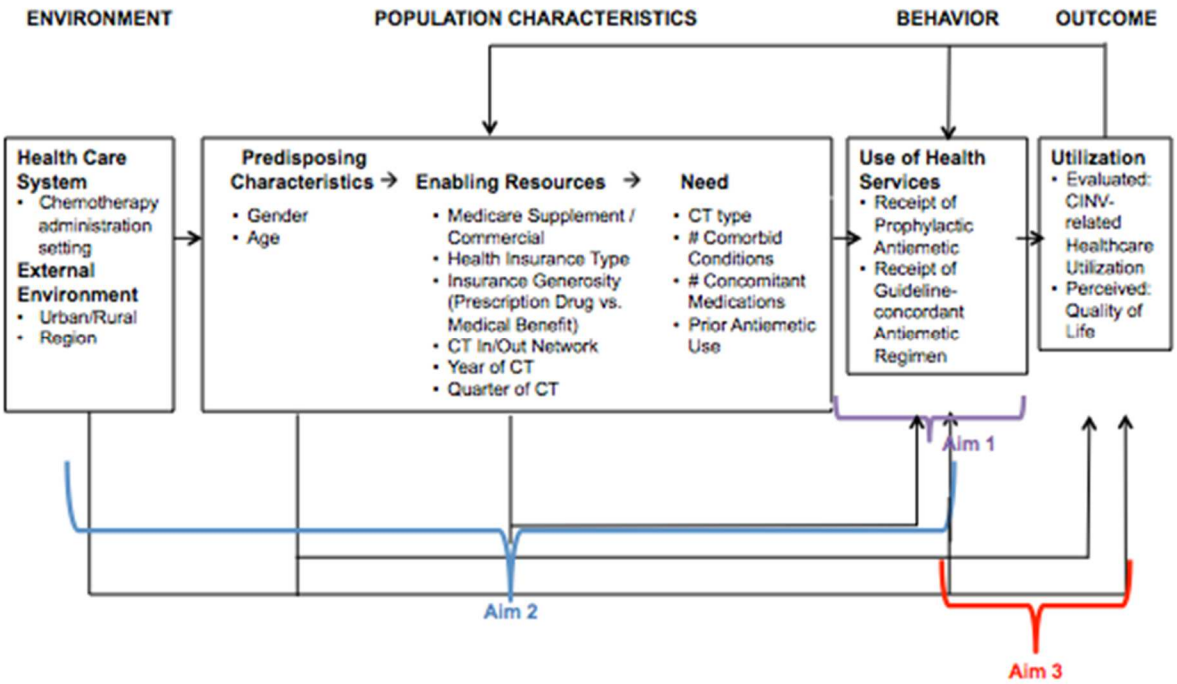
1.2.2 Aim 2: To identify predictors of antiemetic under-use in patients diagnosed with cancer and newly initiating highly emetogenic, intravenous chemotherapy.

In the US, the increased attention on value-based care, including advanced payment models and outcomes-based contracting are incentivizing stakeholders to emphasize high quality, value-based care, which includes guideline adherence.(49) Importantly, guideline adherence can lead to improved patient experiences and outcomes and reduce costs. (50, 51) As such, identifying factors that influence antiemetic discordance will help address gaps in antiemetic prescribing and promote high-quality and high-value care. While prior studies have examined predictors of concordance and discordance, many are in non-US healthcare systems or are limited in scope, highlighting the need to study predictors in the US system.(22, 38, 45) Again, it is crucial to consider these predictors in the context of the healthcare delivery system in which they were assessed given the differences across systems.

The purpose of Aim 2 is to identify predictors of antiemetic under-use as opposed to guideline-concordant use in patients with cancer who are initiating highly emetogenic, intravenous chemotherapy. We focus on under-use in patients initiating highly emetogenic chemotherapy, because for these patients, the definition of over-use is limited to using more pills than recommended or more products (e.g., multiple NK1s) than necessary, as opposed to more potent products than recommended. Additionally, under-use for this population presents a greater opportunity to improve patient outcomes for this population. Data for Aim 2 came from the MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplement database from 2013-2015. Categorization of patients as guideline-concordant or

under-use were based on the results of Aim 1. Potential predictors were identified based on Andersen's Behavioral Model of Health Service Use and the availability of variables in the data set (Figure 1.2). Environmental factors (e.g., chemotherapy setting, urban/rural, and region), predisposing characteristics (e.g., gender and age), enabling resources (e.g., health insurance type, insurance generosity, in/out network chemotherapy administration, year of chemotherapy administration, and quarter of chemotherapy administration), and need factors (e.g., chemotherapy regimen, number of comorbid conditions, number concomitant medications, prior antiemetic use, prior chemotherapy (oral or IV), and prior radiation therapy) were assessed. Given the dichotomous nature of the outcome variable, a modified Poisson regression directly estimating the effect of covariates in terms of relative risks (while controlling for the influence of other factors in the model) was used. Predictors were assessed separately in the Commercial Claims and Medicare supplement data sets.

Figure 1.2 Adapted Andersen's Behavioral Model of Health Services Use to Examine Patterns of Antiemetic Prescribing, Predictors of Guideline Concordance, and Cost Effectiveness



1.2.3 Aim 3: To assess the most cost-effective antiemetic regimen for patients diagnosed with cancer and newly initiating highly emetogenic, intravenous chemotherapy.

In a value-driven environment, it is important to understand the trade-offs between the upfront costs of prophylactic antiemetic use compared to the occurrence of CINV events and the associated increases in healthcare resource use and costs as well as decreases in quality of life. There are many prophylactic treatment regimens that are considered guideline-concordant for patients initiating highly emetogenic chemotherapy, and there is no preferred option. Given the wide range of costs for these regimens, assessing cost-effectiveness across all of the regimens is one way to prioritize products, which has yet to be done. Notably, the 2016 ASCO guidelines (e-published in 2015) specifically highlight the need to evaluate the value of NEPA given its high costs and potential out-of-pocket patient costs as it is an oral product.(52) To date there have been two cost-effectiveness studies that examined the cost-effectiveness of NEPA in patients initiating highly emetogenic chemotherapy from the United Kingdom and Italian payer perspectives.(53) Additionally, in five other studies comparing aprepitant-based regimens to 5HT3A regimens in patients initiating highly emetogenic chemotherapy, aprepitant was found to be either cost-effective at a $50,000/QALY or a dominated standard of care.(54-58) No studies have compared olanzapine in any setting or across all NK1s from a US commercial payer or societal perspective using cost effectiveness.

The purpose of Aim 3 is to assess the health and economic impacts of guideline-concordant antiemetic regimens in patients initiating highly emetic, intravenous chemotherapy using a cost-utility analysis. The primary outcomes are cost (2016 USD), quality-adjusted life days (QALDs) and quality-adjusted life years (QALYs). Regimens were ranked by cost and assessed for efficiency or dominance. Guideline recommendations include: (1) NK1 (aprepitant, fosaprepitant and rolapitant), 5HT3A (first generation: ondansetron, granisetron, and dolasetron and second generation: palonosetron), and a corticosteroid (dexamethasone); (2) Netupitant / palonosetron combination + dexamethasone; (3) Olanzapine + palonosetron + dexamethasone; (4) Olanzapine + aprepitant/fosaprepitant + 5HT3A + dexamethasone; and (5) Aprepitant/Fosaprepitant + 5HT3A + dexamethasone. These results will help

decision-makers prioritize and optimize antiemetic use in clinical practice. Based on the literature, the effectiveness of 5HT3As was assumed to be similar in the presence of NK1-based strategies, so only the NK1s were varied when the NK1 was not specified.(20, 56, 59)

Aim 3 used a Markov model with both one-way and probabilistic sensitivity analyses to estimate the incremental costs and quality-adjusted life years from the perspectives of the US healthcare system and society. The time horizon was five days, including the acute phase (day 1) and delayed phase (days 2-5), which aligns with clinical trials. Patients may have experienced incomplete response, complete response, or complete protection in both the acute and delayed phases. The hypothetical cohorts consisted of 100,000 adults aged 18-65 with cancer, being newly treated with single-day, highly emetogenic, intravenous chemotherapy. As the guidelines of interest are applicable to patients newly initiating highly emetogenic chemotherapy, the model encompassed a single chemotherapy cycle. Clinical inputs were based on randomized controlled trial evidence. Quality of life and cost inputs were based on a literature review. Costs were adjusted to US 2016 dollars using the medical component of the Consumer Price Index. Given the short time frame, cost and quality-of-life outcomes were not discounted.

1.3 Significance

The US healthcare system is under tremendous pressure to reduce costs. This has spurred the development of oncology pathways and guidelines that use rigorous evidence evaluation to create treatment algorithms that exploit value and encourage appropriate use. Additionally, the growing focus on patient engagement and value-based care will require consideration beyond treating disease to balancing patient preferences regarding quality of life (e.g., side-effects) with high costs. Preventing CINV events through guideline-concordant prescribing not only offers the US healthcare system and payers cost-effective care, but also offers improved quality of life for patients.

This dissertation will contribute to understanding and optimizing antiemetic use in patients initiating highly emetogenic chemotherapy. Specifically, the results from Aim 1 characterize current patterns of antiemetic use in the US and assess guideline concordance. From Aim 2, predictors of antiemetic under-use are identified to develop targeted interventions to improve guideline concordance.

Finally, the results from Aim 3, which incorporate measures of patient quality-of-life, considering the trade-offs between cost and effectiveness of antiemetic treatment strategies, will help optimize antiemetic use to prevent CINV in this patient population.

CHAPTER 2: LITERATURE REVIEW

Chapter 2 is presented in five sections and intended to contextualize the three aims of this dissertation. The first section (2.1) provides an overview on CINV including its incidence and associated clinical, economic, and quality of life outcomes. It also details CINV prevention and treatment options, and the evidence generated on these products to date. The second section (2.2) establishes what is known on antiemetic prescribing to date and its impact on clinical and healthcare resource use outcomes to support Aims 1 and 2. This third section (2.3) reviews cost-effectiveness (including cost-utility) studies conducted to date to help design and evaluate Aim 3. The fourth section (2.4) details the conceptual model that motivates this dissertation. The final section (2.5) concludes the literature review by summarizing key points.

2.1 Overview Of Chemotherapy Induced Nausea And Vomiting

Cancer is among the leading causes of mortality in the US, with cancer incidence rates increasing in certain cancer types.(5) In 2016, the National Cancer Institute anticipates over one 1.6 million new cancer diagnoses. Cancer is a particularly challenging disease area to manage given the need to balance high costs, varied patient preferences regarding quality of life (e.g., side-effects), and survival. In addition to being expensive, estimated at $125B in 2010 and projected to increase up to 40% by 2020, cancer treatment is highly heterogeneous even within cancer type.(60, 61) While chemotherapy can be life-saving and life-prolonging, certain types include the risk of significant side-effects including severe nausea and vomiting, which are among the most feared by patients.(15) This section provides an overview on CINV and then reviews its treatment and its impact on clinical, cost, and quality of life outcomes.

2.1.1 Chemotherapy Induced Nausea and Vomiting: Definition

Nausea is "characterized by a queasy sensation and /or the urge to vomit" and vomiting is "characterized by the reflexive act of ejecting the contents of the stomach through the mouth."(62) The five types of CINV, detailed in Table 2.1, are classified by the following two factors: 1) when it occurs relative to initiating chemotherapy and 2) prior prophylactic experience.(1, 7, 63-66) Acute and delayed CINV refer to CINV events that occur within 0-24 and 25-120 hours of chemotherapy initiation. Breakthrough CINV is the occurrence of CINV-events despite appropriate prophylactic treatment. Anticipatory and refractory CINV apply to patients who have CINV events during prior chemotherapy cycles, and experience it either as a conditioned response prior to, or reoccurrence in, future cycles.

Table 2.1 Types of CINV (Adapted from Navari 2016) (1, 7, 63-66)

CINV	Definition
Acute	Occurring within the first 24 hours (1 day) after initiation of chemotherapy
Delayed	Occurring days 2-5 after chemotherapy
Breakthrough	Occurring despite appropriate prophylactic treatment
Anticipatory	Occurring before a chemotherapy treatment as a conditioned response to the occurrence of CINV in previous cycles
Refractory	Recurring in subsequent cycles of therapy (excluding anticipatory)

CINV can also lead to serious metabolic derangements, nutritional depletion and anorexia, deterioration of patients' physical and mental status, esophageal tears, fractures, wound dehiscence, anti-cancer treatment discontinuation, and degeneration of self-care and functional ability.(17)

2.1.1.1 Quality of Life

CINV not only has significant clinical impacts, but also significantly reduces patients' quality of life.(3, 11, 67, 68) This includes, but is not limited to daily functioning (affects 40% of patients and up to 90% when CINV is poorly managed), leisure activities, and ability to eat and drink and thus impacting nutritional status.(3, 10, 69, 70) Quality of life is significantly worse in patients initiating highly emetogenic chemotherapy than those on moderately emetogenic chemotherapy.(3, 71) Moreover, nausea influences quality of life more than vomiting.(6, 71, 72) CINV may also prevent patients from adhering to chemotherapy treatments.(1, 4, 11-13)

2.1.2 CINV Healthcare Resource Use and Cost

Studies have consistently demonstrated that direct costs are higher in patients with uncontrolled CINV versus those who do not experience CINV.(2, 8-10, 58, 72) Additionally, indirect costs are higher not only in patients with uncontrolled CINV, but also patients experiencing more severe CINV.(8, 10) The following section will focus on the US-based CINV related cost studies.

A retrospective cohort study by Burke et al, 2010 using the Premier Perspective TM Database, which includes hospital service data (2003-2007) from 600 hospitals in the United States, found that 18.0% of highly emetogenic chemotherapy users experienced any CINV-related event.(9) These patients were prescribed one or more drugs commonly used for antiemetic prophylaxis, with 95.3% of highly emetogenic users being prescribed a 5HT3A. About 5% of patients were prescribed an NK1. Results based on antiemetic use were not provided. Visits for delayed CINV were more likely than acute CINV across patients (13.7% vs. 0.2%). The average cost of any CINV event in the highly emetogenic group was $5,386 (SD $6,425) in the 30 days following first chemotherapy initiation or 1 day before the next chemotherapy administration. Inpatient visits were most common and expensive ($7,678/patient (SD $6,875), followed by outpatient hospital ($1,461/patient (SD $2,551), and emergency room ($1,007/patient (SD $1,453)). The authors conducted several sensitivity analyses to account for the fact that some of the costs being attributed to CINV may be due to other conditions, and found the average CINV costs to be much lower. Of note, in one sensitivity analysis where the study window was limited to the 6 days following chemotherapy administration, the average cost of a CINV event was $218 (SD 1,393) across all patients translating to $1,210 among those experiencing CINV. (All costs were unadjusted and based on what was reported in the database)

In another retrospective database study by Shih et al, using data from the Medstat MarketScan Health and Productivity management database (1997-2002), representing US large employers, nearly 30% of patients initiating moderate or highly emetogenic chemotherapy experienced uncontrolled CINV despite over 85% of patients using a 5HT3A.(8) It was estimated that the direct medical costs in the uncontrolled CINV group was $1,383 higher than the controlled group. After adjusting for

sociodemographic, comorbidity, cancer type, metastasis, region, and year, the estimated adjusted direct cost of an uncontrolled CINV event was $1,280 per patient per month and $433 per patient per month for indirect costs over 6 months. These cost estimates are much lower than those estimated by Burke et al, 2011 and may be the result of covariate adjustments as well as the inclusion of primary and secondary diagnoses of CINV according to Shih et al.(8, 9) However, even by limiting CINV event to primary diagnosis, Burke et. al's average CINV cost was $4,043, despite the CINV incidence rate being less than Shih et. al's and a shorter follow-up period. Additionally, on average, the cost associated with missed work and reduced productivity were $31.57 and $14.82, respectively. Notably, the costs increase to $112.40 and $67.70 for missed work and reduced productivity among those that were currently employed.(8)

In 2011, Craver et al. used the same data source as the Burke study, but between 2007-2009, and studied CINV events across all types of CINV-risk chemotherapy initiators.(2) In this study, approximately 75% of patient received antiemetic prophylaxis, and the risk of CINV was 20%. Importantly, both studies likely underestimate CINV costs, as non-hospital rescue medications were not captured. Unlike Shih et al, outpatient visits were not only the most common type of hospital encounter, but also the least costly.(8) The average direct CINV costs were $1855 (inpatient: $2422/day, outpatient: $1365/day, emergency room: $1987/day). (2) (All costs were unadjusted and based on what was reported in the database)

Haiderali et. al's assessed CINV-related events in a small (N=178), prospective, multi-site observational study. CINV events were based on self-reporting by adult patients initiating moderately or highly emetogenic chemotherapy and their physicians, and costs were calculated using the Centers for Medicare & Medicaid Services Hospital Outpatient Perspective Payment System.(10) While most patients report receiving some type of antiemetic prophylaxis, 66% of patients experienced a CINV-related event with an average direct cost of $732.14/person (SD $734.00). After including indirect medical costs (i.e. missed work and productivity), the costs increase to $778.53/person (SD $782.61). For patients using highly emetogenic chemotherapy, the average costs were higher with direct costs of $836.70/person (SD

$836.00), direct + medical cost of $898.36/person (SD $898.36), and direct medical + missed work + productivity loss of $905.31/person (SD $863.25).

2.1.3 CINV Risk Factors

CINV-risk is classified as highly, moderately, low, or minimally emetogenic (Table 2.2). (63, 73) Notably most oral and targeted anticancer therapies have minimal and low CINV risk, and are not included in this analysis.(18, 20) Evidence has overwhelmingly demonstrated that the type of chemotherapy initiated is the best determinant of CINV-risk.(14) The types of chemotherapy associated with high CINV risk are detailed in Table 2.3.(18, 20)

Table 2.2 Categories of CINV Risk(63, 73)

CINV Category	Corresponding CINV Risk
Minimal	0-<10%
Low	10-30%
Moderate	>30-90%
High	>90%

Table 2.3 Types of Intravenous Chemotherapy with High Risk of CINV in 2017(18, 20)

Chemotherapy and Targeted Therapy	
• AC combination defined as any chemotherapy regimen that contains anthracycline and cyclophosphamide • Carboplatin ≥ 4** • Carmustine ≥ 250 mg/m^2 • Cisplatin • Cyclophosphamide >1,500 mg/m^2	• Dacarbazine • Dactinomycin* • Doxorubicin ≥ 60mg/ m^2** • Epirubicin ≥ 90 mg/m^2** • Ifosfamide ≥ 2 g/m^2 per dose** • Mechlorethamine • Streptozotocin

Anthracycline therapies: Doxorubicin, Epirubicin, Idarubicin
*Only in ASCO guidelines **Only in NCCN guidelines

Other chemotherapy-related risk factors include shorter infusion time and administration of multiple cycles. Patient-level factors include being female, age<50, history of low alcohol intake (<1.5 oz/day), history of motion sickness, history of nausea and vomiting during pregnancy, history of prior CINV, and extreme anxiety.(4, 67, 73-78)

2.1.4 CINV Prophylaxis

Antiemetic drugs are a highly effective prophylaxis to prevent CINV in the acute and delayed phases and the evidence base to support these products' ability to prevent and reduce CINV, improve

quality-of-life, and generate cost-savings is robust.(1, 4, 10, 79) Antiemetic efficacy is typically assessed using the response measures detailed below:

- Incomplete Response: Having a CINV-related event;
- Complete Response: No emesis, no use of rescue antiemetics; and
- Complete Protection: Complete response and no significant nausea (VAS score of <25 mm).

Other measures of CINV may also assess the risk as well as the grade of nausea and vomiting. For example, nausea is frequently measured using a visual analogue scale in trials ranging from 0mm-100mm and "no nausea" to "nausea as bad as it could be (left to right)," respectively. A commonly used validated, questionnaire used to assess the impact of CINV on daily life in clinical trials is the Functional Living Index-Emesis (FLIE), which includes 9 questions in each of the nausea and vomiting domains.(3, 80) Other tools measuring CINV include, but are not limited to, the MASCC Antiemesis Tool (MAT) and the Rhodes Index for nausea, vomiting and retching (INVR).(81, 82)

Conventional antiemetic drugs used to prevent acute and delayed CINV, in order of least to most potent, are corticosteroids, 5-HT3 receptor antagonists (5HT3A), and NK1 receptor antagonists.(15) Additionally, increasing trial evidence supporting the use of olanzapine for preventing CINV is emerging.(1, 19, 52, 83-86) Table 2.4 summarizes the dosing schedule and cost data for these products, and the below section further delves into these products' evidence-base. Notably, antiemetic products have few safety concerns.(1)

2.1.4.1 Early Antiemetic Prophylactic Therapies

Dopamine-receptor antagonists (e.g., metoclopramide, prochlorperazine, and haloperidol) formed the basis of early antiemetic use.(1, 87) In 1978, the US Food and Drug Administration approved cisplatin, one of the most emetogenic chemotherapy products on the US market.(88) Low-dose metoclopramide was not found to be effective in preventing CINV in patients using cisplatin, spurring increased antiemetic research.(1, 63, 89) Subsequently, it was found that high-dose metoclopramide and glucocorticoids (i.e., dexamethasone) were effective compared to placebo in preventing CINV in patients

using cisplatin, and this was standard of antiemetic care through the 1980s.(1, 87, 90-92) Specifically, a meta-analysis by Ioannidis et. al in 2000 found that the odds of complete protection among dexamethasone users was 2.22 times higher than the odds of patients using placebo (95% CI: 1.89 to 2.60) in the acute phase and 2.04 times higher in the delayed phase (95% CI: 1.63 to 2.56).(92) Today, dexamethasone is the backbone of antiemetic prophylaxis.(19, 52, 83)

2.1.4.2 5HT3As

First-generation 5HT3As have been on the US market since the early 1990s, and include ondansetron, granisetron, and dolasetron.(1) Ondansetron and granisetron are available as IV and oral formulations, while dolasetron is only available as an oral formulation today. Granisetron is also available as a trans-dermal patch.

Table 2.4 Summary of Antiemetic Products Used to as CINV Prophylaxis in the United States – Adapted from 2017 ASCO Guidelines (Methodology in Appendix 4.1)(18)

Agent	Trade Name	Dose	Schedule	Total Cost Per Treatment Cycle (USD)
5HT3A				
Ondansetron IV	Zofran	8mg / 0.15mg/kg	Prechemotherapy, One Dose	$1.10
Ondansetron Oral - Generic	Zofran	8mg	Twice daily on days 1-3	$6.50
Ondansetron Oral - Brand	Zofran	8mg	Twice daily on days 1-3	$268.28
Ondansetron Oral Dissolving Tablet - Generic	Zofran ODT	8mg	Every 12 hours as needed days 1-3	$6.50
Ondansetron Oral Dissolving Tablet - Brand	Zofran ODT	8mg	Every 12 hours as needed days 1-3	$253.14
Ondansetron Oral Soluble Film - Brand	Zuplenz	8mg	Every 12 hours as needed days 1-3	$225.46
Granisetron IV	Kytril	1mg or 0.01 mg/kg IV	Prechemotherapy, One Dose	$3.13
Granisetron Oral	Granisol	1mg	Once (2MG) day 1, 1MG twice daily on days 2,3	$14.36
Granisetron Transdermal	Sancuso	3.1mg	Prechemotherapy, Up to 7 Days	$467.00
Granisetron Subcutaneous***	Sustol	10mg	Prechemotherapy, One Dose	$518.7
Dolasetron Oral	Anzemet	100mg	Once daily on days 1-3	$330.50
Palonosetron IV	Aloxi	0.25mg	Prechemotherapy, One Dose	228.80
Palonosetron Oral**	Aloxi	0.5mg	Prechemotherapy, One Dose	$521.95
NK1 Antagonists				
Aprepitant Oral	Emend	125mg	Prechemotherapy, One Dose	$284.01
Aprepitant Oral	Emend	80mg	Once daily on days 2, 3	$364.28
Fosaprepitant IV	Emend IV	150mg	Prechemotherapy, One Dose	$299.87
Rolapitant	Varubi	180mg	Prechemotherapy, One Dose	$610.50
Combination Products				
NEPA (netupitant, palonosetron)	Akynzeo	300mg/0.5mg	Prechemotherapy, One Dose	$632.35
Atypical Antipsychotics				
Olanzapine - Generic	Zyprexa	5mg	Once daily on days 1-3	$6.50
Olanzapine - Generic	Zyprexa	10mg	Once daily on days 1-3	$6.50
Olanzapine - Brand	Zyprexa	5mg	Once daily on days 1-3	$43.22
Olanzapine - Brand	Zyprexa	10mg	Once daily on days 1-3	$64.62
Dopaminergic Antagonists				
Metoclopramide IV	Reglan	1 to 2 mg/kg	Prechemotherapy, One Dose	$99.50
Metoclopramide Oral - Generic	Reglan	0.5mg/kg	Every 6 hours days 2-4	$6.50
Metoclopramide Oral - Brand	Reglan	0.5mg/kg	Every 6 hours days 2-4	$192.99
Prochlorperazine IV	Compazine	5-10mg	Prechemotherapy, every 6-8 Hours, Max 40mg	$11.93
Prochlorperazine Oral	Compazine	10mg	Every 6 to 8 hours as needed	$6.50
Cannabinoids				
Nabilone Oral	Cesamet	1-2mg	Twice daily days 1-3	$249.63
Dronabinol Oral - Generic*	Marinol	5mg/m2	Every 2-4 hours as needed	$223.94
Dronabinol Oral - Brand*	Marinol	5mg/m2	Every 2-4 hours as needed	$941.80

*Assume 3 Days use, 12 pills per day **Palonosetron oral has been discontinued in the US
*** 75% of AWP as ASP price not available.

A meta-analysis found that adding dexamethasone to a 5HT3A regimen offers incremental benefits.(83, 92) The complete response effectiveness of first-generation 5HT3As + dexamethasone has ranged from 68%-90% in the acute phase and 47%-64% in the delayed phase.(93-101) However, in 2007, a meta-analysis of 44 studies found that the effectiveness of preventing CINV in the acute phase across these three products was comparable, suggesting that there is no need to prioritize one product over another.(59)

In 2003, the Food and Drug Administration approved the second-generation 5HT3A, palonosetron.(102) Its longer half-life and higher binding affinity (estimated at 100-fold compared to the other 5-HT3As), which contribute to its longer inhibition of the 5-HT3 receptor, lead to palonosetron being more effective in preventing CINV in the delayed phase than first-generation 5HT3As in the moderately emetogenic chemotherapy group.(1, 20, 101, 103-105) Palonosetron + dexamethasone was more effective than ondansetron + dexamethasone (41% vs. 25%, p=.021), and granisetron + dexamethasone (57% vs. 44.5%, p=.0001) in preventing emesis in the delayed phase but rates of emesis in the acute phase were similar in patients on highly emetogenic chemotherapy.(20, 106, 107)It is important to note that neither of these studies evaluated the effectiveness of palonosetron in the presence of an NK1, which would be prescribed for highly emetogenic chemotherapy.(20) Additionally, palonosetron is much more expensive than first generation 5HT3As (Table 2.4).

2.1.4.3 NK1s

Since 2003, a new class of highly effective and more expensive (<$600/cycle) antiemetics, NK1s, has entered the marketplace with the introduction of oral aprepitant as well as IV fosaprepitant, an aprepitant prodrug, in 2008.(1) In particular NK1s conferred significant benefit in preventing vomiting in the delayed phase.(20) More recently FDA approved NEPA (netupitant and palonosetron combination) in 2014, and rolapitant, in 2015.(108, 109) Both of these newer NK1s are oral products. Several trials and observational studies have assessed aprepitant regimens versus standard-of-care, which center on 5HT3As.(19, 52, 83) Key aprepitant and fosaprepitant trial data are detailed in Table 3.7.

While an initial meta-analysis found that aprepitant regimens had higher rates of complete protection than 5HT3A regimens in the delayed phase, there was no difference in the acute phase in patients initiating highly emetogenic chemotherapy.(110) However, authors recommend "cautiously interpreting" the acute phase results given trial inconsistency. Subsequently, a more robust meta-analysis, which includes patients receiving moderately and highly emetogenic chemotherapy, found that patients on aprepitant had higher rates of complete protection compared to those on standard-of- care (primarily consisting of a 5HT3A+dexamethasone).(111) A pooled analysis also found that aprepitant regimen was even more effective in patients on concomitant emetogenic chemotherapy (doxorubicin or cyclophosphamide) than patients on an ondansetron regimen on day 1 than the general population.(112) Another trial found that the aprepitant-based regimen was also more effective than an ondansetron (5HT3A)-based regimen used on days 1-4, whereas in most trials patients received 5HT3A (ondansetron or another 5HT3A) only on day 1 in patients initiating highly emetogenic chemotherapy.(113)Non-inferiority trials support the use of infused fosaprepitant (day 1) as comparative with orally administered aprepitant (days 1-3).(114, 115) Trial data also supports that NEPA and rolapitant regimens are more effective in preventing CINV than 5HT3As regimens than patients initiating highly emetogenic chemotherapy (Table 3.7).

In 2016, a meta-analysis found that the NK1 regimens (as a group) offered a "clinically relevant benefit" over 5HT3A regimens (as a group) for no vomiting and nausea in patients initiating highly emetogenic chemotherapy. The risk difference for control was better than nausea for both cisplatin-based (risk difference: 21% vs. 8%) or AC-based highly emetogenic chemotherapy (risk difference 14% vs. 4%).(116) Two indirect network analyses have also compared the effectiveness of the NK1s (aprepitant, fosaprepitant, netupitant (NEPA), and rolapitant), though a limitation of both studies is cross-trial comparisons and heterogeneity within studies included in the analysis.(117, 118) Both of these studies also included casopitant, which is no longer under clinical investigation so these results are not reviewed in this section. In general, both studies found that triple-regimens including NK1s were more effective than dual-regimens without an NK1. However, Zhang et. al found that NEPA in the acute phase, demonstrated non-significant superiority over dual-therapy regimens.(118) Furthermore, complete

response across triple therapy regimens containing NK1s were similar in the acute, delayed, and overall phases as were treatment-related adverse events, suggesting NK1s as interchangeable.(118) In contrast, Abdel-Rahman found that aprepitant-regimens are better than rolapitant-regimens in achieving complete response, though the confidence interval should be noted given that the lower bound is near the null (OR 1.28, 95% CI 1.01–1.59).(117) Another point of difference is that Zhang found equivalent effects in triple regimens containing palonosetron versus a first-generation 5HT3A while Abdel-Rahman's results suggested that patients on NK1 regimens containing palonosetron actually had worse complete response rates than those that did not.(117, 118) Regardless, both studies support the use of less expensive, first-generation 5HT3As over palonosetron. Zhang et al also found similar rates of complete response in NK1 users regardless of dexamethasone dose suggesting that a lower dose of dexamethasone is appropriate (118) The difference in these two network meta-analyses results, which generally included the same trial data for patients initiating highly emetogenic chemotherapy highlights the need for more and more indirect analyses as new evidence is generated for newer NK1s and comparative effectiveness studies across NK1s. A network meta-analysis assessing NK1s in only patients initiating cisplatin-based chemotherapy suggested NEPA was the best with regards to complete response.(119)

2.1.4.4 Olanzapine

A potentially promising treatment to prevent CINV and treat breakthrough CINV is olanzapine, an atypical antipsychotic, which is inexpensive compared to the newer antiemetics (<$10.00/cycle). (1, 19, 52, 83) Early evidence on the use of olanzapine to prevent CINV is limited to small phase II and phase III studies comparing the current standard of care to olanzapine monotherapy and olanzapine plus standard of care in previously chemotherapy naïve patients. These studies have consistently demonstrated that olanzapine regimens were as effective or better in preventing CINV during the acute and delayed phases in patients initiating highly emetogenic chemotherapy than standard regimens, which included various combinations of aprepitant, 5HT3A, and dexamethasone.(24, 25, 28, 29, 84-86, 120-122) A larger multi-center randomized controlled trial of olanzapine + standard of care (i.e., aprepitant+5HT3A+ dexamethasone) versus standard of care in patients initiating highly emetogenic chemotherapy supporting

these early findings (i.e., complete response rates of 85.7%, 66.9% and 63.6% respectively in the acute, delayed, overall phases versus 64.6%, 52.4%, and 40.6 % in the standard of care group ($p<.001$)) was published in 2016.(28) The evidence supporting olanzapine, which is also summarized in multiple meta-analyses, is overwhelmingly positive for both olanzapine as a monotherapy, and combination therapy with standard of care in preventing CINV and treating breakthrough CINV compared to standard of care.(84, 85, 123, 124) Given that olanzapine is an antipsychotic, physicians are concerned about adverse events such as sedation and drowsiness. Additionally, some researchers and clinicians voiced concerns over the study design of some of the olanzapine studies.(28, 125) However, in Navari's 2016 large clinical trial testing 10mg of olanzapine in combination with aprepitant or fosaprepitant, patient in the olanzapine-arm had significantly higher complete response rates in the acute, delayed and overall phases. Additionally, there were no major adverse events, and many patients who experienced drowsiness in the early phase, adapted to it in the delayed phase.(28) Notably, the 2016 meta-analysis by Chiu and colleagues found that the 5mg dose was as effective as the 10mg dose.(84) Olanzapine studies are detailed in Table 3.8.

2.1.5 Breakthrough CINV Treatment

Patients with breakthrough CINV are those that experience it despite receiving appropriate prophylactic antiemetics. It is estimated that up to 40% of patients on moderately or highly emetogenic chemotherapy experience breakthrough CINV.(7) Notably, the conventional antiemetics described in section 2.1.3 used as CINV prophylaxis are generally not effective in treating CINV.(7, 16, 17) As such, non-traditional antiemetics may be used as rescue therapies to treat CINV in patients who failed conventional prophylactic therapy, and experienced breakthrough CINV. (19, 20, 52) Specifically, non-traditional antiemetics for CINV-treatment include: antipsychotics (i.e., olanzapine), benzodiazepines (e.g., lorazepam), cannabinoids (e.g., nabilone and dronabinol), and phenothiazines (e.g., prochlorperazine), among others (Table 2.5). These products are also used to treat anticipatory and refractory CINV. There is sparse evidence on the treatment of breakthrough CINV using these products, which include a few phase II studies. Two small studies (each with less than 30 patients) that used self-

reporting measures found that prochlorperazine, 5HT3As, and a topical product containing lorazepam might be effective in treating breakthrough CINV; but more rigorous studies that use objective measures are necessary to confirm these findings. (7, 126, 127) Notably, nabilone and dronabinol are approved by the Food and Drug Administration to treat breakthrough CINV in patients who have failed to respond to conventional antiemetic treatments.(128, 129) However, the widespread use of cannabinoids is controversial due to side-effects (i.e., disturbing psychotomimetic reactions).(83, 129-131) The most robust evidence for breakthrough CINV is for olanzapine, which is described below.(7, 29) Notably, there is no preferred treatment of breakthrough CINV.(7, 132)

Table 2.5 Products Used to Treat Breakthrough CINV (15, 19, 52, 133)

• Atypical antipsychotic (olanzapine) • Benzodiazepine (lorazepam) • Cannabinoid (dronabinol, nabilone) • Other (Haloperidol, metoclopramide, scopolamine)	• Phenothiazine (prochlorperazine, promethazine), • 5HT3A (Dolasetron, granisetron, ondansetron)* • Corticosteroid (dexamethasone)

*Anecdotal and limited trial evidence suggest switching 5HT3A may be effective

2.1.5.1 Olanzapine

In 2013, Navari et al, conducted the first phase III randomized controlled trial comparing olanzapine and metoclopramide in controlling nausea and vomiting outcomes among patients who initiated highly emetogenic chemotherapy and experienced breakthrough CINV.(24) In this study, olanzapine was statistically significantly better in preventing both nausea (70% vs. 31%, $p<0.01$) and vomiting (68% vs. 23%, $p<0.01$) compared to metoclopramide. Meta-analyses published in 2014 and 2016 supported that olanzapine was more effective than prochlorperazine, metoclopramide, and dexamethasone in preventing emesis – the impact on preventing nausea could not be assessed as not enough studies reported on it.(84, 134) More recently, in an open label randomized controlled trial comparing olanzapine, palonosetron, and ondansetron among patients initiating hematopoietic stem cell transplantation found that olanzapine was significantly more effective in controlling CINV than palonosetron, which showed no difference compared to ondansetron.(121) In the only small retrospective

electronic medical record study, 88% experienced improved nausea, while 21% had improved vomiting among breakthrough CINV patients who used olanzapine.(84)

2.1.6 Antiemetic Guidelines Recommendations

The Multinational Association of Supportive Care in Cancer (MASCC) / European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) offer recommendations on the appropriate use of antiemetic drugs based on the likelihood of emesis of the chemotherapy regimen.(19, 52, 83, 135) These recommendations are based on rigorous, systematic evidence reviews. The 2017 ASCO and NCCN recommendations are detailed below in Table 2.6, though MASCC and ESMO recommendations are similar.(135) While ASCO and NCCN both utilize rigorous evidence-reviews to inform their guideline recommendations, NCCN also leverages consensus-driven physician opinion, which may offer more rapid uptake of certain products. Additionally, NCCN updates their guidelines yearly, while ASCO that has not conducted a major update in five years.

2.1.7 NCCN and ASCO Guideline Recommendations for CINV Prophylaxis in Patients Initiating Highly Emetogenic Chemotherapy

NCCN and ASCO guidelines include similar recommendations on the use of antiemetics for CINV prophylaxis (Table 2.6). (15, 18-21) Both, the 2017 NCCN and 2017 ASCO guidelines recommend that patients receive a triple therapy combination of an NK1, 5HT3A, and glucocorticoids on day 1.(18, 20) Additionally, in 2017 both ASCO and NCCN guidelines recommended olanzapine + aprepitant/fosaprepitant + 5HT3A+ dexamethasone as an effective CINV-prevention strategy. This is the first time, ASCO recommended olanzapine, an atypical antipsychotic, as a strategy for CINV prevention despite not having FDA approval. The key difference between the ASCO and NCCN guidelines is that NCCN also recommends the use of olanzapine in conjunction with palonosetron, while ASCO does not. Notably, all highly emetogenic chemotherapy antiemetic recommendations are now category 1, the highest level recommendation (meaning the evidence level is high and there was uniform NCCN consensus). From a maintenance perspective, both guidelines recommend that patients who initiate

aprepitant on day 1 continue it on days 2 and 3, patients who initiate olanzapine continue it on days 2-4, and all patients, regardless antiemetic regimen strategy, continue corticosteroids on days 2-4.

Table 2.6 2017 ASCO and 2017 NCCN Prophylactic Antiemesis Guideline Recommendations in Patients Initiating Highly Emetogenic Chemotherapy Intravenously * (15, 19, 52, 133)

	ASCO	NCCN*
Day 1 (Acute)	• NK1, 5-HT3A, and corticosteroid • NEPA and corticosteroid • Olanzapine+aprepitant+5HT3A+ corticosteroid**	• NK1, 5-HT3A, and corticosteroid • NEPA and corticosteroid • Olanzapine, palonosetron, and corticosteroid** • Olanzapine+aprepitant+5HT3A+ corticosteroid***
Days 2-5 (Delayed)	• Aprepitant on days 2-3 (if aprepitant on day 1) • Corticosteroid days 2-4 • Olanzapine days 2-4 (if olanzapine on day 1)	• Aprepitant on days 2-3 (if aprepitant on day 1) • Corticosteroid days 2-4 • Olanzapine days 2-4 (if olanzapine on day 1)

*Corticosteroid: Dexamethasone; 5-HT3A: Granisetron, Ondansetron, Palonosetron, Dolasetron; NK1s: Aprepitant, Fosaprepitant, Rolapitant
**This strategy is only recommended in NCCN guidelines
***2017 NCCN and ASCO guidelines newly recommend olanzapine + aprepitant + 5HT3A + dexamethasone

2.1.8 Guideline Recommendations for Breakthrough CINV Treatment

Recommendations on treating breakthrough CINV are sparse given the limited evidence on treating CINV and the lack of a superior product class demonstration, but generally center on adding a product that is from a different drug class from the current treatment regardless of chemotherapy risk.(19, 52, 83) ASCO's recommendation is as follows:

> Clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT3 antagonist or adding a dopamine antagonist to the regimen. (19, 52)

NCCN's recommendations to treat breakthrough CINV (organized alphabetically) are as detailed in Figure 2.1. NCCN also states that it is easier to prevent breakthrough CINV than to treat it.(133) Consequently, NCCN suggests guideline concordant-prescribing and that prescribers "strongly consider routine around-the-clock administration rather than PRN [*as the situation arises*] dosing." Physicians are also debating what antiemetics to send patients home with following chemotherapy in anticipation of

breakthrough CINV in days 2-5 (as opposed to patients filling products as they develop CINV symptoms).

Figure 2.1 NCCN Breakthrough Treatment Options (organized alphabetically)(64)

- Atypical Antipsychotic
  - Olanzapine 10 mg PO daily for 3 days
- Benzodiazepine
  - Lorazepam 0.5-2 mg PO/SL/IV every 6h
- Cannabinoid
  - Dronabinol 5-10 mg PO every 3-6 h
  - Nabilone 1-2 mg PO BID
- Other
- Haloperidol 0.5-2 mg PO/IV every 4-6 h
- Metoclopramide 10-40 mg PO/IV every 4-6 h
- Scopolamine transdermal patch 1 patch every 72 h
- Phenothiazine
  - Prochlorperazine 25 mg sup pr every 12 h or 10 mg PO/IV every 6 h
  - Promethazine 25 mg sup pr every 6 h or 12.5-25 mg PO/IV (central line only) 4-6h
- Serotonin 5HT3A
  - Dolasetron 100 mg PO daily
  - Granisetron 1-2 mg PO daily or 1 mg PO BID or 0.01 mg/kig (maximum 1 mg) IV daily
  - Ondansetron 16 mg PO/IV daily
- Steroid
  - Dexamethasone 12 mg PO/IV daily

2.2 Antiemetic Prescribing

Antiemetic drugs are a highly effective prophylaxis to prevent CINV and thus improve quality-of-life, and generate cost-savings. (1-4) However, use of antiemetics is suboptimal. In general, patients are receiving at least one type of antiemetic in the acute phase, but receipt of an antiemetic in the delayed phase is much lower. (22, 31, 34, 39, 136) This section will describe general patterns of prophylactic antiemetic prescribing with a focus on patients initiating highly emetogenic chemotherapy organized by region as well as summarize breakthrough-prescribing patterns. Notably, many of these studies take place in Asia and Europe where both the healthcare systems and antiemetic product availability differ from the U.S. Asian and European studies are detailed in Appendix 2. Unsurprisingly there is much country-level heterogeneity in prescribing patterns highlighting the inability to generalize one country's study findings to another. Furthermore, patterns of antiemetic prescribing among patients initiating highly emetogenic chemotherapy has not been well studied in the United States, especially in recent history or in a large, nationally representative study.

2.2.1 United States Studies

One small US-based study examining patterns of antiemetic use was identified supporting the need to assess prescribing patterns in a larger, generalizable dataset. This prospective observational study used electronic health data from practices in Georgia, Tennessee and Florida and includes 460 patients using highly emetogenic, single-day chemotherapy.(22) The primary objective of this study was to assess guideline concordance and its associated outcomes, which are discussed in the next section (2.2.4), but characterizing antiemetic products' used was part of the authors' process for assessing guideline concordance (Table 2.7). Notably all patients received an antiemetic in the acute phase and only 1.1% did not receive a product in the delayed phase. (22) In another US-based study, using IntrinsiQ clinical warehouse data between July 2006-April 2008, again a high proportion of patients initiating highly emetogenic chemotherapy received an antiemetic (>80%), but NK1 use was only 11%.(30) The authors suggest that the low uptake of NK1s is a result of poor clinical understanding by prescribers as aprepitant was FDA-approved in 2003, and guidelines incorporated NK1s into recommendations in 2006 and 2009 respectively for ASCO for NCCN.(30)

Table 2.7 Summary of Antiemetic Regimens Administered or Prescribed on Day 1 (N=460) (22)

Phase and Regimen	No.	%
Acute Phase		
Corticosteroid+NK1+5HT3A	417	90.7
Corticosteroid+5HT3A	36	7.8
Other regimen	7	1.5
Delayed phase		
NK1-RA + 5HT3A	284	61.7
Corticosteroid+NK1+5HT3A	131	28.5
5HT3-RA	29	6.3
No primary antiemetic	5	1.1
NK1-RA	5	1.1
Corticosteroid + 5HT3A	2	0.4
Corticosteroid +NK1	2	0.4
Corticosteroid	1	0.2

2.2.2 Guideline-based Prescribing Patterns

Clinical trial data suggest that guideline-concordant antiemetic prescribing is estimated to prevent CINV in 80% of patients.(137) Most studies demonstrate that patients who receive guideline-concordant prescribing have fewer CINV-events and less healthcare resource use (Table 2.8). (The exception were two studies – 1) a retrospective claims data analysis, that may have unmeasured confounding due to a lack of being able to measure patient/provider engagement as well as being unable to capture non-hospital related CINV events and healthcare resource use and 2) a small study (n=102) that found no association (Table 2.8).)

Table 2.8 The Effect of Guideline Concordance on CINV-events and Healthcare Resource Use

Study	Population	Country	Study Design	Data Source	Size	Results
Aapro et al. 2012(31)	HEC and MEC	Pan-Western European	ProObs	Daily Diaries	800	• Complete response, no nausea, no vomiting, and no nausea and vomiting was higher in concordant patients (AOR 1.43 p<.05) • Higher proportion of patients using HCRU with specialist visits and ER being statistically significant among discordant patients
Chan et al. 2012(36)	HEC (F-BC-AC)	Singapore	ProObs	Interview	361	• Significantly higher proportion of adherent than non-adherent patients achieved delayed complete control (26.8% vs. 16.4%, P = 0.020)
Yu et al. 2015(35)	HEC and MEC	Pan-Asian and Australia	ProObs	Electronic	648	• Patients who were prescribed an antiemetic regimen adhering to quality guidelines had significantly higher odds of no emesis in cycle 1 (adjusted OR, 2.03; 95 % CI, 1.39–2.96)
Abunahlah et al. 2016(138)	Multi	Turkey	ProObs	Daily Diary	100	• Complete control for both nausea and vomiting was higher in GAG; the difference was highly significant in the first cycle for both the acute and delayed phase of the CINV (p<0.05)
Check et al. 2016(139)	HEC (AC)	US	Retro	Claims Data	1130	• Unexpectedly, compared to women who did not receive an NK1 for the prevention of CINV, women who did experienced higher CINV-related utilization as measured through post-chemotherapy inpatient or outpatient visits for nausea and vomiting, volume depletion, dehydration, or hypovolemia (aRR = 1.34, 95 % CI = 1.07–1.68, p = 0.01)
Gilmore et al. 2014(22)	HEC and MEC	US	ProObs	EHR Data	1295	• Over 5 days post-chemotherapy, the incidence of no CINV was significantly higher in the concordant cohort than the non-concordant cohort (53.4% v 43.8%; P .001). The aOR of no CINV with concordance was 1.31 (P< .037) • Concordant use resulted in significantly higher adjusted odds of no CINV and no clinically significant nausea for patients who received HEC
Caracuel et al. 2014(43)	All except minimal risk	Spain	ProObs	Questionnaire	102	• No statistically significant difference between adherence to the protocols and complete response in any of the groups

HEC: Highly Emetogenic Chemotherapy
MEC: Moderately Emetogenic Chemotherapy
HER: Electronic Health Record
ProObs: Prospective Observational
Retro: Retrospective
F-BC-AC: Female, Breast Cancer, AC-based Therapy
HCRU: Healthcare Resource Use

Table 2.9 Guideline Concordance Across Multiple Types of CINV-Risk

Authors	Study Population	Study Size	Data Source	Country	Time Frame	Study Design	Guideline Concordance	Common Reasons for Discordance
DeTursi et. al 2015(140)	Patients receiving CT on a single pre-specified day were included	502	Multi-center, electronic data capture	Italy	7/2013-2/2014	ProObs	General: 19.3%	
Franca et al. 2015(40)	Adults initiating IV CT on day 1	105	Institution database	Brazil	9/2011-2/2013	Retro Chart Review	General: 22% • 30% of discordant had double discordance	General: • Higher CSC, 5HT3A, and NK1 dose Double Discordance: • Higher CSC dose • 5HT3A use
Abunahlah et al. 2016(138)	CT naive patients initiating CT	100	Daily Diary	Turkey	5/2015-9/2015	ProObs	Acute: 80% Delayed: 28%	Acute: • Over-prescription: 55% • Inappropriate Dose: 70% • Under prescription: 35% • Inappropriate Prescription: 0% Delayed: • Over-prescription: 33% • Inappropriate Dose: 4% • Under prescription: 25% • Inappropriate Prescription: 65%
Caracuel et al. 2014(43)	Adults patients initiating any CT except LER	100 Rxs	Questionn-aire	Spain	4 months	ProObs	Acute: 73% Delayed: 65%	
Aapro et al. 2012(31)	CT-naive adults initiating single-day MEC and HEC for cancer	991	Daily Diary	8 Western European Countries	9/2009 -6/2010	ProObs	Acute: 55% Delayed: 46% Overall: 29%	
Burmeister et al. 2011(39)	Patients starting a new CT	299	Institution electronic patient management system	Switzer-land	11/2008-4/2009	Retro	Acute: 61% Delayed: 11%	Acute: • Incorrect use of aprepitant Delayed: • Over-prescribing of 5HT3A • CSC dose not reduced

CT: Chemotherapy
LER: Low Emetogenic Risk
Dex: Dexamethasone
Acute: Day 1
MEC: Moderately Emetogenic Chemotherapy
ProObs: Prospective Observational
CSC: Corticosteroid
Delayed: Days 2-5
HEC: Highly emetogenic Chemotherapy
Retro: Retrospective
IV: Intravenous
Overall: Day 1-5

Despite this, it is suggested that the rate of guideline-discordant CINV-related antiemetic prescribing is high across CINV-risk ranging from 20%-80%, and higher in the delayed phase than the acute phase (Table 2.9). Guideline-discordant prescribing includes both under and over-prescribing. Under prescribing is prescribing a product that is less potent (including lower doses) than recommended or excluding drugs that should be included. Furthermore, under-prescribing of antiemetic drugs leads to the occurrence of preventable CINV-related events and their associated resource use and costs.(1-4) Over-prescribing is prescribing: 1) a more potent drug or 2) more complex drug regimens than recommended, while under-prescribing is prescribing a product that is less potent than recommended or excluding drugs that should be included. Over-prescribing of antiemetics is an important issue to address, as those drugs that are intended to treat high-risk CINV are more expensive than low-risk CINV drugs. For example, NK1 combinations can cost as much as $650/chemotherapy regimen, while olanzapine costs <$10.00. Notably, in 2013, the Choosing Wisely Campaign partnered with several US professional societies to identify and communicate ineffective and inefficient healthcare practices in their specialty.(47) Under the Campaign, ASCO identified antiemetic over-use in cancer patients treated with chemotherapy (specifically the use of the products that are intended to prevent CINV in patients initiating highly emetogenic chemotherapy in patients initiating lower CINV risk) as a potentially wasteful oncology practice. Additionally, prescribing more complex antiemetic regimens than necessary raises questions of excess costs. Section 2.2.5 will describe the antiemetic guideline-concordant literature related to patients initiating highly emetogenic chemotherapy with an emphasis on US-based studies.

2.2.3 Breakthrough Prescribing

Breakthrough antiemetic prescribing has been studied less than prophylactic antiemetic prescribing. Notably, prescribing of breakthrough products is more common in patients receiving highly emetogenic chemotherapies versus other types of chemotherapy and was more likely to be prescribed in the acute phase.(23, 34) A retrospective claims study in commercially insured US patients estimated that 32.5% of patients initiating highly or moderately emetogenic chemotherapy received breakthrough products on day one. Similarly, breakthrough product prescribing in European based studies was lower

ranging from 29-39%. (23, 31) Breakthrough product use among patients initiating highly emetogenic chemotherapy in Asian based studies was higher ranges from 31% - 62% with the most common products being metoclopramide and chlorpheniramine, which have a different mechanism of action than preventative antiemetics.(34-37)

2.2.4 Guideline-Concordant Prescribing in Patients Initiating Highly Emetogenic Chemotherapy

Remarkably, while patients on highly emetogenic chemotherapy are more likely to receive antiemetics and guideline concordant care compared to chemotherapy with lower CINV risk, the concordance rate is still poor (Table 2.10). Studies examining general guideline concordance in patients initiating highly emetogenic chemotherapy spanned US, Asia, and Europe and used both prospective and retrospective study designs. Data sources include claims data, daily diaries, patient interviews, and clinical systems, which offer advantages and disadvantages. Clinical systems include data on what was prescribed, while claims data offers data on what was filled. Patient interviews and daily diaries can capture what the patient actually took, though this is subject to respondent bias. The studies detailed below are listed in Table 2.10.

Studies that do not specify whether the acute or delayed phase of prescribing was examined estimate discordance rates ranging from 26%-99%.(37, 45, 141) The proportion of patients receiving guideline-discordant antiemetic in the delayed phase (60%-90%) was typically much higher than in the acute phase (10%-70%), mirroring trends across multiple types of CINV-risk.(22, 31, 34, 39, 136) Discordance rates across the five day acute and delayed periods (i.e., overall period) range from 60%-90%; notably female patients on doxorubicin (AC) therapy had higher proportion of concordance compared to patients on other types of highly emetogenic chemotherapy.(22, 31, 34, 36) Specifically in the US, a prospective observational study using practice data from southeastern states estimated the proportion of patients receiving guideline-concordant antiemetics at 90.7%, 28.9%, and 28.7% in the acute, delayed, and overall phases.(22) While these results suggest that guideline discordance may be lower in the US than other countries, the authors note the implementation of a standardized antiemetic electronic medical record protocol by prescribers, which automates the prescribing process. Additionally,

it is important to consider that product availability and guidelines vary by country. However, another US-based study assessing guideline concordance in patients with breast cancer initiating highly emetogenic chemotherapy using claims representing 1) the US commercial insured and supplemental Medicare (MarketScan) and 2) the Medicare populations (SEER Medicare), 22.4% and 22.8% of patients were respectively adherent on day 1 throughout the study period.(45) Notably, adherence was over 80% in both populations in 2005 prior to the release of the updated ASCO guidelines incorporating NK1s as a recommended antiemetic for patients initiating highly emetogenic chemotherapy in 2006, while adherence was less than 3% in 2007, suggesting that new product uptake and guideline dissemination contributed to this drastic drop. Adherence in both populations increased over time, and reached as high as 56.4% in 2013 for the MarketScan population, which also had a more rapid increase compared to the SEER Medicare population.(45) This study focuses only on breast cancer, and did not breakdown under versus over prescribing in detail.

Studies examining over and under-prescribing are detailed in the next two sections. While three US-based guideline concordance studies were identified. (22, 38, 45) Two of the three focused on discordant prescribing in general – it is crucial to discriminate between under and over prescribing rates because of their different implications on the healthcare system (disparity versus cost).(22, 45) Additionally, these studies had limited generalizability given that one was a small southeast practice with an EMR-based antiemetic prescription system and the other used two large claims data sets, but only focused on breast cancer. The third study assessed overprescribing in a large claims data set, but under-prescribing was not assessed.(38)

2.2.4.1 Under-prescribing in Patients Initiating Highly Emetogenic Chemotherapy

Under-prescribing specifically is not well researched, especially in the US. In regards to patients initiating highly emetogenic chemotherapy, a UK-based study estimates that 58.8% of patients are under-prescribed antiemetics while a Swiss-based study found that 19% of patients were undertreated in the acute phase.(39, 141) Under prescribing in patients initiating highly emetogenic chemotherapy primarily centers on non-prescribing of an NK1 which comprises 51%-80% of the reasons for discordances. (22,

31, 39, 45, 46) However, in the delayed phase, discordances commonly resulted from the non-prescribing of corticosteroids and 5HT3As or lack of dose reduction in corticosteroids. (31, 39)

2.2.4.2 Over-prescribing in Patients Initiating Highly Emetogenic Chemotherapy

Over-prescribing in patients initiating highly emetogenic chemotherapy is characterized by receiving higher dose or more products than recommended with estimates ranging from 5.9%-10%. (39, 141) In particular, prior studies have found that unnecessary 5HT3As and higher dosing of corticosteroids than recommended are prescribed.(23, 32, 34) Encinosa and Davidoff estimate that over-prescribing in patients initiating moderately or highly emetogenic chemotherapy at 34.1% on day 1 using US commercially insured and supplemental Medicare claims data (MarketScan) between a class level and not by the number of products of received.(38) A British study estimated overprescribing at 5.9%, based on prescribing of cyclizine in the delayed phase. However, cyclizine is again, typically used for breakthrough CINV.(141)

Table 2.10 Guideline Concordance in Patients Initiating Highly Emetogenic Chemotherapy*

Authors	Study Population	Study Size	Data Source	Country	Time Frame	Study Design	Guideline Concordance	Common Reasons for Discordance
Gilmore et al. 2013(22)	Adult patients initiating HEC or MEC for the first time	1,295	Multisite Practice EHR	United States (GA, TN, FL)	4/2011-3/ 2012	ProObs	Acute: 90.7% Delayed: 28.9% Overall: 28.7%	Acute: • Non-prescribing of NK1 Delayed: • Non-prescribing of CSC
Chavez-MacGregor et al. 2015(45)	Adult patients with breast cancer initiating AC, FAC, and TAC	5,569	SEER/TCR Medicare	United States	2005-2009	Retro	General: 22.4% • Dramatic decrease in in 2006, followed by increase over time (2005,2006-2010: 83.7%, 1.0%-19.6%)	General: • Non-prescribing of NK1 (82.7%)
Chavez-MacGregor et al. 2015 Chavez-MacGregor, 2015 #66}	Adult patients with breast cancer initiating AC, FAC, and TAC	25,971	MarketScan	United States	2005-2012	Retro	General: 22.8 • Dramatic decrease in 2006, followed by increase over time (2005, 2006-2013: 87.8%, 0.9%-56.4%)	General: • Non-prescribing of NK1 (83.4%)
Encinosa & Davidoff 2016(38)	Adults who started CT during the observation period	678,220	MarketScan database and its Medicare Supplement	United States	1/2008-3/2015	Retro		HEC+ MEC IV: 32.4% received breakthrough treatment
Aapro et al. 2012(31)	CT-naïve adults initiating single day MEC and HEC for cancer	991	Daily Diary	8 Western European Countries	9/2009-6/2010	ProObs	Acute: • HEC: 43% • F-AC: 32% Delayed: • HEC: 12% • F-AC: 63% Overall: • HEC: 11% • F-AC: 39%	Acute: • HEC and F-AC: Non-prescribing of NK1 (51.8%) Delayed: • HEC: Non-prescribing of CSC (16.15-38.7%) • F-AC: Non-prescribing of CSC (6.3%) and 5HT3A (29.6%)

Authors	Study Population	Study Size	Data Source	Country	Time Frame	Study Design	Guideline Concordance	Common Reasons for Discordance
Burmeister et al 2011(39)	Patients starting a new CT	299	Institution electronic patient management system	Switzerland	11/2008-4/2009	Retro	Acute: 71% • Under-prescribing: 19% • Over-prescribing: 10	Acute: • NK1 prescribing • CSC not reduced
Molassiotis et al. 2008(141)	Patients starting first CT	102	Self-report	United Kingdom	NR	ProObs	General: 35.3% • Under-prescribing: 58.8% • Over-prescribing: 5.9%	
Hori et al. 2013(34)	Patients treated with selected injectable CT agents	9,978	Nationwide distributed research network with 39 hospitals	Japan	1/2010-6/2011	Retro	Acute: 28.1%-39.3% • Increased compliance directly proportional with new NK1 uptake Delayed: 9.7%-15% Overall: 9.4%	Delayed: • Unnecessary 5-HT3A use
Tamura et al. 2014(37)	Patients scheduled to receive first MEC or HEC	1,910	Daily Diary	Japan	4/2011-12/2012	ProObs	General: 74%	
Chan et al, 2012(36)	Adult breast cancer patients receiving AC	361	Patient Interview, Standard Diary	Singapore	12/2006-1/2011	ProObs	Delayed: 42.1%	

CT: Chemotherapy MEC: Moderately Emetogenic Chemotherapy HEC: Highly emetogenic Chemotherapy
LER: Low Emetogenic Risk ProObs: Prospective Observational Retro: Retrospective
Dex: Dexamethasone CSC: Corticosteroid IV: Intravenous
Acute: Day 1 Delayed: Days 2-5 Overall: Day 1-5 NR: Not Reported
*In studies where multiple types of risk were studied; only HEC-specific results are included in this table

2.3 Cost Effectiveness

As discussed in (section 2.1.7), guideline recommendations for preventing CINV in patients initiating highly emetogenic chemotherapy center on triple-regimens containing an NK1 (aprepitant, fosaprepitant, netupitant, and rolapitant), 5HT3A (first generation: ondansetron, granisetron, and dolasetron and second generation: palonosetron), and a corticosteroid (dexamethasone) as well as newer recommendations for using triple regimens containing olanzapine + palonosetron + dexamethasone or quadruple regimens consisting of olanzapine + aprepitant/fosaprepitant + 5HT3A + dexamethasone. As outlined in section 2.1.4.3, clinical trials, meta-analyses, and network meta-analyses have found similar effectiveness across the NK1s. However, differences in 5HT3As in combination with NK1s has not been previously studied. Additionally, while studies to date support that regimens containing olanzapine are more effective than ones that do not (including ones with aprepitant), this evidence-base is still being developed. As such, there is no preferred antiemetic regimen for preventing CINV in patients initiating high CINV risk chemotherapy based on effectiveness. However, given the varied cost of available treatment strategies, identifying the most cost-effective strategy can help inform value-driven prescribing in this clinical context. Notably, the 2015 ASCO guidelines specifically highlight the need to evaluate the value of NEPA given its high costs to payers and potential out-of-pocket spending implications for patients.(142)

To date there have been two studies that examined the cost effectiveness of NEPA in patients initiating highly emetogenic chemotherapy.(53, 143, 144) These two cost-utility studies, conducted from the perspectives of the UK National Health Services and Italian National Health Services, found that NEPA was dominant (i.e., was more effective and less costly) strategy over aprepitant and fosaprepitant-based strategies (no olanzapine-based strategies were studied). It is important to note that the cost of NEPA and all antiemetics are cheaper in both the UK and Italy.(18, 143, 144) Additionally, in five other studies comparing aprepitant-based regimens to 5HT3A-regimens in patients initiating highly emetogenic chemotherapy, aprepitant was either found to be cost-effective at a willingness-to-pay threshold of $50,000/QALY or dominated (Table 2.11).(54-58)

Table 2.11 Studies Assessing the Cost Effectiveness of NK1s

Author	Perspec-tive	Intervention	Popu-lation	Model	Time Horizon	Results
Annemans et. al(55)	Belgium payer	I: apr (days 1–3), ond (day 1), dex (days 1-4) C: ond (days 1-4), dex (1-4)	Cis-based	M: Decision Tree O: Cost/ QALY	TH: 4 cycles Cycle: 21 Days	The apr-based regimen is associated with 0.003 more QALYs in HEC and with per patient savings of €66.84 (trial) and €74.62 (real-life based) for HEC. Apr is both more effective and less expensive (=dominant)
Chan et. al(56)	Hong Kong payer	I: v1-v2: apr (days 1-3) + ond (day 1) and dex (days 1-4)v3: aprep (days 1-3) + ond (day 1) and dex (days 1-4) C: v1: ond (day 1) and dex (days 1-3), v2: ond (day 1-4) and dex (days 1-4), v3: ond (day 1-3) and dex (day 1)	HEC (v1& v2: Cis, v3: AC-based)	M: Decision Tree O: Cost/ QALY Cost/ QALD Cost/ Events Avoided	TH:5 days Cycle: 1 day (Acute) /4 days (Delayed)	The use of apr-containing regimens is associated with an improvement in QALYs compared with non-apr regimens. For cisplatin-based chemotherapy, the incremental cost/QALY gained is HKD 239,644 /when ondansetron is administered on day 1 only. The incremental cost/QALY is HKD 440,950 when ondansetron is used on day 1 to 4. For AC-based chemotherapy, the apr-containing regimen is associated with incremental cost of HKD 195,442/QALY gained. Similar results were obtained when other 5HT3As are used. The use of apr was associated with higher cost of drug but lower costs of emesis-related management. With the cost-effectiveness threshold set at the WHO endorsed criteria of three times GDP per capita, the apr-containing regimen was cost-effective.
Humphreys et. al(57)	UK payer	I: aprep (days 1-3), ond (day 1), dex (days 1-3) C: v1: ond (day 1), dex (days 1-2), met (days 2-3), v2: ond (day 1-3), Dex (day 1)	HEC in Breast Cancer	M: Decision Tree O: Cost/ QALY	TH: 5 days Cycle: 1 day (Acute) /4 days (Delayed)	During 5 days after chemotherapy, 64% of patients receiving the apr regimen and 47% of those receiving the v1 had a complete response to antiemetic therapy (no emesis and no rescue antiemetic therapy). A mean of £37.11 (78%) of the cost of apr was offset by reduced health care resource utilization costs. The predicted gain in QALY with the apr regimen was 0.0048. The ICER with apr, relative v1, was £10,847/ QALY, which is well below the UK £20,000–£30,000/QALY threshold.
Lordick et. al(58)	German payer and patient	I: aprep (days 1-2), ond (day 1), dex (days 1-4) C: ond (Day 1), Dex (days 1-4)	HEC	M: Decision Tree O: Cost/ QALY	TH:5 days Cycle: 1 day (Acute) /4 days (Delayed)	Patients were estimated to have gained an equivalent of 15 additional hours of perfect health per cycle (0.63 QALD) with apr-based regimen compared to control regimen. Cost/ QALY gained with apr was estimated at €28,891. Incremental benefits materialized in a cost-effective fashion.
Moore et. al(54)	US Payer	I: ond 32 mg IV (day 1), dex (days 1-4), aprep (days 1-2) C: v1: ond (day 1)	Cis-based	M: Decision Tree O: Cost/	TH:5 cycles Cycle: 28 Days	Adding apr after CINV occurred cost $264 per HDE ($96,333/QALY). The three-drug strategy cost $267/HDE with a 95% confidence range of $248-$305/ HDE ($97,429/QALY; $90,396–$111,239/QALY). Routine aprepitant use appears most

Author	Perspec-tive	Intervention	Popu-lation	Model	Time Horizon	Results
		and dex (days 1-4), v2: conv. management until CINV, v1		QALY (HDE)		cost-effective when the likelihood of delayed CINV or the cost of rescue medications is high
D'agostino et. al(53, 144)	UK National Health System	I: NEPA C: Apr+palo, palo	HEC or MEC	M: Markov O: Cost/ QALD	TH:5 days Cycle: 1 day (Acute) /4 days (Delayed)	In HEC patients, the NEPA strategy was more effective than apr (QALDs of 4.263 versus 4.053; incremental emesis and CINV free days of +0.354 and +0.237 respectively) and was less costly (£80 versus £124), resulting in NEPA being the dominant strategy.
Restelli et al.(143)	Italian National Health System	I: NEPA C: Apr+palo fos+palo , apr+ond, fos+ond	HEC or MEC	M: Markov O: Cost/ QALD	TH:5 days Cycle: 1 day (Acute) /4 days (Delayed)	NEPA is more effective and less expensive (dominant) compared with APR + PALO (HEC) fAPR + PALO (HEC), APR + ONDA (for HEC), fAPR + ONDA (for HEC). The use of NEPA would lead to a 5-year cost decrease €42.7 million.

Apr: Aprepitant Palo: Palonosetron Met: Metoclopramide Dex: Dexamethasone HEC: Highly emetogenic Chemotherapy
MEC: Moderately Emetogenic Chemotherapy WHO: World Health Organization I: Intervention C: Comparator
M: Model O: Outcome TH: Time Horizon QALY: Quality Adjusted Life Year
ICER: Incremental cost effectiveness ratio HDE: Healthy Day Equivalent QALD: Quality Adjusted Life Day
GDP: Gross Domestic Product Cis: Cisplatin NEPA: Neupitant-Palonesetron

Studies included perspectives from payers and patients, ranged from 5-28 day cycles, had 1-5 cycles, and used decision-tree and Markov model study designs. Two other cost models were identified, but one was used to calculate the optimal price of NK1s from the perspective of the Canadian payer and the other was a cost-minimization model comparing NEPA and aprepitant for the Scottish Medicines Consortium. (145, 146) No studies have compared olanzapine in any setting or all NK1s from a US commercial payer perspective.

2.4 Theoretical Framework

Aday and Andersen's Behavioral Model of Health Services Use will serve as the theoretical foundation for this dissertation (Figure 2.2).(147) Aday and Andersen's Behavioral Model of Health Services Use stipulates that environmental, population characteristics, and behavior are predictors of the use of health services by patients.(148) Environmental factors include the healthcare system and the external environment. Population characteristics include predisposing characteristics that may affect antiemetic use, enabling resources that affect access to antiemetics, and need for antiemetics. Health behavior factors include personal health practices and use of health services. Finally, outcome measures include perceived health status and evaluated health status. Because antiemetic use is multifaceted and factors associated with its use span guideline-adherence, cancer care, and preventive care, all three bodies of evidence were assessed to build this conceptual model. Notably, Table 2.12 summarizes predictors identified in the studies looking at both antiemetic prescribing and guideline-concordance discussed earlier in section 2.2. However, the variables included in this dissertation, and ultimately in the model, are limited to those that are measurable in the dataset used.

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Table 2.12 Predictors of Guideline Concordance*

Authors	Country	Study Design	Data Source	Study Size	Predictors: Patient Characteristics	Predictors: Treatment	Predictors: Coverage	Predictors: Provider / Setting
Franca et. al(40)	Brazil	Retro	Institution database	105		• General: HEC		
Zong et. al(32)	China	Retro	CHIRA	14,548	• General Antiemetic Acute: Female • General Antiemetic Delayed: Older age	• General Acute: Kidney cancer, myeloma, cervical cancer		• General Acute: First-grade hospital • General Delayed: General hospital (vs. cancer center)
Hori et. al(34)	Japan	Retro	Nationwide research network	9,978	• Acute & Delayed HEC: Younger patients, opioid users • General Acute Breakthrough: Younger, female, opioid users	• HEC Acute & Delayed: Later CT-cycles, AC or EC vs.-cisplatin • General Acute and Delayed: HEC • HEC Acute & Delayed Breakthrough: HEC, prophylactic guideline discordant		• Acute HEC: Inpatient • Delayed HEC: Outpatients • General Delayed Breakthrough: Inpatient
Chan et. al(36)	Singapore	ProObs	Patient interview and diary	361	• HEC: Lower educational levels, lower consumption of alcohol	• Non-AC chemotherapy regimen naïve		
IGAR(23)	Italy	ProObs	Patient interview	1,956		• General: CINV-risk		• HEC: Past antiemetic collaborative research
Caracuel et. al(43)	Spain	ProObs	Question-naire	102 Rxs	• HEC: Younger, no previous N+V			
Burmeister et. al(39)	Switzerland	Retro	Institution electronic patient system	299	• General: Female, older age	• General: Solid tumor, highly emetogenic chemotherapy		• General: Inpatient treatment

Authors	Country	Study Design	Data Source	Study Size	Predictors: Patient Characteristics	Predictors: Treatment	Predictors: Coverage	Predictors: Provider / Setting
Chavez-MacGregor et. al(45)	United States	Retro	SEER/TCR Medicare	5,569	• HEC: White	• HEC: Year of treatment, time to initiation		
Chavez-MacGregor et. al(45)	United States	Retro	MarketScan	25,971		• HEC: Year of treatment, time to initiation, AC-based chemo		
Encinosa & Davidoff* (38)	United States	Retro	MarketScan database and Medicare Supplement	678,220	• Overuse: Female, older age, no chronic conditions, hourly worker, union worker		• Overuse: HMO, HDHP, in-network CT, and Commer-cial plan (versus Medicare)	• Overuse: Rural

CT: Chemotherapy HEC: Highly emetogenic Chemotherapy ProObs: Prospective Observational Retro: Retrospective
IV: Intravenous Acute: Day 1 Delayed: Days 2-5
SEER: National Cancer Institute's Surveillance Epidemiology and End Result linked with Medicare fee-for-service claims
CHIRA: China Health Insurance Research Association Database Rxs: Prescriptions
Prescriptions IGAG: Italian Group for Antiemetic Research NV: Nausea and Vomiting
HMO: Health Management Organization HDHP: High Deductible Health plan

While this section focuses on patient, treatment, and external predictors of antiemetic concordance, it is crucial to remember that the role of the physician (e.g., knowledge and belief of antiemetics) and healthcare system factors (e.g., automated prescribing in an EMR system) are arguably among the most important factors in predicting guideline adherence as they are the one prescribing the antiemetic regimen.(42, 137) (Though the onus is on the patient to fill and take the medication.) Reasons for low guideline adherence result from: 1) physician (and institution) awareness and knowledge of guidelines that have not only many antiemetic options (over 400 antiemetic regimens are estimated to exist across CINV-risk categories), but also guideline-concordant options and 2) healthcare stakeholders' historical emphasis on eliminating care efficiencies to maximize revenue versus high-quality outcomes.(23, 42, 137, 149) Prescriber characteristics and healthcare system factors cannot be measured in the proposed data source, but they highlight opportunities for future research.

However, especially in the US, the increased focus on value-based care, including advanced payment models and outcomes-based contracting are incentivizing patients to focus on high quality, value-based care, which includes guideline adherence. As such, identifying patient-level factors that influence both antiemetic guideline concordance and discordance will help address guideline discordance. (22, 38, 45) Again, it is crucial to consider these predictors in the context of the healthcare delivery system in which they were assessed given the differences across systems limiting the generalizability of one system's findings to another.

2.4.1 Conceptual Model: Environment

2.4.1.1 Environment: Healthcare System

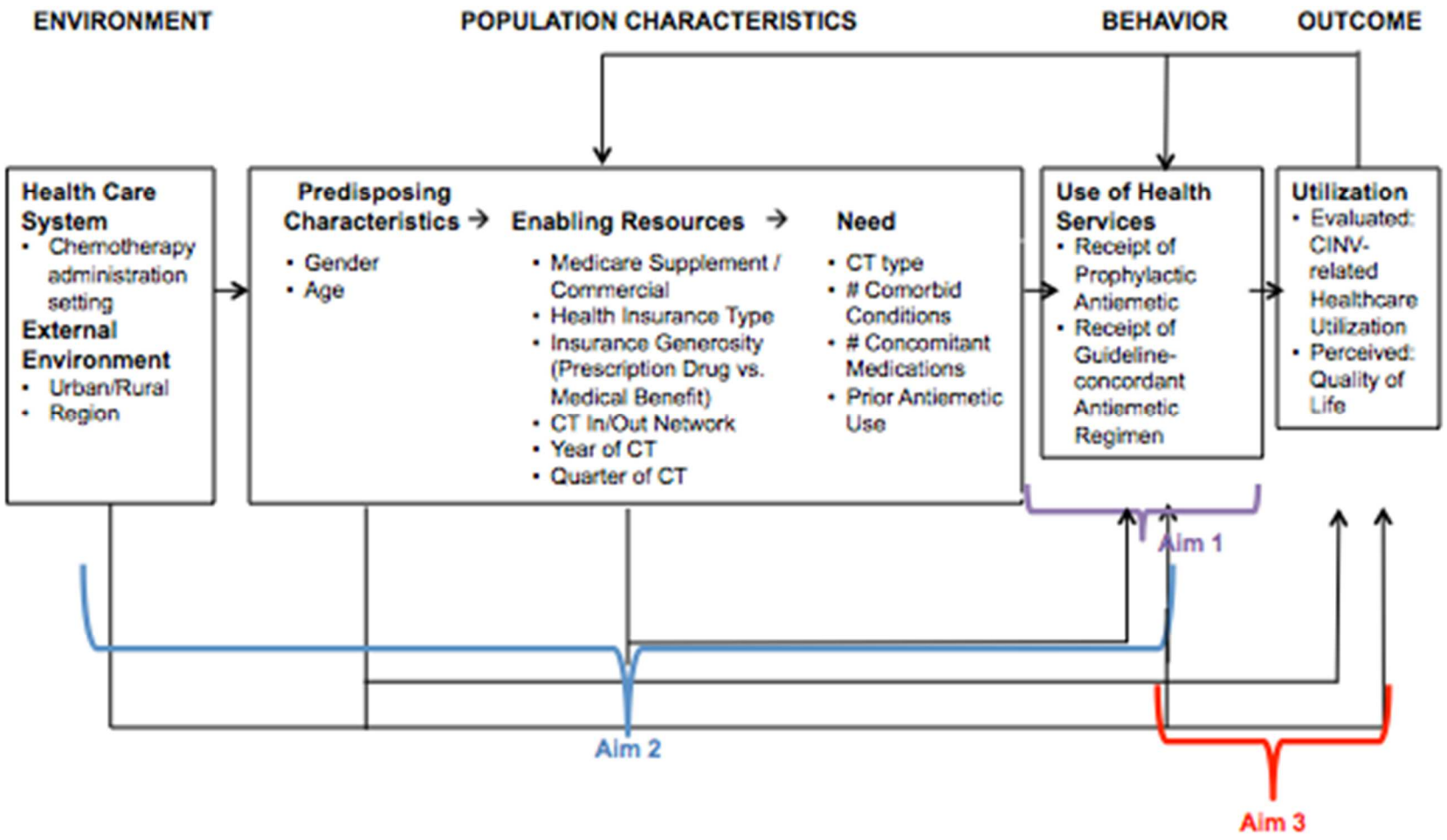
The healthcare system includes whether the patient received the highly emetogenic chemotherapy in an inpatient our outpatient setting as well as whether the outpatient setting was affiliated with a hospital or a physician office. Prior studies have shown that patients who receive care in an inpatient setting are more likely to receive guideline-concordant antiemetics, especially in the acute setting. (34, 39) This may be because providers can ensure that patients take their antiemetic medication in an inpatient setting if all medications were received in the inpatient setting (versus picking up antiemetics at a community

pharmacy). However, inpatient chemotherapy is associated with lower patient satisfaction and higher costs.(150-153) Furthermore, cancer care in an outpatient setting affiliated with a physician's office is associated with lower costs than with a hospital, which may be due to hospitalizations and billing practices; however, no other differences in chemotherapy care patterns exist.(154-156) Please note that because we are unable to discern the type of chemotherapy administered in an inpatient setting in this data set, whether the chemotherapy was administered in a physician-affiliated or hospital-affiliated outpatient setting will be examined. Notably, supportive cancer care including antiemetic use was not examined. Another factor associated with treatment and guideline concordance, but not measured in this research project include whether the institution where care was provided had participated in antiemetic research.23)

2.4.1.2 Environment: External Environment

The external environment includes geographic region as well as whether care is delivered in a rural or urban setting. Many studies have shown that there is large regional variation in terms of the availability of cancer care including National Cancer Institute (NCI) designated comprehensive cancer centers, Commission on Cancer (CoC) Accredited Hospitals, academic-medical centers, and any specialized cancer care.(157) Travel time to a NCI designated comprehensive cancer center, which includes access to a full range of diagnostic and treatment services as well as cutting-edge novel treatments that may not be available elsewhere, was 5 times, 3 times, and 2 times longer in the south, west, and Midwest respectively compared to the Northeast. The Northeast also had the highest per capita number of oncologists.(157) The 2003 Institute of Medicine Report on "Unequal treatment: Confronting Racial And Ethnic Disparities In Health Care" stated that quality of care at rural hospitals is lower than urban teaching hospitals highlighting the gap between rural and urban care.(158) Patients who received care in a rural setting were more likely to receive over-prescribing compared to those in an urban setting.(38) Furthermore, increased rurality was associated with increased risk of cancer-related death.(159) Additionally, gaining access to cancer care in a rural setting is challenging given the limited availability of care professionals and facilities, long distances to services, and poor public transportation. (157, 158, 160, 161)

Figure 2.2 Adapted Andersen's Behavior Model Used to Examine Patterns of Antiemetic Prescribing, Predictors of Guideline-Concordant Antiemetic Prescribing, and Cost-Effectiveness of CINV Strategies in Cancer Patients Initiating Highly Emetogenic Chemotherapy



2.4.2 Conceptual Model: Population Characteristics

2.4.2.1 Population Characteristics: Pre-disposing Characteristics

Studies have identified the pre-disposing characteristics gender, age, and employment status as predictors of guideline-concordant antiemetic use. (32, 34, 38, 39) In general, female patients are more likely to receive guideline concordant antiemetic products and breakthrough therapy compared to men across CINV-risk as well as in high CINV-risk chemotherapy. Only one study found that male patients were more likely to receive prophylactic antiemetics than women in the delayed phase. (32, 34, 39) Additionally, women are more likely to be over-prescribed antiemetics compared to men.(38) Two potential reasons for this are 1) women are more likely to use preventative care services and cancer care and 2) women are known to be at higher risk for CINV.(4, 162) While conflicting results exist, generally, younger patients were more likely to receive the guideline-concordant antiemetics compared to older patients, likely because being under 50 is associated with higher risk of CINV. (4, 32, 34, 39, 43, 74) Across cancer care and guideline-concordance studies, it has been shown that black patients receive worse care than white patients and patients with a lower deprivation index (based on educational opportunities, labor force skills, economic, and housing conditions) had higher cancer-related mortality.(45, 46, 159) Unfortunately, the data used for the proposed study does not include race or socioeconomic status. Other patient-level predictors of guideline-concordance that are not measurable in this dataset include lower educational levels and lower consumption of alcohol.(38, 136)

2.4.2.2 Population Characteristics: Enabling Resources

Prior studies have demonstrated that the health insurance type and whether the chemotherapy was administered in/out of network influence guideline concordant antiemetic-use. Related to health insurance, patients on a health maintenance organization plan or a high-deductible health plan were more likely to receive over-prescribing of antiemetics compared to a fee-for-service plan.(38) These are surprising findings given that 1) enrolling in a high deductible health plan generally results in lower healthcare utilization including prescription drug use and 2) by definition, managed care organizations aim to prevent unnecessary healthcare resource use.(163, 164) Patients who receive chemotherapy out-of-

network are less likely to receive over-prescribing of antiemetics, possibly due to higher out-of-pocket expenses associated with out-of-network care.(165) Studies have also shown that as out-of-pocket costs increase, medication adherence generally decreases.

Finally, because we only have co-pay and deductible data on drugs filled, we aim to use insurance generosity as a surrogate of the effect of co-pay and/or deductibles on antiemetic use, as it hypothesized these out-of-pocket costs could impact guideline adherence.(166) We are distinguishing creating separate measures for prescription drug versus medical benefit insurance generosity as antiemetics can be administered orally and covered through the prescription drug benefit or intravenously and covered through the medical benefit.

2.4.2.3 Population Characteristics: Need

Prior studies have shown that need variables such number of concomitant medication use, number of comorbid conditions, cancer type, year of chemotherapy administration, quarter of chemotherapy administration, and prior antiemetic use are associated with guideline concordance. Antiemetic overuse decreased with an increased number of concomitant medications.(38) Interestingly, studies have also shown that patients with cancer and other comorbidities are less likely to receive treatment, but among those that do, they are over-treated, though this does not include supportive care.(167) Furthermore, it is known that patients with multiple chronic conditions and more concomitant therapies have lower medication adherence due to treatment burden.(168, 169) Prior studies have shown that chemotherapy type is associated with guideline-concordance. Specifically, studies have found that patients on anthracycline (epirubicin or doxorubicin) and cyclophosphamide combination were more likely to receive guideline-concordant care compared with cisplatin-based chemotherapy.(34) Studies have also shown that certain types of cancer are associated with higher rate of antiemetic guideline concordance including solid tumor, kidney cancer, myeloma and cervical cancer.(32, 39) While cancer type is available in the dataset, we anticipate it being collinear with chemotherapy type, and are not including it in the model. Unsurprisingly, the relationship between breakthrough use and guideline-concordance is inversely proportional.(34)

Year of chemotherapy administration is also associated with guideline-concordance – this may be the result of new guideline diffusion and/or new product entrance.(45) While not specifically examined in relation to antiemetics in prior research, we hypothesize that the quarter in which chemotherapy is administered may be a predictor of concordance. Specifically, patients may have reached annual out-of-pocket costs in later quarters, and more likely to fill guideline-concordant antiemetic treatments. Prior antiemetic use should also be included in the conceptual model. Specifically, antiemetics used to prevent chemotherapy induced nausea and vomiting can also be used to prevent nausea and vomiting in other conditions such as gastroenteritis, as well as nausea and vomiting that is the side-effect of other drugs such opioids.(170, 171) Notably, patients on opioids were more likely to receive guideline-concordant antiemetics than those that are not, because opioids have their own risk of nausea and vomiting.(34) Additionally, prior chemotherapy or radiation induced nausea and vomiting is a risk factor for future CINV.(4, 74) Studies have shown that patients with prior nausea and vomiting are less likely to receive guideline-concordant antiemetic regimens, but patients undergoing later cycles of chemotherapy are more likely to receive guideline-concordant antiemetic regimens, likely responding to prior experience.(34, 36, 43) While this data set does not reliable capture prior nausea and vomiting related to the chemotherapy or radiation, we will use prior chemotherapy (oral or IV) as well as prior or radiation therapy exposure as a proxy. Additionally, we hypothesize that physicians might be more diligent in prescribing guideline-concordant antiemetics to patients who are undergoing concomitant radiation therapy and chemotherapy. Notably, guidelines recommend that when radiation and chemotherapy are combined, the chemotherapy regimen dictates the prophylactic antiemetic regimen.(20) Time to chemotherapy initiation following diagnosis has also shown to be a predictor of guideline-concordant, but is not measured in this dataset.(45)

2.4.3 Conceptual Model: Behavior

The primary behavior measured is use of health services or, specifically, appropriate antiemetic use. Antiemetic use will be stratified by whether products were filled in the acute (day 1) or delayed phase (days 2-5) as well as whether products were guideline-concordant.

2.4.4 Conceptual Model: Outcomes

The outcomes of this model are based on evaluated and perceived health status. Specifically, the evaluated health status is the cost associated with CINV-related healthcare utilization. This includes rescue antiemetic use, emergency department visits, inpatient visits, outpatient visits, and ordered labs. Perceived health status will be measured using quality-adjusted life years, based on utilities.

2.5 Conclusion

In conclusion, chapter 2 provides a history of antiemetic availability and use in the United States and summarizes the literature associated with antiemetic prescribing, antiemetic guideline-concordance, and antiemetic cost-effectiveness. First, with regard to prescribing and assessing guideline-concordance, most studies take place in Europe or Asia, which have different availability of products and healthcare systems. As such these studies have limited generalizability to the United States. Furthermore, studies in the US that have examined prescribing and concordance in the US have limitations in that they only examine over-prescribing, do not distinguish between over and under-prescribing, or use targeted sub-populations (i.e., breast cancer and a southeast practice). (22, 38, 45) The proposed project aims to fill these gaps by assessing antiemetic use and concordance (including over prescribing and under prescribing) among patients initiating highly emetogenic chemotherapy. Second, there are several guideline-concordant antiemetic regimens for patients initiating highly emetogenic chemotherapy. While the cost-effectiveness of aprepitant-based strategies versus 5HT3A-based strategies is established, no studies have compared the cost-effectiveness of all NK1s. As such, it is important to compare the cost effectiveness across these regimens. (53-58)

CHAPTER 3: METHODS

Chapter 3 outlines the methods used in this dissertation including the data source, study design, variables, and statistical analysis by aim.

3.1 Aim 1: To characterize antiemetic use (including types, regimens, and concordance) in patients diagnosed with cancer who newly initiated highly emetogenic, intravenous chemotherapy from 2013-2015.

3.1.1 Data Source

We used the IBM Watson's/Truven's MarketScan Commercial Claims and Encounters Database (Commercial Claims Database) and Medicare Supplemental and Coordination of Benefits (MCOB) for patients initiating highly emetogenic chemotherapy between January 2013 through December 2015. The Commercial Claims Database includes a nationally representative sample of patients with employer-sponsored insurance in the US.(172) The Medicare Supplement data represents retirees on Medicare with employer-sponsored supplemental plans and largely includes fee-for-service plan data. The specific research files used were enrollment, inpatient services, outpatient services, and prescription drugs, which include patient-level data on enrollment, clinical utilization, and expenditures.(172) Files were linked based on unique enrollee ID.

The study aims were reviewed by the University of North Carolina at Chapel Hill's Institutional Review Board (IRB) and are exempt.

3.1.2 Study Design – Aim 1

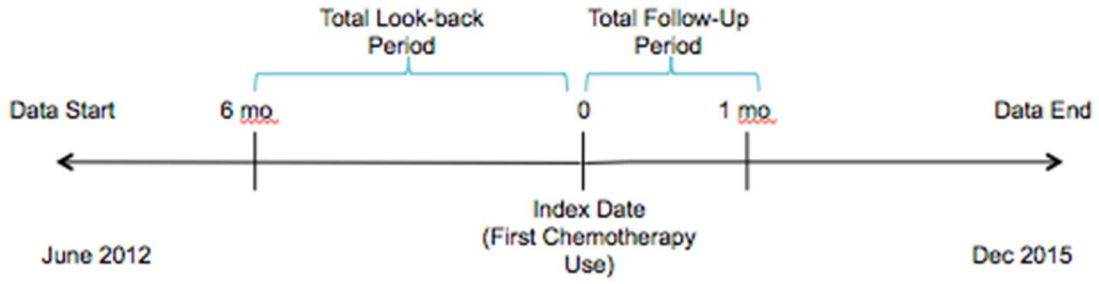
This aim used a prospective cohort study design using retrospective data.

3.1.3 Study Cohort – Aim 1

The study population was adult patients (age 18-64) with cancer who newly initiated highly emetogenic chemotherapy between January 2013 and December 2015 (Figure 3.1). We applied several inclusion/exclusion criteria. First, we identified adult patients' first use of a highly emetogenic

intravenous chemotherapy using the J-Codes listed in Table 3.1 in the outpatient files between 2013 and 2015.(173, 174) Highly emetogenic chemotherapies were identified using NCCN and ASCO guidelines.(19, 20, 52) Because we do not have data on body surface area, we assigned chemotherapies that are assigned risk based on quantity per body surface area to the highly emetogenic group when relevant.(38)

Figure 3.1 Identification of First Highly Emetogenic Chemotherapy Use



Second, we required patients to have at least six months of continuous health plan enrollment prior to the index chemotherapy treatment date (first observed chemotherapy treatment in the study period) to ensure they were newly initiating highly emetogenic chemotherapy, and to have a follow-up of at least one month after chemotherapy initiation to ensure adequate follow-up time (Figure 3.1). Highly emetogenic IV chemotherapy codes were identified using the October 2017 ASP files and the National Cancer Institute Chemotherapy Lookup Tables.(175, 176) For patients starting chemotherapy between January 2013 and March 2013, we required access to data from 2012 to ensure appropriate look-back. Third, we required that patients have a primary diagnosis of cancer recorded on the claim with the chemotherapy infusion. Cancer diagnosis codes were identified using the Agency for Healthcare Research and Quality International Classification of Diseases (ICD)-9 and ICD 10 Clinical Classification Software (CCS)) for "neoplasm." Cancer diagnosis was required, as some chemotherapies may be used off-label for other diseases (e.g., bevacizumab for wet age-related macular degeneration (AMD)).(177) Fourth, we excluded patients who were pregnant using AHRQ CCS codes (i.e., "Certain conditions originating in the perinatal period," "Complications of pregnancy; childbirth; and the puerperium," "congenital abnormalities") in patients aged 45 or younger. Fifth, we excluded patients with conditions for which olanzapine is used to

treat, including schizophrenia and bipolar disorder using AHRQ CCS codes (i.e., "Mental Illness"). This is because we would have been unable to distinguish whether olanzapine was used to treat one of these conditions or to prevent CINV, leading to potential exposure misclassification. Finally, we required that MarketScan included the patients' prescription drug file to ensure that "no fills" were in fact due to a lack of filling and not missing data.

Table 3.1 J-Codes for Intravenous Chemotherapy Administration with Risk of Highly Emetogenic Chemotherapy in 2015(19, 133, 175, 176)**

IV Chemotherapy	JCode1	
Carmustine	C9437	J9050
Cisplatin	209622 C9418	J9060 J9062
Cyclophosphamide ≥ 1,500 mg/m^2	C9420 C9421 J8530 J9070 J9080 J9090 J9091	J9092 J9093 J9094 J9095 J9096 J9097
Dacarbazine	C9423 J9130	J9140
Doxorubicin ≥ 60 mg/m^2 *	C9415 J9000 J9001 J9002	Q2048 Q2049 Q2050
Epirubicin ≥ 90 mg/m^2*	C1167 J9178	J9180
Ifosfamide ≥ 2 g/m^{2}per dose *	C9427	J9208
Mechlorethamine	J9230	
Streptozocin	J9320	
AC combination defined as either doxorubicin, idarubicin or epirubicin with cyclophosphamide	See Above	

*Denotes highly emetogenic chemotherapy classification only in NCCN

**While 2011 ASCO Guidelines include dactinomycin as highly emetogenic, 2015 NCCN guidelines classify it as highly emetogenic in certain patients, but do not specify the characteristics of those patients. Furthermore, 2017 ASCO guidelines not only exclude dactinomycin from the highly emetogenic category, but also from the guideline altogether. As such, dactinomycin is not included in this analysis given the ambiguity related to when it is considered highly emetogenic.

3.1.4 Measures – Aim 1

This aim describes type of antiemetic (i.e., product, class, and administration route) filled, number of antiemetic products filled, as well as regimens filled and their associated costs by commercially insured and Medicare insured individuals who received highly emetogenic chemotherapy in the United States between 2013 and 2015. Guideline concordance was also assessed.

3.1.4.1 Antiemetic Identification

To identify antiemetics filled, we created person-level binary indicators for each antiemetic product (0=no/1=yes), including prophylactic and breakthrough.(38) Antiemetics were identified using J-codes for intravenously administered products and National Drug Codes (NDC) codes for oral products in the outpatient file as well as prescription drug files (Table 3.2).(38) NDC codes were identified using the Red Book in IBM Watson's / Truven's MarketScan by conducting text string searches for each product's generic name. While orally administered products should be included in the prescription drug files and intravenous products should be listed in the outpatient medical files, we checked all files for both prescription and intravenous claims to ensure complete capture of products filled.

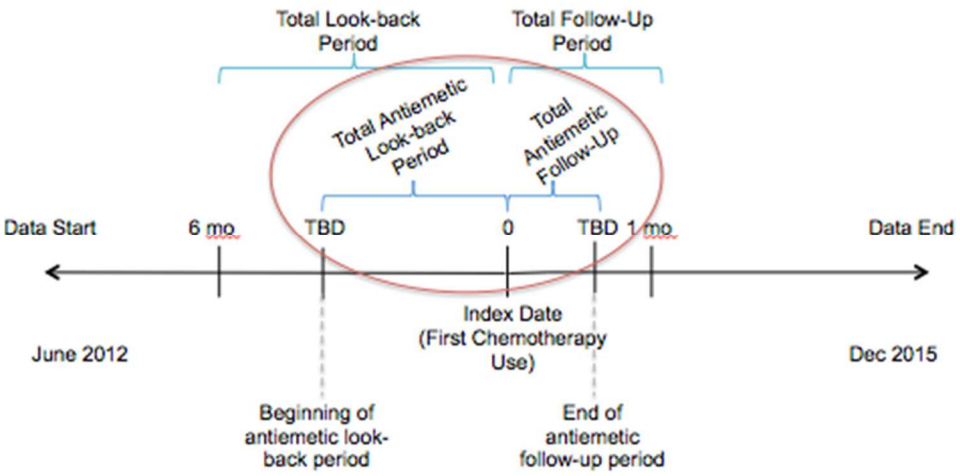
Intravenously (IV) administered products were assessed on the day of HEC administration. Post-hoc boundary identification was necessary to determine the look-back period for oral antiemetic use, as physicians often prescribe antiemetics and chemotherapy simultaneously, well in advance of the chemotherapy administration date. Often the antiemetic regimen is filled immediately, while the use of payer management tools, such as prior authorization, delay chemotherapy regimen filling. To identify the boundaries, we created a histogram of preventative antiemetic fills during the study period (six months prior to highly emetogenic IV chemotherapy administration) for both study populations (Appendix Table A.1 and Appendix Table A.2). Subsequently, the number of days at which 75% of antiemetics were filled before the date of highly emetogenic intravenous chemotherapy administration was used as the fill date boundary (Figure 3.2). This was -32 days and -53 days prior to first IV HEC administration for the CCAE and Medicare Supplement populations.

Table 3.2 J-Codes for Antiemetic Drugs Administered Intravenously(178)

Code	Antiemetic
Preventative	
Glucocorticoids	
J1100	Dexamethasone IV
J7312	Dexamethasone intra implant
J8540	Dexamethasone oral
5HT3A**	
J2405	Ondansetron IV
Q0162	Ondansetron oral
J1626	Granisetron IV
Q0166	Granisetron Oral
J1260	Dolasetron IV*
Q0180	Dolasetron Oral
J2469	Palonosetron IV
NK1	
J8501	Aprepitant Oral
J1453	Fosaprepitant IV
J8670	Rolapitant
Q9981	Rolapitant
J8655	Netupitant / Palonosetron Combination
Q9978	Netupitant / Palonosetron Combination
Q0181	Unspecified oral form of an IV antiemetic substitute
Atypical Antipsychotic	
J2358	Olanzapine**
Typically Used as Rescue Products for Breakthrough CINV	
Dopaminergic Antagonists	
J2765	Metoclopramide IV
J0780	Prochlorperazine IV
Q0164	Prochlorperazine Oral
Q0165	Prochlorperazine Oral
J2550	Promethazine IV
Q0169	Promethazine Oral
Q0170	Promethazine Oral
J1630	Haloperidol IV
J1631	Haloperidol Decanoate IV
Cannabinoids	
Q0167	Dronabinol Oral
Q0168	Dronabinol Oral
Benzodiazepine	
J2060	Lorazepam IV

*No longer used for CINV as of 2011(179)
**While 5HT3As and olanzapine may also be used as rescue therapies, they were classified as preventative in this analysis.

Figure 3.2 Antiemetic Look-back Period



3.1.4.1.1 Primary Characterization Analysis: Antiemetics Filled for CINV Prophylaxis or in Anticipation of Rescue Therapy Necessity

Characterization (i.e., product, class, administration route, and patterns) of antiemetics filled for CINV prophylaxis or in anticipation of needing rescue therapy ranged from the beginning of the look-back period through day 1 for oral products and day 1 for IV products. We also calculated the associated total and out-of-pocket costs (i.e., deductible + copay + coinsurance) based on the transactional prices available in the data. All costs were inflation-adjusted to 2016 USD using the medical component of the Consumer Price Index. Claims with "zero-dollar" total costs or negative copay, deductible, coinsurance, or net pay costs were excluded.

3.1.4.1.2 Secondary Characterization Analysis: NK1 Use in the Post Period

Guidelines recommend that NK1 only be used as prophylaxis and not as rescue medication. In this secondary analysis, we assessed the use of NK1 in the five days following IV chemotherapy administration to assess potential over-use. We assumed products filled during this post-period are likely used as rescue medication.

3.1.4.2 Guideline Concordance

To assess guideline concordance for preventing CINV in patients initiating highly emetogenic chemotherapy, we compared the combination of antiemetic products identified in Section

3.1.4.1.1(Antiemetics Filled for CINV Prophylaxis or in Anticipation of Rescue Therapy Necessity) against the most recent ASCO and NCCN antiemetic guidelines in 2015 (Table 3.3).(19, 133) These guidelines were used as the reference given that our study period ranges from 2013 to 2015. We also examined the frequency of products used by class to determine which products are most and least frequently used among guideline-concordant users. Some chemotherapy regimens (i.e., cyclophosphamide only and anthracycline only regimens) are considered highly emetogenic based on a surface area doing threshold level, which was not available in the claims data. As a result, we also assessed under-use by type of chemotherapy received (i.e., anthracycline + cyclophosphamide on the same day, cyclophosphamide only, anthracycline only, and other).

3.1.5 Data Analysis – Aim 1

Descriptive statistics were used to assess patterns of use as well as guideline-concordant antiemetic drug use in newly diagnosed adult patients with cancer who initiated highly emetogenic chemotherapy. Mean/standard deviation and median/interquartile ranges were provided for cost variables. Analyses were run on the commercially insured and Medicare Supplement data sets separately. The two data sets are representative of two very different populations, which may result in different factors influencing their antiemetic prescribing. In fact, a prior study found that patients enrolled in Medicare were less likely to receive over-prescribing of antiemetics compared to commercially insured patients.(38)

3.1.5.1 Power Calculation

Because this aim is descriptive and no hypotheses are tested, a power calculation was unnecessary.

Table 3.3 NCCN and ASCO Guideline-Concordant Strategies*(19, 133)

Strategy Number #			1	2	3	4	5	6	7
Acute	Day 1	Aprepitant	■					■	
		Fosaprepitant		■					■
		Rolapitant			■				
		NEPA				■			
		Olanzapine					■	■	■
		Palonosetron					■		
		Any 5HT3A	■	■	■			■	■
		Dexamethasone	■	■	■	■	■	■	■
Delayed	Day 2	Aprepitant	■					■	
		Fosaprepitant							
		Rolapitant							
		NEPA							
		Olanzapine					■	■	■
		Palonosetron							
		Any 5HT3A							
		Dexamethasone	■	■	■	■		■	■
	Day 3	Aprepitant	■					■	
		Fosaprepitant							
		Rolapitant							
		NEPA							
		Olanzapine					■	■	■
		Palonosetron							
		Any 5HT3A							
		Dexamethasone	■	■	`	■		■	■
	Day 4	Aprepitant							
		Fosaprepitant							
		Rolapitant							
		NEPA							
		Olanzapine					■	■	■
		Palonosetron							
		Any 5HT3A							
		Dexamethasone	■	■	■	■		■	■
	Day 5	Aprepitant							
		Fosaprepitant							
		Rolapitant							
		NEPA							
		Olanzapine							
		Palonosetron							
		Any 5HT3A							
		Dexamethasone							

NEPA: Netupitant / Palonosetron Combination

3.2 Aim 2: To identify predictors of antiemetic under-use in patients diagnosed with cancer and newly initiating highly emetogenic, intravenous chemotherapy.

3.2.1 Data Source – Aim 2

Aim 2 used the same data sources as Aim 1. This data source is described in section 3.1.1.

3.2.2 Study Design – Aim 2

This aim used the same design outlined in section 3.1.2 to assess predictors of guideline under-use (Table 3.6). We calculated frequencies for each covariate to assess variation and missing data. How we handled missing data for each variable is described in section 3.2.4.1.

3.2.3 Study Cohort – Aim 2

Aim 2 used the same study cohort as Aim 2 except that patients had to initiate highly emetogenic chemotherapy on or before October 2015 (as opposed to on or before December 2015). This is because one of the covariates described in section 3.1.4.2 uses an algorithm using ICD-9 codes that has not yet been translated for use in ICD-10 codes, and ICD-10 went into effect in October 2010.

3.2.4 Measures – Aim 2

The variables measured for this aim are described in Table 3.6. The justification for the dependent and independent variables are described in section 3.2.3.1 and 3.2.3.2, respectively.

3.2.4.1 Dependent Variable

Aim 1 has one outcome variable, guideline concordance, with two categories: antiemetic under-use and guideline-concordant antiemetic use. Identification of antiemetics and their level of concordance are detailed earlier, in sections 3.1.4.1 and 3.1.4.2, respectively.

3.2.4.2 Independent Variables

The independent variables in Table 3.5 were considered for model inclusion as potential predictors of antiemetic under-use. Specifically, these variables are organized as environmental factors (healthcare system and external environment) and population characteristics (pre-disposing, enabling, or need characteristics) and described below. This categorization aligns with Andersen's Behavioral Model of Health Services Use as described in Section 2.4

Table 3.4 Definition and Characteristics of Dependent and Independent Variables

Category	Variable	Type	Data Source	Description
DEPENDENT VARIABLES				
Behavior				
Use of Health Service	Guideline-Concordant Antiemetic Use	Categ	IP/OP/PD	Guideline-concordant, under-use
INDEPENDENT VARIABLES				
Environment				
Healthcare System	Chemotherapy Setting	Categ	OP	Hospital-affiliated OP, Physician-affiliated OP
External Environment	Geographical Setting	Binary	Enroll	Urban (Municipal Statistical Area > 0) / Rural (Municipal Statistical Area = 0)
	Region	Categ	Enroll	e.g., Northeast, North Central, South, West, Unknown
Population Characteristics				
Predisposing Character-istics	Age	Binary	Enroll	18-50, 50-64, 65-75, 75-85, 85+
	Gender	Binary	Enroll	Male / Female
Enabling Resources	Health Insurance Type	Categ	Enroll	Point of Service, Health Maintenance Organization, Preferred Provider Organization, Consumer-driven Health Plan / High Deductible Health Plan, Other
	Insurance Generosity – Intravenous Medication	Categ	IP/OP	No/Poor/Fair Coverage, Good Coverage
	Insurance Generosity – Prescription Drug	Categ	PD	No/Poor/Fair Coverage, Good Coverage
	Chemotherapy Network	Binary	OP	In-Network / Out-of-network
	Year of Chemotherapy	Categ	OP	2013, 2014, 2015
	Chemotherapy Quarter	Categ	OP	Quarter 1 / 2 / 3 / 4
Need	Chemotherapy Type	Categ	OP	Anthracycline Only, Cyclophosphamide Only Anthracycline + Cyclophosphamide, Carmustine, Cisplatin and Other
	Prior Antiemetic Use	Binary	PD	Yes/No
	Chronic Condition Number	Count	IP/OP	NCI Comorbidity Index
	Concomitant Medication Number	Count	PD	≥ 0
	Prior IV Chemotherapy	Binary	OP	Yes/No
	Prior or Concomitant Radiation Therapy	Binary	IP/OP	Yes/No

OP: Outpatient, PD: Prescription Drug, Categ: Categorical, Enroll: Enrollment IV: Intravenous

3.2.4.3 Environment: Healthcare System

Healthcare system variables were coded using MarketScan data as follows:

- Chemotherapy setting is a categorical variable that describes the setting in which chemotherapy was received. While 46 settings exist in MarketScan, the main categories used were hospital-affiliated outpatient, physician-affiliated outpatient, and other.

3.2.4.4 Environment: External Environment

External environment variables were coded using MarketScan data as follows:

- Geographic setting was assessed as a binary variable (0=urban, 1=rural). Urban areas were those that are assigned a metropolitan statistical area (MSA) while rural areas were those that do not have an MSA. Assigning urban/rural status was based on the 2010 US Census Rural/Urban Classification. Metropolitan statistical area was derived in the dataset based on 5-digit employee ZIP code.
- Region was defined as a categorical variable (0=northeast, 1=north central, 2=south, 3=west, 4= north central, and 5=unknown). It is derived in the data set based on 5-digit employee ZIP code, to which we do not have access.

3.2.4.5 Population Characteristics Predisposing Characteristics

Predisposing characteristics were coded using MarketScan data as follows:

- Age was defined as the patient's age, in years, on the first day of newly initiating highly emetogenic, intravenous chemotherapy. Younger patients tend to be more adherent, likely because being under age 50 is a known risk factor for CINV. (4, 32, 34, 39, 43, 74) As a result, we dichotomized age in the CCAE population as younger commercial adults (18-49) and older commercial adults (50-64). In the Medicare Supplement population, patients were categorized as younger Medicare adult (65-74), middle aged Medicare adult (75-85), and older Medicare adult (85+).
- Sex was measured as a binary variable (0=male, 1=female).

3.2.4.6 Population Characteristics: Enabling Characteristics

Enabling characteristics were coded using MarketScan data as follows:

- Health insurance type was a categorical variable based on the plan type in which the patient is enrolled on the first day of newly initiating highly emetogenic, intravenous chemotherapy. This variable was coded the same in both CCAE and MCOB raw data and was coded as follows: 1 = basic/major medical, 2 = comprehensive, 3 = exclusive provider organization (EPO), 4 = health management organization (HMO), 5 = point of service (POS), 6 = preferred provider organization (PPO), 7 = POS with capitation, 8 = consumer-driven health plan (CDHP), and 9 = high deductible health plan (HDHP). Due to similarities in plan structure and administration and limited patient frequencies across some categories, we combined the CDHP and HDHP into a single category and created an "other" category consisting of basic/major medical, comprehensive, EPO, and POS with capitation. As some patients were missing health insurance type, a "missing" category was created.
- Insurance generosity was assessed both for medical benefit and prescription drug benefit. Insurance generosity-medical benefit was used as a proxy for copay / deductible for intravenously administered antiemetics. (166) Insurance generosity-prescription drugs was used as a proxy for copay / deductible for oral antiemetics. Insurance generosity was defined as the average proportion of patient cost sharing for all intravenous drugs in the inpatient and outpatient setting for medical benefit and all prescription drugs for prescription drug benefit in the six months prior to initiating highly emetogenic chemotherapy. Claims with "zero-dollar" total costs or negative copay, deductible, coinsurance, or net pay costs were dropped. The following thresholds were initially used: >0.8 = no / poor coverage, 0.20-0.80 = fair coverage, <0.20 = good coverage. However, after assessing category distributions, modifications were necessary. First, there were a limited number of patients in the Medicare Supplement population with "no/poor"

prescription drug coverage, so it was combined with "fair" in both populations and benefits for consistency. Second, we were unable to calculate insurance generosity for the prescription drug benefit for some patents in both populations because of a lack of prior drug fills. Because this was the case for over 1,000 CCAE patients, a "missing" category across both populations in both the medical and prescription drug benefit was created to maintain consistency. However, the frequency of the "missing" category was extremely small in the Medicare Supplement population, so it was combined with the "no/poor/fair" category in both populations for consistency. We combined "missing" with "no/poor/fair" as opposed to "good" because "missing" meant a lack of insurance usage, and thus any out-of-pocket cost maximums had likely not been met.

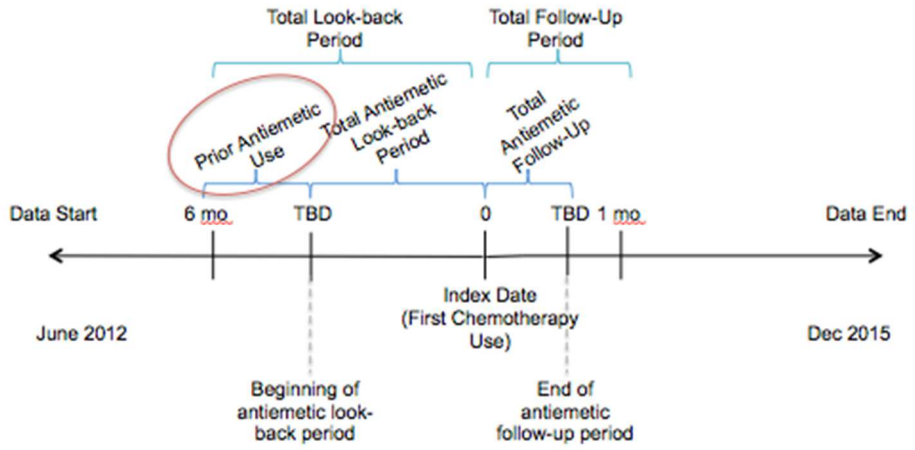
- Whether chemotherapy was administered in or out of network was coded as a binary variable (0=out of network, 1=in network). This was based on whether the network provider indicator associated with the new initiation of highly emetogenic chemotherapy claim was "yes" or "no" in the data set. A "missing" category was also included for patients for whom the network status was unknown. Because out-of-network chemotherapy administration is extremely expensive, it was also a proxy for financial toxicity. Ultimately, this variable was dropped from the model due to the lack of variation (more than 95% of patients were in-network).
- Year of Chemotherapy Administration was categorical and based on the year of the date of the chemotherapy administration claim (0=2013, 1=2014, 2=2015).
- Quarter of Chemotherapy Administration was coded as a categorical variable based on the month of the date of the chemotherapy administration claim (1=Quarter 1 (Jan-Mar), 2=Quarter 2 (Apr-Jun), 3=Quarter 3 (Jul-Sep), 4=Quarter 4 (Oct-Dec)).

3.2.4.7 Population Characteristics: Need Characteristics

Need characteristics were coded using MarketScan data as follows:

- Chemotherapy type was categorized based on whether the chemotherapy was anthracycline (doxorubicin, epirubicin, idarubicin) and cyclophosphamide–based (i.e., administered on the same day), cyclophosphamide only, anthracycline only, carmustine or other. These categories reflect chemotherapies that are considered highly emetogenic at certain surface area thresholds or in certain combinations (0=Anthracycline + Cyclophosphamide, 1=Anthracycline Only, 2=Cyclophosphamide Only, 3=Carmustine, 4=Other). Anthracycline only, cyclophosphamide only, and carmustine are surface-area-based dosing highly emetogenic chemotherapies.
- Prior antiemetic use was classified as any preventative or breakthrough antiemetic fills between the six months prior to the chemotherapy initiation date and the start of the antiemetic look-back period (Figure 3.3). It was denoted using an indicator variable (0=No, 1=Yes). Oral products were assessed in the prescription drug file and intravenous products were assessed in the outpatient file.

Figure 3.3 Prior Antiemetic Use Look-back Period



- The number of chronic conditions was coded as a count variable based on the National Cancer Institute Comorbidity Index, which combines the Klabunde comorbidity index, a validated algorithm for physician claims data specifically for patients with cancer, and the Charleson Comorbidity Index.(180-182) We used a look-back period of six months in both the inpatient and outpatient services files.
- Number of unique concomitant medications was calculated based on the number of prescription drugs filled in the 30 days prior to initiating highly emetogenic chemotherapy. Preventative and rescue treatment drugs were excluded. Number of unique concomitant medications was identified by NDC codes in the prescription drug file and mapped back to the Red Book.
- Prior chemotherapy use (IV) was coded as a binary variable (0=no, 1=yes). It was defined as any type of IV chemotherapy within the six months prior to initiating highly emetogenic chemotherapy. IV chemotherapy claims were identified in the outpatient services file using "J9XX" codes.
- Prior or concomitant radiation therapy was coded as a binary variable (0=no, 1=yes). It was defined as any exposure to radiation therapy six months prior to initiating highly emetogenic chemotherapy. Radiation J-codes in the outpatient services files and CPT codes in the inpatient services file were identified using the National Cancer Institute Radiation Therapy Lookup Tables.

3.2.5 Data Analysis – Aim 2

Analyses were conducted in the Commercially Insured and Medicare Supplement populations separately. First, we calculated descriptive statistics for each variable in the model. T-tests were used to assess differences in continuous outcome variables, and chi-squared tests were used to assess differences in categorical variables across antiemetic under-use and guideline-concordant use. Next, we assessed the effect of each variable on predicting antiemetic under-use versus guideline-concordant use while all other

covariates were held constant. As the outcome is binary, we used a modified Poisson regression. Exponentiation of the coefficients provides the relative risk. Though a Poisson distribution is traditionally used for count data, it may also be applied to binomial data, though the error term is over-estimated.(183) However, this can be corrected if the standard errors are calculated using sandwich estimates or Huber-White standard errors, and subsequently can directly estimate risks and relative risks. The general estimating equation used an independent correlation structure and log link function.

3.2.5.1 Sensitivity Analysis

To account for the fact that cheaper generic drugs might have a higher co-pay and/or deductible, we ran a sensitivity analysis excluding all oral drugs with a total cost of $50 when calculating the prescription drug insurance generosity measure.

3.2.5.2 Power Calculation

Based on existing studies, the difference in guideline-concordant use across types of CINV-risk ranged from 5 to 25%. Using cancer epidemiology in the US and rates of chemotherapy use, we estimated that approximately 5,000 patients will be at risk of CINV in the MarketScan® database. The number of patients in the study provided adequate power for calculating effect sizes of at least 5%.

3.3 Aim 3: To assess the most cost-effective antiemetic regimen for patients diagnosed with cancer and who are newly initiating highly emetogenic, intravenous chemotherapy.

3.3.1 Study Design and Comparators – Aim 3

Our aim was to prioritize ASCO and NCCN antiemetic guideline recommendations in patients initiating highly emetogenic chemotherapy by assessing the health and economic impact through conducting a cost-utility analysis. We used a Markov model built in MS Excel to evaluate the following antiemetic treatment comparators:

- NK1 (aprepitant), 5HT3A (first generation: ondansetron, granisetron, and dolasetron and second generation: palonosetron), and a corticosteroid (dexamethasone);
- NK1 (fosaprepitant), 5HT3A (first generation: ondansetron, granisetron, and dolasetron and second generation: palonosetron), and a corticosteroid (dexamethasone);

- NK1 (rolapitant), 5HT3A (first generation: ondansetron, granisetron, and dolasetron and second generation: palonosetron), and a corticosteroid (dexamethasone);
- Netupitant + palonosetron combination + dexamethasone;
- Olanzapine + palonosetron + dexamethasone;
- Olanzapine + aprepitant + 5HT3A + dexamethasone; and
- Olanzapine + fosaprepitant + 5HT3A + dexamethasone.

This model reflects only the first chemotherapy cycle because the guidelines of interest are only applicable to patients newly initiating highly emetogenic chemotherapy. Prescribers should use patients' experience from their first cycle to inform future antiemetic use.(19, 20, 52).

3.3.2 Time Horizon and Cycle - Aim 3

The time horizon for analysis was five days, including the acute phase (day 1) and delayed phase (days 2-5), which aligns with the timing of outcomes measured in clinical trials and guideline recommendations. Patients transitioned once a day, for a total of five cycles.

3.3.3 Perspective - Aim 3

The recommendations from the Panel on Cost-Effectiveness in Health and Medicine are considered the gold standard in cost-effectiveness methods in the US. In the 2016 update, the panel recommended that models should include both the healthcare perspective and societal perspective.(184) As such, we modeled from the 1) US healthcare perspective, which includes direct costs of medical care (reimbursed by payer or paid out-of-pocket by patient) and the 2) societal perspective, which includes all medical costs (direct and indirect) regardless of who is responsible for the cost or receives the benefit. Per the Panel's recommendations, we included an impact inventory, which lists the formal health care, informal health care, and non-health care sector consequences included for each perspective for this model (Table 3.5). Notably, indirect costs were limited to productivity because that was only estimate we could find for indirect costs for this population in the literature.

Because patients with cancer who are commercially insured often reach their out-of-pocket maximums, the results from the US healthcare perspective may be applicable to the US commercial payer

perspective. This is further supported by the fact that the main difference between the healthcare and commercial payer perspectives is the cost of the healthcare resource use associated with each health state, which would be modeled by reducing the total costs by a standardized percentage. This would not alter the ICER. In addition to having no out-of-pocket maximums, the reimbursement of the medical benefit and prescription drug benefit for patients covered by Medicare is different. Exploring the cost-effectiveness across guideline-concordant antiemetic options for patients initiating highly emetogenic chemotherapy in the Medicare population is an important area of future research.

Table 3.5 Impact Inventory*(184)

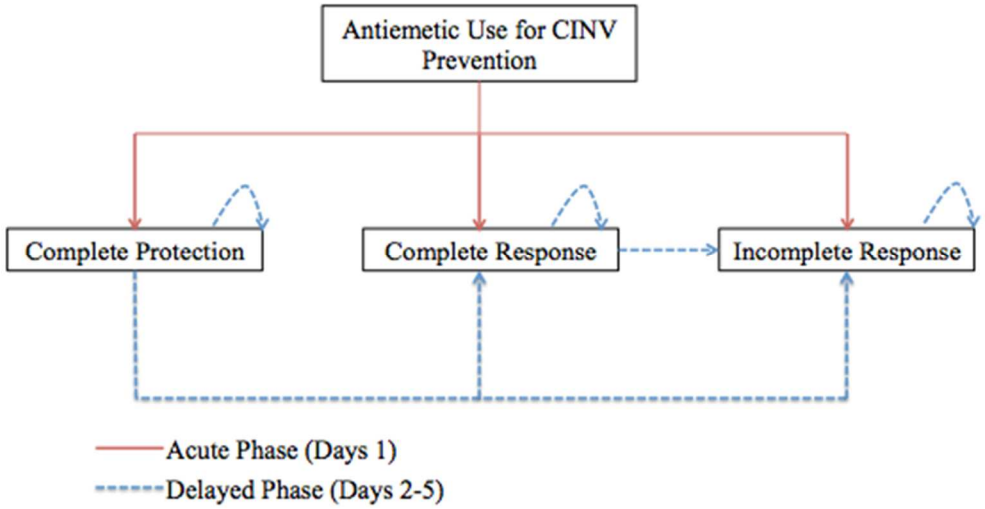
Sector	Type of Impact	Perspective	
		Healthcare Sector	Societal
Formal Health Care Sector			
Health	*Health Outcomes (Effects)*		
	CINV Events	X	X
	HRQoL	X	X
	Medical Costs		
	Paid by third-party payer	X	X
	Paid by patient, out-of-pocket	X	X
Non-Healthcare Sector			
Productivity	*Productivity*		
	Cost of unpaid lost productivity due to illness		X

*No inputs available on informal health care sector costs

3.3.4 Hypothetical Cohort, and Patient Flow - Aim 3

The hypothetical cohorts consist of 100,000 adults aged 18-65 with cancer who are being newly treated with single-day, highly emetogenic chemotherapy. The Markov model and how patients flow through it are described in Figure 3.4.(143, 144) In the acute phase (day 1), a patient may experience incomplete response (having emesis and/or using rescue medication), complete response (no emesis + no use of rescue medications), or complete protection (no emesis + no use of rescue medication + no significant nausea (Visual Analogue Scale score of <25 mm)). Notably, complete response and complete protection are modeled as two distinct, mutually exclusive health states with the difference being whether significant nausea is experienced. Subsequently, in the delayed phase (days 2-5), patients may remain in the same health state or transition to a worse health state (i.e., complete protection to complete response, complete protection to incomplete response, or complete response to incomplete response). This patient flow model and assumptions regarding phases of protection were utilized to provide consistency between our analysis and the two most recent cost effectiveness analyses assessing antiemetics.(143, 144)

Figure 3.4 Patient Flow for Patients Who Initiate High-CINV Risk Chemotherapy in A Markov Model(143, 144)



3.3.5 Clinical Inputs - Aim 3

3.3.5.1 Clinical Inputs - Source

As mentioned, efficacy measures for guideline-concordant antiemetic prescribing include the probability of having one of three response options: complete response, complete protection, or incomplete response. These transition probabilities, in addition to dosing and administration schedules (Table 3.6), were obtained from randomized clinical trials (Table 3.7 and 3.8). Many of the studies were used to seek Food and Drug Administration approval and supported "high quality of evidence" guideline recommendations by ASCO and/or NCCN. Trials were identified based on existing meta-analyses that were supplemented by a literature review. ((84, 85, 117, 118, 123, 124) The meta-analysis results were ultimately not used as inputs because the baseline effectiveness was not specified, involved several indirect comparisons, had inconsistent results across NK1 comparisons, combined various olanzapine strategies, and combined CINV risk groups in many olanzapine studies).

Table 3.6 Highly Emetogenic Chemotherapy – Acute and Delayed Emesis Prevention (Adapted from NCCN Guidelines)(19, 20, 52)

Acute (Day 1)	Delayed (Days 2-4)
• Aprepitant 125 mg PO once • 5HT3RA (Choose one) – Palonosetron .25 mg IV once – Granisetron 10 mg SQ once, or 2mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first CT dose Ondansetron 16-24 mg PO once, or 8-16 mg IV once – Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once	• Aprepitant 80 mg PO daily on days 2,3 • Dexamethasone 8 mg PO/IV daily on days 2,3,4
• Fosaprepitant 150 mg IV once • 5HT3RA (Choose one) – Palonosetron .25 mg IV once – Granisetron 10 mg SQ once, or 2mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first CT dose Ondansetron 16-24 mg PO once, or 8-16 mg IV once – Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once	• Dexamethasone 8 mg PO/IV daily on day 2, then dexamethasone 8 mg twice daily on days 2,3,4
• Rolapitant 180 mg PO once • 5HT3RA (Choose one) – Palonosetron .25 mg IV once – Granisetron 10 mg SQ once, or 2mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first CT dose – Ondansetron 16-24 mg PO once, or 8-16 mg IV once – Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once	• Dexamethasone 8 mg PO/IV twice daily on days 2,3,4
• Netupitant 300 mg/palonosetron 0.5 mg PO once • Dexamethasone 12 mg PO/IV once	• Dexamethasone 8 mg PO daily on days 2,3,4
• Olanzapine 10 mg PO once • Palonosetron .25 mg IV once • Dexamethasone 20 IV once	• Olanzapine 10 mg PO daily on days 2,3,4
• Aprepitant 125 mg PO • 5HT3RA (Choose one) – Palonosetron .25 mg IV once – Granisetron 10 mg SQ once, or 2mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first CT dose Ondansetron 16-24 mg PO once, or 8-16 mg IV once – Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once • Olanzapine 10 mg PO once	• Aprepitant 80 mg PO daily on days 2,3 (if aprepitant on day 1) • Dexamethasone 8 mg PO/IV daily on days 2,3,4 • Olanzapine 10 mg PO daily on days 2,3,4
• Fosaprepitant 150 mg IV once • 5HT3RA (Choose one) – Palonosetron .25 mg IV once – Granisetron 10 mg SQ once, or 2mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24-48 h prior to first CT dose Ondansetron 16-24 mg PO once, or 8-16 mg IV once – Dolasetron 100 mg PO once • Dexamethasone 12 mg PO/IV once • Olanzapine 10 mg PO once	• Aprepitant 80 mg PO daily on days 2,3 (if aprepitant on day 1) • Dexamethasone 8 mg PO/IV daily on days 2,3,4 • Olanzapine 10 mg PO daily on days 2,3,4

CT: Chemotherapy

Table 3.7 NK1 Randomized Clinical Trial Results in Adult Patients Initiating Highly Emetogenic Chemotherapy

			Complete Response			Complete Protection		
Trial	**Pt Number**	**Regimens***	**Acute %**	**Delayed %**	**Overall %**	**Acute%**	**Delayed %**	**Overall %**
2003 Chawla(185)	131	A+D+O	82%	73%	71%	79%	67%	64%
	126	D+O	71%	44%	44%	67%	41%	40%
2003 de Wit(186)	80	A+D+O	NA	NA	64%	NA	NA	NA
	84	D+O	NA	NA	49%	NA	NA	NA
2003 Hesketh (187)	260	A+D+O	89%	75%	73%	85%	66%	63%
	260	D+O	78%	56%	52%	75%	52%	49%
2003 Poli-Bigelli(188)	261	A+D+O	83%	68%	63%	80%	61%	56%
	263	D+O	68%	47%	43%	65%	40%	41%
2005 Warr(189)	433	A+D+O	76%	55%	51%	NA	NA	NA
	424	D+O	69%	49%	42%	NA	NA	NA
2006 Schmoll (113)	243	A+D+O	88%	74%	72%	NA	NA	NA
	241	D+O	79%	63%	61%	NA	NA	NA
2008 Herrington(190)	27	A+D+P	70%	59%	52%	NA	NA	NA
	16	D+P	56%	31%	31%	NA	NA	NA
2009 Roila(191)	327	C+D+O	92%	78%	78%	NA	NA	NA
	82	A+D+O	90%	76%	76%	NA	NA	NA
2009 Yeo(192)	62	A+O+D	72%	64%	47%	67%	56%	39%
	62	O+D	73%	58%	42%	73%	58%	42%
2010 Takahashi(193)	146	A+G+D	87%	73%	71%	84%	65%	62%
	150	G+D	83%	52%	50%	82%	44%	43%
2011 Grunberg (115)	1109	F+O+D	89%	74%	72%	NA	NA	NA
	1138	A+O+D	88%	74%	72%	NA	NA	NA
2013 Saito(194)	173	F+G+D	94%	65%	64%	90%	58%	58%
	167	G+D	81%	49%	47%	77%	46%	44%
2014 Aapro(195)	724	N+P+D	88%	77%	74%	82%	67%	64%
	725	P+D	85%	70%	67%	81%	60%	58%
2014 Hesketh(196)	135	N+P+D	99%	90%	90%	97%	84%	83%
	134	A+O+D	95%	89%	87%	90%	82%	78%
2014 Hu(197)	204	A+G+D	79%	74%	70%	NA	NA	NA
	207	G+D	79%	59%	57%	NA	NA	NA
2015 Rapoport (HEC)(198)	90	R+D+O	88%	64%	63%	52%	33%	30%
	91	D+O	67%	49%	47%	49%	24%	23%
2015 Rapoport (HEC1)(199)	264	R+G+D	84%	73%	70%	80%	66%	63%
	262	G+D	74%	58%	56%	69%	52%	50%

			Complete Response			Complete Protection		
Trial	**Pt Number**	**Regimens***	**Acute %**	**Delayed %**	**Overall %**	**Acute%**	**Delayed %**	**Overall %**
2015 Rapoport (HEC2) (199)	271	R+G+D	83%	70%	68%	82%	65%	63%
	273	G+D	79%	62%	60%	78%	58%	57%
2016 Ando(200)	48	A+D+P/G/ AZ	98%	88%	85%	NA	NA	NA
	45	F+D+P/G/AZ	98%	84%	82%	NA	NA	NA
2013 Wenzell(201)	20	A+P+D	75%	65%	65%	NA	NA	NA
	20	A+O+D	55%	45%	40%	NA	NA	NA

Incomplete Response = 1- Complete Response

A: Aprepitant F: Fosaprepitant R: Rolapitant N: Netupitant / Palonosetron Combination D: Dexamethasone G: Granisetron O: Ondansetron D: Dolasetron P: Palonosetron Dual: 5HT3A+Dex AZ: Azasetron

Table 3.8 Olanzapine Randomized Clinical Trial Results in Adult Patients Initiating Highly Emetogenic Chemotherapy (Adapted from Yang 2017)(124)

			Complete Response		
Trial	**Pt Number**	**Regimens***	**Acute %**	**Delayed %**	**Overall %**
Tan et al. 2009*(122)	121	O+Aza+D	94%	84%	84%
	108	Aza+D	94%	68%	68%
Navari et al.,2011(27)	121	O+P+D	97%	77%	77%
	120	A+P+D	87%	73%	73%
Mizukami et al., 2014(202)	22	O+D+5HT3A+A	100%	100%	100%
	22	D+5HT3A+ A	86%	16%	68%
Mukhopadhyay et al., 2015(86)	50	O+P+D	98%	96%	94%
	50	P+D	94%	42%	40%
Shumway et al., 2009(203)	8	O+P+D	75%	63%	44%
	9	A+P+D	44%	56%	20%
Babu et al., 2016 (120)	50	O+P+D	84%	77%	78%
	50	A+P+D	86%	73%	80%
Navari et al., 2016(28)	192	O+5HT3A+D+NK1	86%	67%	64%
	188	5HT3A+D+NK1	65%	52%	41%

*Denotes HEC and MEC mixed population O: Olanzapine A: Palonosetron D: Dexamethasone G: Granisetron Ond: Ondansetron Az: Azasetron

Table 3.9 Complete Response and Complete Protection Transition Probabilities- Base Case and Confidence Interval**

Complete Response (True)***	Overall -BC	LCI	UCI	Acute - BC	LCI	UCI	Delayed -BC	LCI	UCI
Fos+5HT3A+Dex	0.712	0.640	0.820	0.899	0.890	0.980	0.734	0.650	0.840
NEPA+Dex	0.767	0.740	0.900	0.900	0.880	0.990	0.790	0.770	0.900
Rol+5HT3A+Dex	0.678	0.630	0.700	0.842	0.830	0.880	0.702	0.640	0.730
Olanz+Palo+Dex	0.796	0.440	0.940	0.930	0.670	0.980	0.830	0.770	0.960
Fos/Apr+5HT3A+Dex+Olz*	0.900	0.641	1.000	0.950	0.859	1.000	0.917	0.672	1.000
Apr+5HT3A+Dex	0.681	0.400	0.870	0.849	0.550	0.980	0.712	0.450	0.890
Complete Protection	**Overall -BC**	**LCI**	**UCI**	**Acute - BC**	**LCI**	**UCI**	**Delayed -BC**	**LCI**	**UCI**
Fos+5HT3A+Dex*	0.578	0.520	0.636	0.896	0.806	0.986	0.664	0.520	0.730
NEPA+Dex	0.668	0.640	0.830	0.846	0.820	0.970	0.584	0.670	0.840
Rol++5HT3A+Dex	0.582	0.300	0.630	0.768	0.520	0.820	0.700	0.330	0.650
Olanz+Palo+Dex	0.612	0.300	0.830	0.833	0.520	0.970	0.653	0.330	0.840
Fos/Apr+5HT3A+Dex+Olz*	0.612	0.300	0.830	0.833	0.520	0.970	0.653	0.330	0.840
Apr+5HT3A+Dex	0.618	0.390	0.780	0.822	0.670	0.850	0.664	0.560	0.820

*Unless denoted, confidence intervals are based on the literature. Because complete protection rates for Fos+5HT3A+Dex only had one study, we calculated a range using +/-10% of the base case. There was only one study assessing the effectiveness of Apr+5HT3A+Dex+Olz, and we used the relative risk data versus the actual complete response probability to calculate the base-case input value. The actual complete response probability was used as the lower confidence interval.

**Incomplete response = 1- Complete Response

***Complete Response rate used in model = Complete Protection - Complete Response (True)

The following search strategy was used: ("generic name of drug") AND (("chemotherapy induced nausea and vomiting") OR ("CINV")).” Studies where results of patients initiating moderately emetogenic and highly emetogenic chemotherapy were combined unless there were no other studies examining the drug combination of interest. Because most strategies' evidence base included multiple randomized controlled studies, effect estimates for antiemetic efficacy were pooled and averaged for the base case clinical inputs (Table 3.9). The ranges of trial-specific estimates were used in the sensitivity analyses.

3.3.5.2 Clinical Inputs - Assumptions and Manipulations

The effectiveness of 5HT3As was assumed to be similar in the presence of NK1-based strategies.(59, 117, 118) This is because meta-analyses have demonstrated that the effectiveness of 5HT3As is similar across first-generation 5HT3As.(59) Furthermore, no study has directly compared the effectiveness of NK1s in the presence of palonosetron versus first-generation 5HT3A in a superiority trial, though meta-analyses have suggested that the effect is similar if not better in 5HT3As compared to palonosetron.(117, 118) We did not include adverse events in the model because they are minimal and similar across strategies.(18, 20)

The probabilities of entering each of the health states in the acute phase and overall phase were used as the transition probabilities for day 1 and day 5, respectively.(143, 144) Because trials typically do not report day-specific outcomes, we used linear interpolation between the acute and overall phase to calculate event probabilities for days 2-4. Additionally, olanzapine trials did not capture complete protection rates. We estimated olanzapine complete protection transition probabilities by averaging the pooled complete protection rates of each of the NK1-based strategies. Finally, there is only one study comparing the effectiveness of an NK1-based strategy with an olanzapine and NK1-based strategy, specifically aprepitant/fosaprepitant. While this study that found that the strategy with olanzapine (apr/fos+olz+5HT3A+dex) had statistically significant higher complete response and complete protection rates, the NK1-only strategy (apr/fos+5HT3A+dex) had much lower acute and overall complete response and complete protection rates than in other studies. To reflect the rest of the evidence base, we used the average pooled results of the aprepitant- and fosaprepitant-based strategies and the relative risk from this

trial to estimate the complete response and complete protection rates for the olanzapine-based strategy in the base case. The actual complete response value of the olanzapine-based strategy was used as the lower bound of the range of values in the probabilistic sensitivity analysis.

3.3.6 Cost Inputs - Aim 3

3.3.6.1 Cost Inputs - Source

Input costs were based on healthcare resource use associated with each health state and include the direct and indirect costs depending on the perspective. Input costs were identified through a literature review and listed in Table 3.10. Direct costs are the costs associated with any healthcare resource use including prophylactic antiemetics, rescue antiemetics, inpatient visits, outpatient visits, emergency department visits, and laboratory use. While there are many indirect costs (e.g., unpaid care-giver costs, transportation costs, social services costs, legal/criminal costs, education costs, etc.), we focused on productivity loss, as it is the only source of indirect costs we were able to identify in patients experiencing chemotherapy induced nausea and vomiting.(8, 10, 184, 204)

3.3.6.2 Cost - Assumptions and Manipulations

All costs were inflation-adjusted to 2016 dollars using the medical component of the Consumer Price Index. Given the short time horizon of this study (i.e., five days in the base-case), costs were not discounted. It was assumed that resource use among patients with complete response and complete protection was the same, as neither outcome had vomiting or used a rescue antiemetic. Because 5HT3As have multiple options with a wide range of costs, we used the median product cost (ondansetron generic) for the base case unless a 5HT3A is specified. We used the full range of 5HT3A product costs in the probabilistic sensitivity analysis. The cost of 10 mg of generic olanzapine was used for the base case, but +25% of the brand costs was used as the confidence interval. Rescue medications also have a wide range of options and costs, so we assumed that generic olanzapine and generic ondansetron were used for the base case. Again, the full range of product costs was used in the probabilistic sensitivity analysis. For other antiemetic products, +/-25% of the base case cost was used for the range. A full list of all antiemetic products and their associated costs are listed in Table 2.4.

Table 3.10 Direct and Indirect Costs Associated with Antiemetics and CINV (Inflation Adjusted to 2016 USD)

Direct Costs	Base Case	Range	
Preventative Antiemetic Use(15, 18)			
Aprepitant	$649.00	$486.75	$811.25
Fosaprepitant	$300.00	$225.00	$375.00
Netupitant	$632.00	$474.00	$790.00
Rolapitant	$610.50	$457.88	$763.13
Olanzapine	$10.00	$4.88	$80.78
All 5HT3A	$6.50	$1.10	$468.16
Dexamethasone	$3.59	$2.69	$4.49
Palonosetron	$228.80	$171.60	$286.00
CINV Event			
HCRU*(2, 8-10)	$1754.60	$1297.55	$2355.41
Rescue Medication Cost**(18)	$13.00	$6.50	$941.00
Indirect Costs			
Productivity(8, 10)	$332.74	$72.26	$593.21

*Inpatient and outpatient services **Olanzapine and ondansetron
5HT3A: Ondansetron, Dolasetron, Granisetron, Palonosetron

3.3.7 Utilities - Aim 3

3.3.7.1 Utility Inputs – Source

Utilities for complete protection, complete response, and incomplete response were obtained from previous studies involving patients whose clinical characteristics align with the hypothetical cohort used in this model, which is described in 3.3.1 (Table 3.11). Specifically, our cohort and the studies from which utilities were derived represent patients initiating chemotherapy for any cancer and assess utilities for our specific outcomes of interest.

3.3.7.2 Utility Inputs - Assumptions and Manipulations

Given that the model uses day lengths as a cycle, the outcome quality adjusted life days (QALD) was used in the model. However, results are presented in both QALYs and QALDs. QALDs are a variation of a common measure, QALYs. It was assumed that utility values for a QALY would be the same for a quality-adjusted life day, and as such, QALDs were calculated by multiplying the number of days spent in each health state by the utility value. QALDs were converted into QALYs by dividing QALD by 365 days. Utilities were not discounted given the five-day time horizon. While utility values established in

prior cost-effectiveness studies were used for the base-case, probabilistic sensitivity analysis used the full range of potential utility values (Table 3.11).

Table 3.11 Proposed Utility Values

State	Base Case(58, 144)	Range (145, 205-207)*
Complete Protection	0.90	(.79-1.0)
Complete Response	0.70	(.60-.76)
Incomplete Response	0.20	(.18-0.50)

*Studies used to establish the range of utility values for the base-case.

3.3.8 Analysis –Aim 3

The primary outcomes include the costs (US dollars in 2016), Quality Adjusted Life Day, and Quality Adjusted Life Years (QALYs) for all guideline-concordant treatment strategies over the analytic horizon. These metrics allow us to compare the economic and health impact of both strategies and, if indicated (i.e., in the absence of strong dominance), to identify which is more efficient via an incremental cost effectiveness ratio (ICER) (i.e., cost/QALY). Because we compared multiple treatment strategies, we could not simply calculate the ICER and compare it to a predetermined willingness-to-pay threshold (i.e., the traditional $50,000/QALY for the base-case).(208) Instead, we used the following process:

- Rank alternatives by costs from lowest to highest;
- Calculate incremental cost-effectiveness ratios;
- Drop dominated strategy(ies);
- Drop extended dominated strategy(ies); and
- Re-rank and re-calculate ICERs.(209, 210)

3.3.8.1 Sensitivity Analyses - Aim 3

We conducted three types of sensitivity analyses from the perspective of the US Healthcare System. First, we conducted a probabilistic sensitivity analysis using Oracle's Crystal Ball Excel plugin to assess the impact of uncertainty of all clinical, cost, and utility inputs using the minimum and maximum values. Specifically, a Monte Carlo simulation with 1000 trials was conducted across the ranges of all input variables. Beta distributions were used for clinical inputs and gamma distributions were used for cost and utility inputs. Because willingness-to-pay is a fluid concept, we assessed cost-

effectiveness at a variety of thresholds ranging from $0-$250,000.(184) Higher willingness-to-pay thresholds may be acceptable for life-saving treatments such as chemotherapy or immunotherapies. These results were displayed using cost effectiveness acceptability curves, which show different probabilities of cost effectiveness at differing willingness-to-pay levels. Second, we conducted one-way sensitivity analyses for each input variable to identify which variables have the largest impact on cost effectiveness, holding all other variables at their base case values. Finally, we conducted scenario analyses by removing the olanzapine strategies due to clinicians' hesitancy toward using olanzapine given its safety concerns as well as the limited evidence base supporting this strategy.

CHAPTER 4: RESULTS

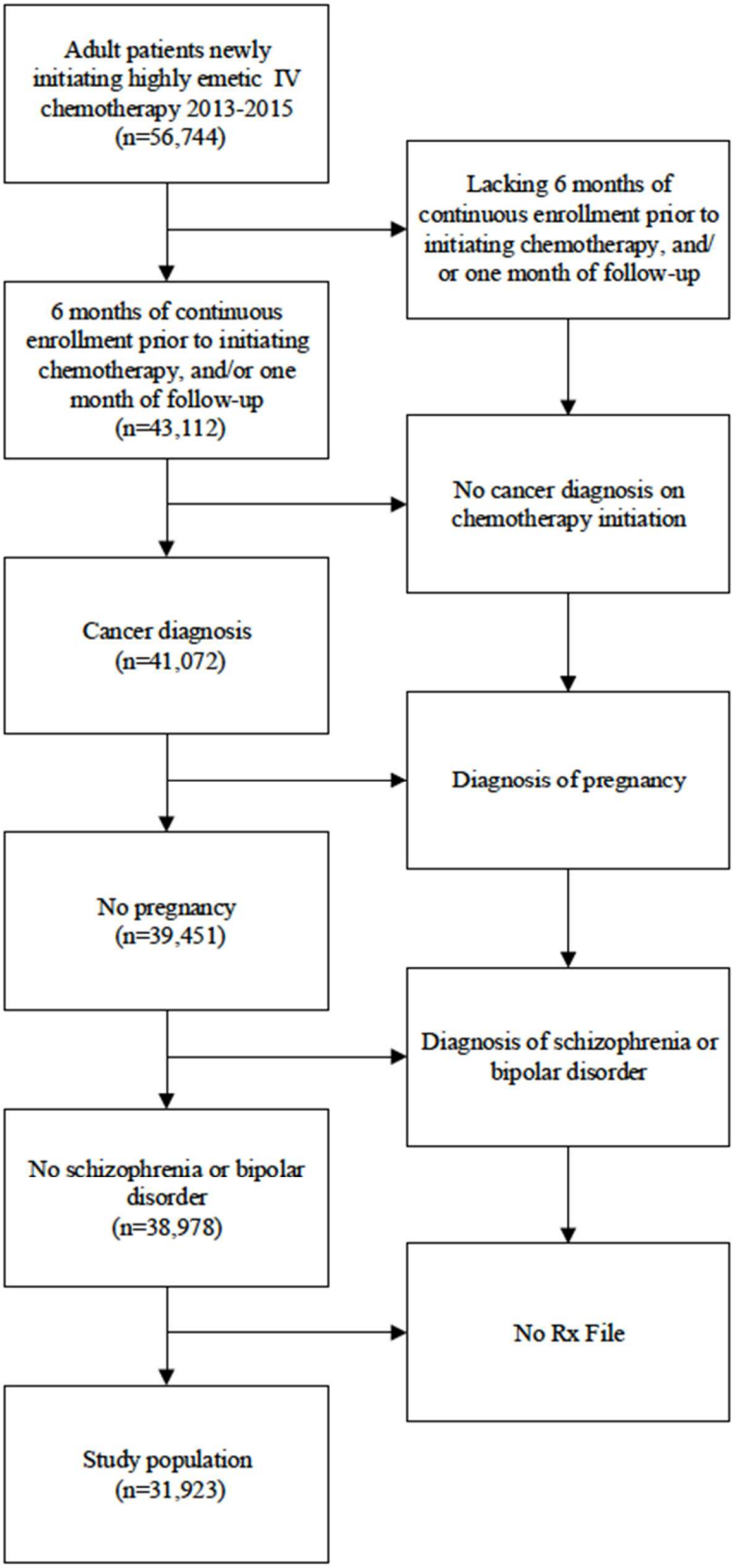
4.1 Aim 1 Results

4.1.1 Aim 1 Results-CCAE Population

4.1.1.1 Aim 1 – CCAE Population: Cohort Selection

The inclusion / exclusion criteria used to develop our CCAE study cohort is described in Figure 4.1. We identified 56,744 adult patients (age 18-64) initiating highly emetogenic chemotherapy between 2013 and 2015. Of these patients, 43,112 had the required six months of continuous enrollment prior to initiating chemotherapy and one-month follow-up. Subsequently, 41,072 patients had a cancer diagnosis on the claim associated with the highly emetogenic chemotherapy administration. We then excluded 1,591 patients for being pregnant and 473 for having a diagnosis of either schizophrenia or bipolar disorder. Finally, 7,055 patients who lacked prescription drug data were excluded. The final study population consisted of 31,923 patients.

Figure 4.1 Consort Diagram for CCAE Study Cohort Creation



4.1.1.2 Aim 1 – CCAE Population: Primary Characterization: Antiemetic Fills in the Pre-period

Approximately 97% of patients (N=31,047) receiving highly emetogenic intravenous chemotherapy filled at least one antiemetic drug, with a median of three unique products (Figure 4.2); number of antiemetic filled by class by patient is presented in the Appendix 3. Dexamethasone, 5HT3A, NK1, and rescue therapies had at least one fill for 85%, 88%, 58%, and 68% of patients (Figure 4.3). The number of patients with at least one olanzapine fill in the pre-period was negligible at <1%.

Of the 119,728 antiemetic claims, aprepitant and fosaprepitant were the primary NK1s filled (12% and 88%, respectively), with 0.2% NEPA fills and no rolapitant fills. Among 5HT3As, there were a higher proportion of second-generation 5HT3A, palonosetron (67%) versus first-generation 5HT3As (33%) fills, and there were limited dolasetron fills (<1%) (Figure 4.4). Preventative products were more likely to be intravenously administered (61%) as opposed to orally administered (39%) (not displayed). Out-of-pocket costs were generally low across preventative antiemetics, with IV products having $0 median out-of-pocket costs (Table 4.1). Notably, the oral NK1, NEPA, had a median out-of-pocket cost of $52.11.

Figure 4.2 Number of Unique Antiemetic Products Filled/Administered in the Pre-Period (N=31,923 Patients)

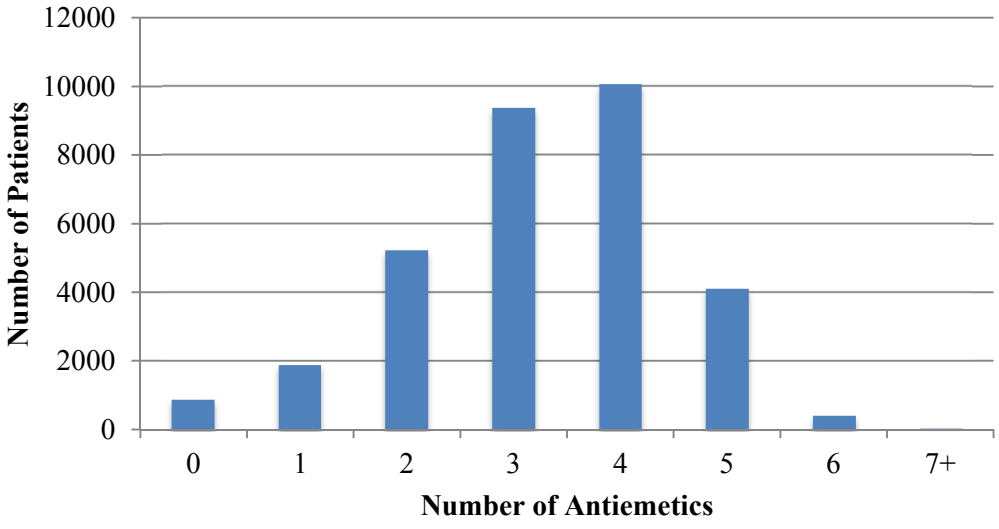
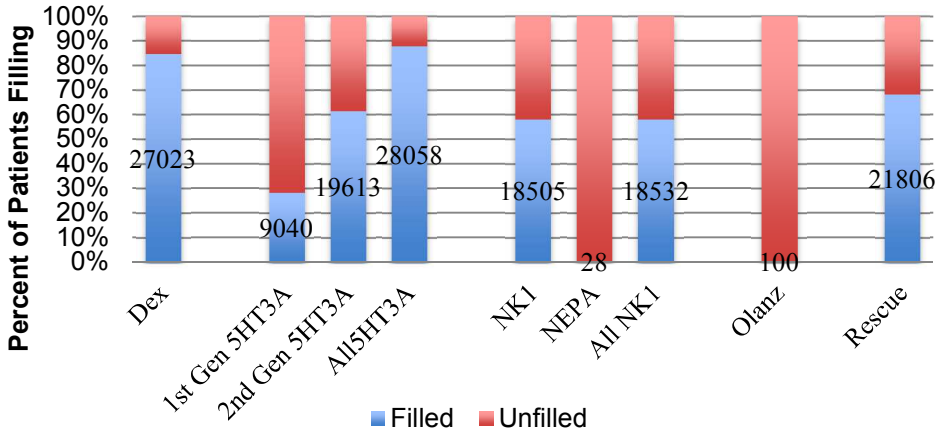


Figure 4.3 Percent of Patients Using At Least One Antiemetic Among All Patients Initiating Highly Emetogenic Chemotherapy



First Generation 5HT3A: Ond, Gran, Dol Second Generation 5HT3A: Palo
NK1: Aprep, Fos, Rol, NEPA (NK1+5HT3A Combo)

Figure 4.4 Number of Products Filled by Class (N=119,728 Antiemetic Claims)

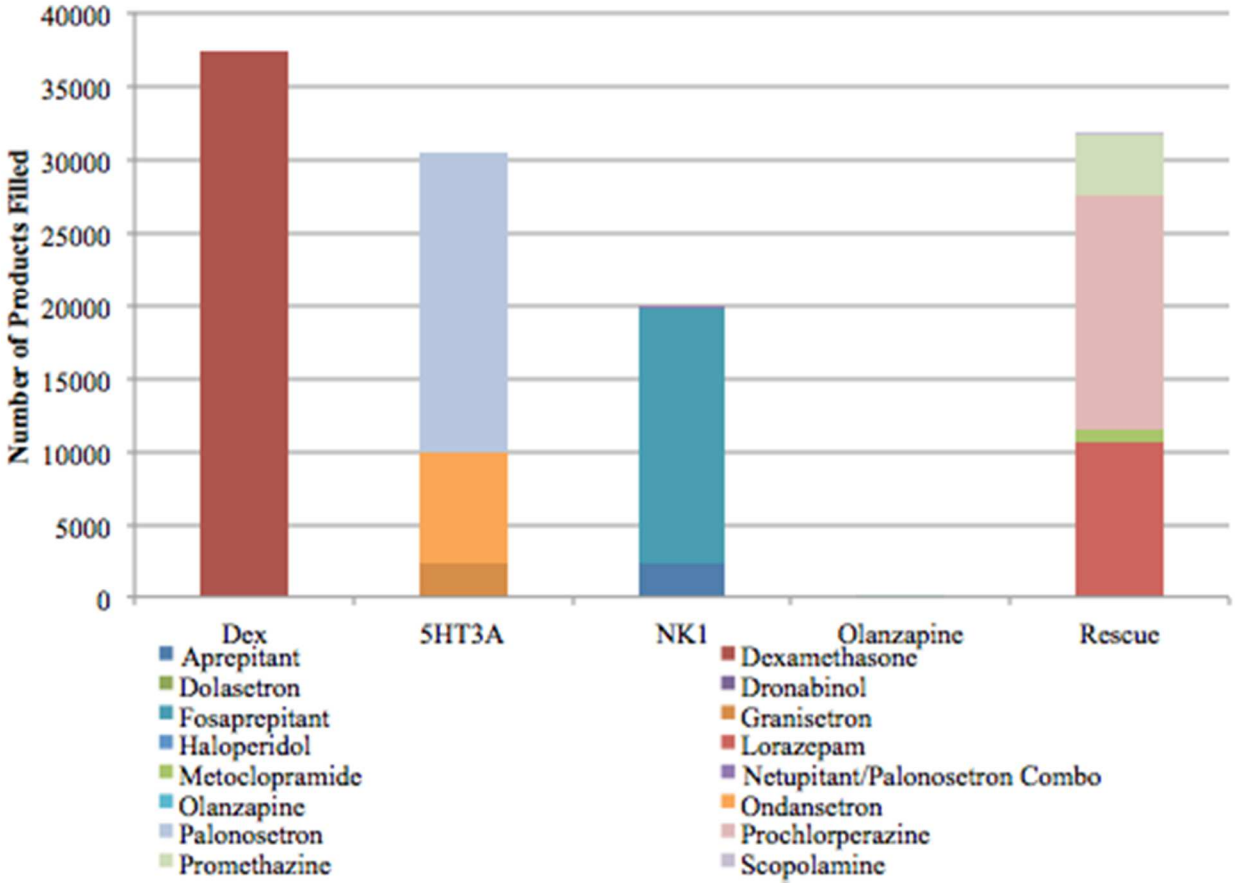


Table 4.1 Total and Out-of-Pocket Costs for Preventative and Rescue Antiemetics*

		Transactional Cost (2016 USD$)				Out-of Pockets (2016 USD$)			
Admin	**Antiemetic**	**Mean**	**Std**	**Median**	**IQR Ranger**	**Mean**	**STD**	**Median**	**IQR**
					Corticosteroid				
IV	Dex	20.71	316.03	2.47	5.10	0.71	26.15	0.00	0.00
Oral	Dex	10.50	52.83	6.33	8.57	5.07	6.57	4.36	6.87
					NK1				
Oral	Apr	538.93	360.10	447.66	146.10	53.22	74.93	39.24	47.70
IV	Fos	489.57	409.78	330.27	273.02	13.30	55.64	0.00	0.00
Oral	NEPA	604.37	302.47	519.84	17.55	84.34	108.65	52.11	92.47
					5HT3A - First Generation				
IV	Dol	46.07	31.91	51.01	63.23	3.99	6.92	0.00	11.98
Oral	Dol	598.10	847.49	314.57	242.11	48.90	16.76	49.05	21.80
IV	Gran	58.57	171.58	14.73	51.50	2.56	21.70	0.00	0.00
Oral	Gran	499.82	582.21	290.92	759.84	35.11	54.02	10.90	53.00
IV	Ond	51.64	158.10	9.40	44.86	1.04	9.79	0.00	0.00
Oral	Ond	51.83	343.34	5.00	37.98	0.95	6.89	0.00	0.00
					5HT3A-Second Generation				
IV	Pal	467.51	606.12	319.81	274.97	12.88	51.11	0.00	0.00
Oral	Pal	692.98	486.23	428.45	718.97	91.42	113.35	54.50	80.25
					Atypical Antipsychotic				
Oral	Olanz	37.11	56.24	12.09	33.52	5.52	5.96	4.98	8.40
					Rescue Medications (Dopaminergic Antagonists, Cannabinoids, Benzodiazepines, Other)				
Oral	Dron	397.83	340.89	293.93	270.43	20.90	64.70	10.60	7.06
IV	Halo	16.30	0.70	16.30	0.99	0.00	0.00	0.00	0.00
Oral	Halo	8.20	6.57	5.37	9.49	5.07	4.28	5.36	5.68
IV	Loraz	11.67	165.90	1.24	3.39	0.17	1.28	0.00	0.00
Oral	Loraz	8.35	21.40	3.86	7.01	4.46	4.50	2.99	4.38
IV	Meto	11.82	19.38	3.37	17.35	0.13	0.52	0.00	0.00
Oral	Meto	5.88	4.44	4.57	3.75	4.16	3.24	4.12	3.78
IV	Proch	27.29	31.68	13.12	40.17	1.76	10.75	0.00	0.00
Oral	Proch	9.53	18.20	6.28	5.55	5.30	4.16	4.82	4.85
IV	Prom	15.05	23.93	3.64	11.98	0.51	1.93	0.00	0.00
Oral	Prom	15.07	33.73	7.43	8.62	6.39	16.73	5.33	6.34
Oral	Scop	100.14	66.45	74.87	131.51	35.16	29.13	31.80	28.85

*We identified some "fosaprepitant" claims in the prescription drug file even though fosaprepitant is administered intravenously. We excluded these claims from the cost analysis.

Apr: Aprepitant, Dex: Dexamethasone, Dol: Dolasetron, Dron: Dronabinol, Fos: Fosaprepitant, Gran: Granisetron, Hal: Haloperidol, Loraz: Lorazepam, Meto: Metoclopramide, NEPA: Netupitant/Palonosetron Como, Olanz: Olanzapine, Ond: Ondansetron, Palo: Palonosetron, Proch: Prochlorperazine, Prom: Promethazine, Scop: Scopolamine

IQR: Interquartile Range

4.1.1.3 Aim 1 - CCAE Population: Secondary Characterization: NK1 Fills in the Post-period

NK1 fills in the five days following first intravenous highly emetogenic chemotherapy administration (i.e., excluding day of intravenous highly emetogenic chemotherapy administration) was minimal. Of the 18,863 fills in the post-period, only 717 were for NK1 (3.8%). This translated to less than 2% of patients filling an NK1 in the period.

4.1.1.4 Aim 1 - CCAE Population: Guideline Concordance

Approximately 49% of patients filled antiemetic regimens that are considered under-use by guidelines (Figure 4.5). Of concordant strategies, 0.19% consisted of olanzapine+ palonosetron+ dexamethasone (Not Displayed). The most common reason for under-use was not filling an NK1 (N=85%). Interestingly, among the 58% of patients filling an NK1, 87% were concordant. The most common reason for discordance among patients who filled an NK1 was lacking a dexamethasone fill. Among those who filled at least one, second-generation 5HT3A, the concordance rate was 65% versus 41% among those who filled at least one first-generation 5HT3A.

Among patients initiating anthracycline + cyclophosphamide regimens and non-surface-area-based IV HEC, guideline under-use decreased to 35% and 39%, respectively (Figure 4.6). For surface-area-based chemotherapies, under-use was high at 69% for anthracycline only regimens and 78% for cyclophosphamide therapies.

Figure 4.5 Percentage of Patients Filling Guideline Concordant Preventative Antiemetic Strategies

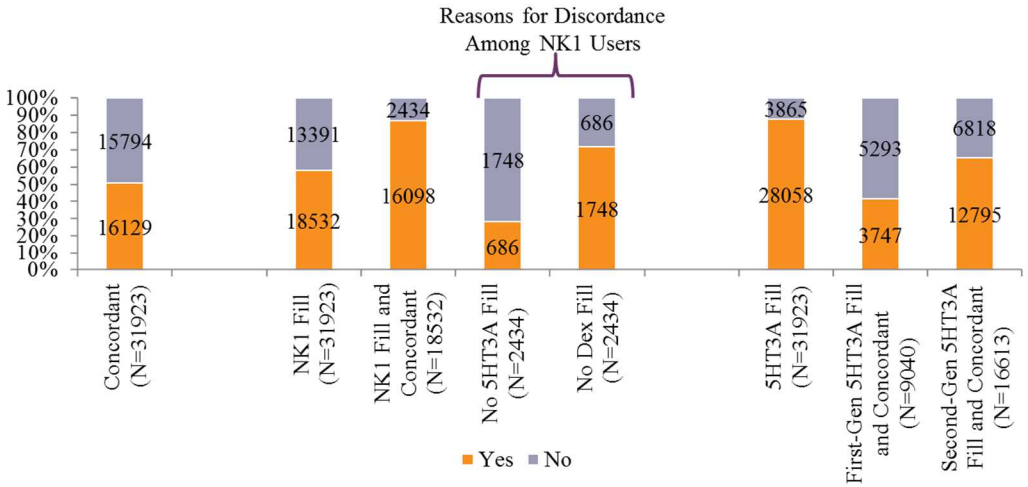
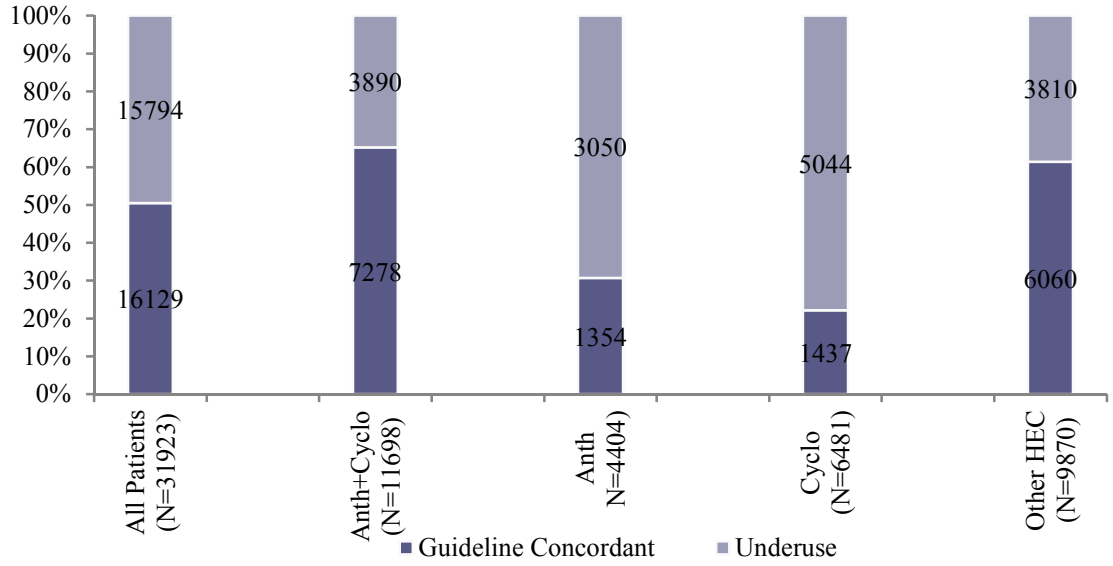


Figure 4.6 Chemotherapy Type Concordance Versus Under-use of Antiemetic Strategies by Chemotherapy Type



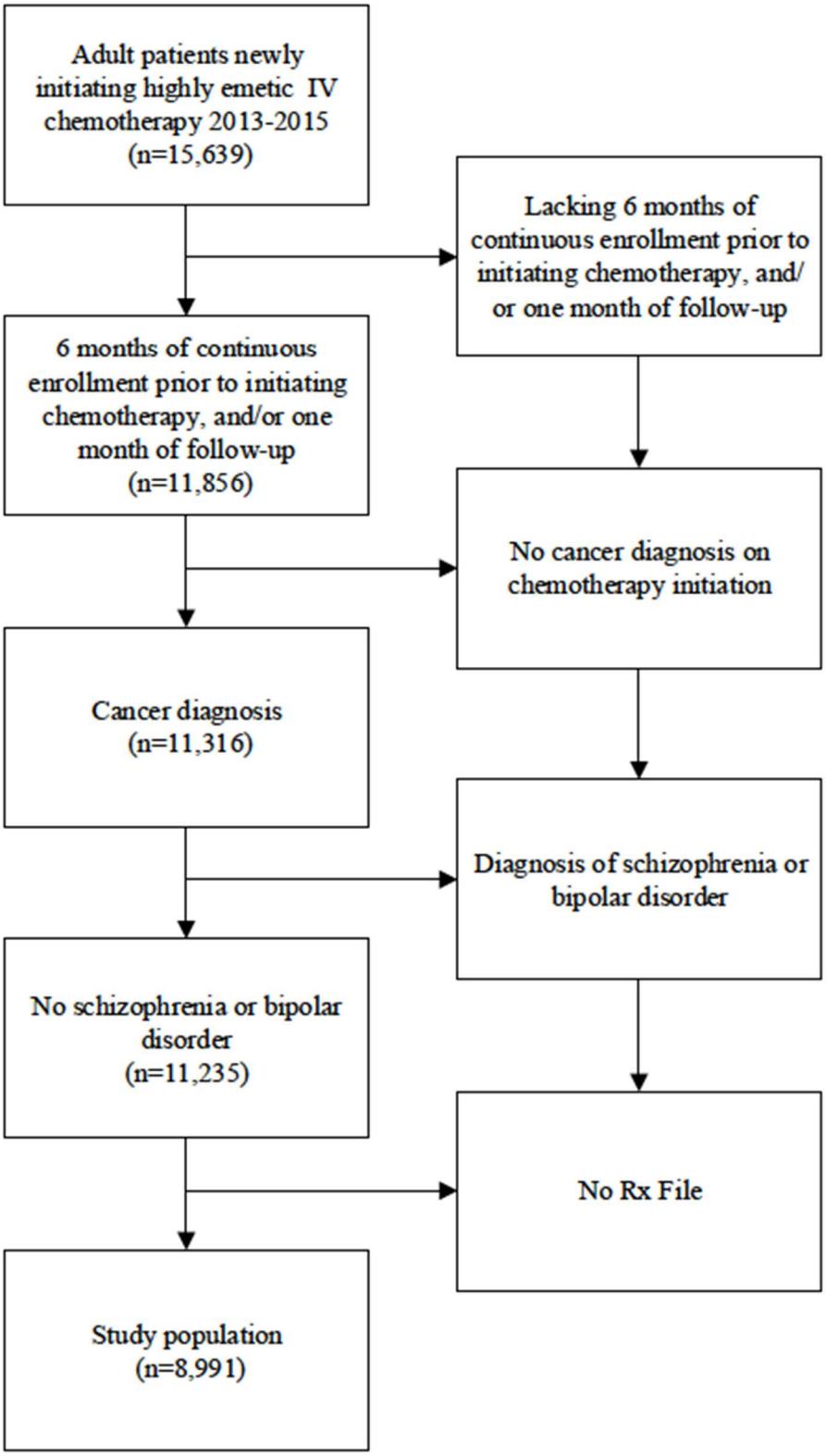
AC = Cyclophosphamide + Anthracycline (doxorubicin, epirubicin, idarubicin) ON THE SAME DAY
Surface Area Chemotherapies = Anthracycline and Cyclophosphamide
Other HEC: Given the limited frequencies (<1%) of carmustine, dacarbazine, mechlorethamine, streptozocin, and ifosfamide, we grouped them together with cisplatin (76%).

4.1.2 Aim 1 Results-Medicare Supplement Population

4.1.2.1 Aim 1 – Medicare Supplement Population: Cohort Selection

The inclusion / exclusion criteria used to develop our Medicare Supplement study cohort is described in Figure 4.7. We identified 15,639 adult patients (aged 65 and older) initiating highly emetogenic chemotherapy between 2013 and 2015. Of these patients, 11,856 had the required six months of continuous enrollment prior to initiating chemotherapy and one-month follow-up. Subsequently, 11,316 patients had a cancer diagnosis on the claim associated with the highly emetogenic chemotherapy administration. After excluding 81 patients with a diagnosis of either schizophrenia or bipolar disorder and 2,244 patients who lacked prescription drug data the final study population consisted of 8,991 patients.

Figure4.7 Consort Diagram for Medicare Supplement Study Cohort Creation



4.1.2.2 Aim 1 – Medicare Supplement Population: Primary Characterization: Antiemetic Fills in the Pre-period

Approximately 93% of patients (N=31,047) receiving highly emetogenic intravenous chemotherapy filled at least one antiemetic drug, with a median of three unique products (Figure 4.8); number of antiemetic filled by class per patient is presented in Appendix 3. Dexamethasone, 5HT3A, NK1, and rescue therapies had at least one fill for 72%, 72%, 39%, and 59% of patients (Figure 4.9). Less than 1% of patients had at least one olanzapine fill.

Of the 25,801 antiemetic claims, aprepitant and fosaprepitant were the only types of NK1s filled (14.58% and 85.42% of NK1 use, respectively); there were no NEPA and rolapitant fills. 5HT3As, there were a higher proportion of second-generation 5HT3A, palonosetron (72%) versus first-generation 5HT3As (28%) fills, and there were limited dolasetron fills (<1%) (Figure 4.10). Preventative products were more likely to be intravenously administered (60%) as opposed to orally administered (40%) (not displayed). Out-of-pocket costs were generally low across preventative antiemetics, with IV products having $0 median out-of-pocket costs (Table 4.2). While proportion of out-of-pocket costs for oral dexamethasone and oral olanzapine is high (>50%), their total transactional median costs are nominal at less than $15.00.

Figure 4.8 Number of Antiemetics Filled/Administered in the Pre-Period (N=8,991)

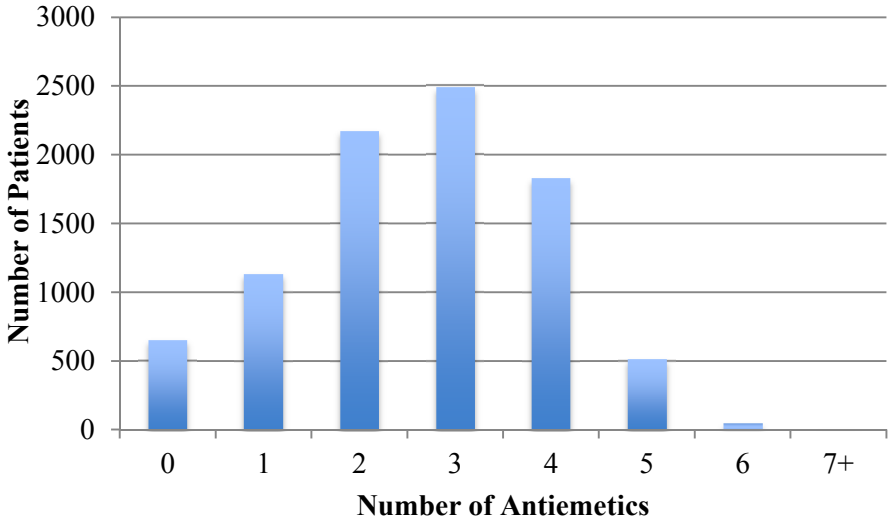
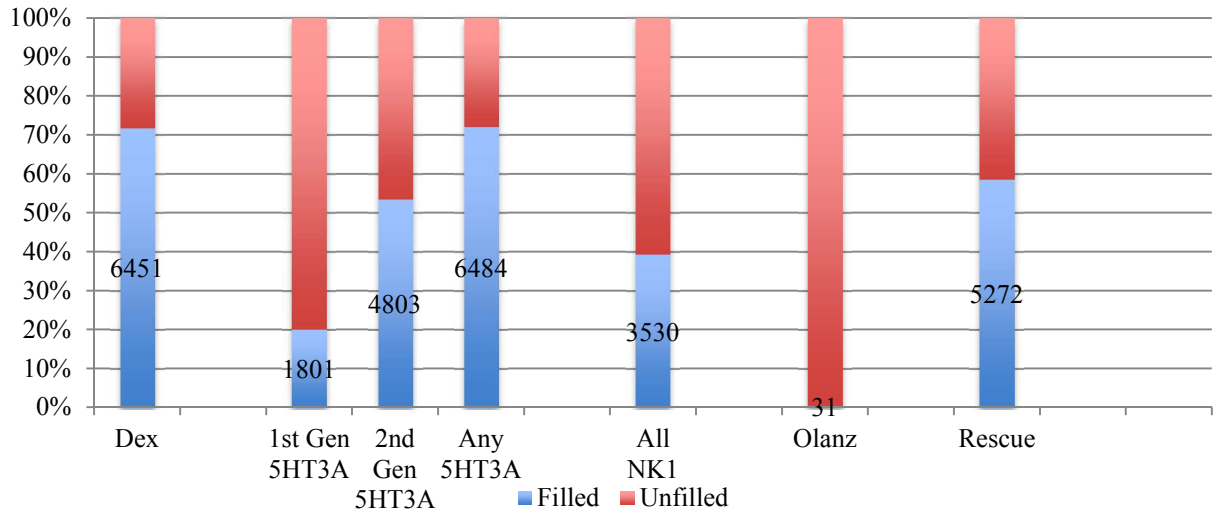


Figure 4.9 Percent of Patients Using At Least One Antiemetic Among All Patients (N=8,991)



First Generation 5HT3A: Ond, Gran, Dol Second Generation 5HT3A: Palo
NK1: Aprep, Fos, Rol, Palo (NK1+5HT3A Combo

Figure 4.10 Percent of Patients Using At Least One Antiemetic Among All Patients Initiating Highly Emetogenic Chemotherapy (N=25,801)

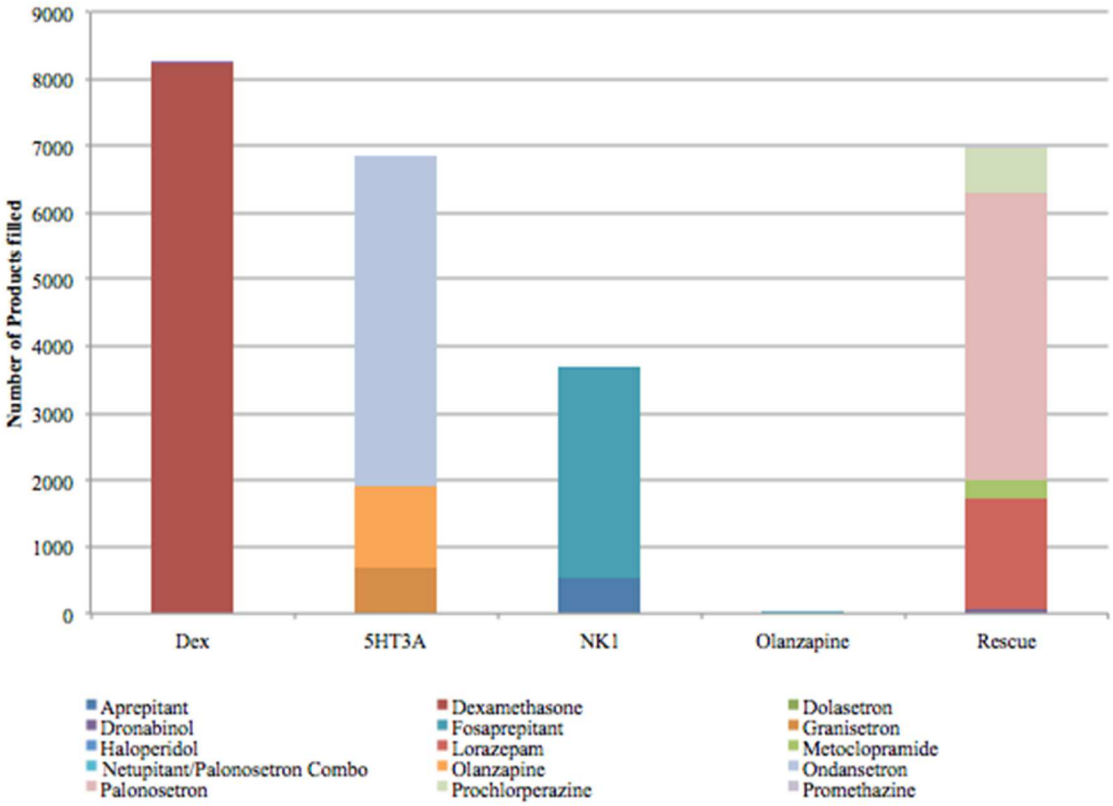


Table 4.2 Total and Out-of-Pocket Costs for Preventative and Rescue Antiemetics*

		Transactional Cost (2016 USD$)				Out-of-Pocket (2016 USD$)			
Admin	**Antiemetic**	**Mean**	**Std**	**Median**	**IQR Ranger**	**Mean**	**STD**	**Median**	**IQR**
				Corticosteroid					
IV	Dex	64.13	743.69	1.65	1.82	1.75	33.21	0.00	0.05
Oral	Dex	11.73	110.27	5.58	6.74	4.45	5.40	3.52	4.87
				NK1					
Oral	Apr	512.43	283.27	445.34	90.52	43.95	51.15	35.97	32.70
IV	Fos	424.52	718.83	276.40	50.35	11.52	42.57	0.00	5.62
				5HT3A - First Generation					
IV	Dol	11.91	.	11.91	0.00	0.00	.	0.00	0.00
IV	Gran	50.75	103.50	6.48	25.37	1.24	5.41	0.00	0.19
Oral	Gran	576.04	576.37	410.33	793.44	45.95	95.59	11.99	47.63
IV	Ond	85.60	788.04	2.66	15.17	0.74	10.43	0.00	0.03
Oral	Ond	108.57	652.78	4.33	11.52	1.20	4.61	0.00	0.06
				5HT3A - Second Generation					
IV	Palo	365.36	1015.13	208.56	71.89	8.91	23.60	0.00	4.24
Oral	Palo	812.58	483.37	840.75	842.56	63.97	43.12	64.34	74.20
				Atypical Antipsychotic					
Oral	Olanz	89.52	188.63	14.35	46.89	12.34	14.05	9.09	7.66
Rescue Medications (Dopaminergic Antagonists, Cannabinoids, Benzodiazepines, Other)									
Oral	Dron	349.52	197.23	301.70	205.25	28.18	78.99	10.60	12.23
Oral	Halo	12.54	12.04	6.97	4.96	7.71	4.90	6.97	0.97
IV	Loraz	4.39	16.59	0.77	0.59	0.04	0.13	0.00	0.01
Oral	Loraz	6.52	9.38	3.64	4.44	3.90	4.10	2.84	3.74
IV	Meto	10.36	13.35	1.20	22.52	0.76	2.21	0.00	0.02
Oral	Meto	6.90	6.36	5.19	4.07	4.26	3.21	4.12	4.00
IV	Proch	6.96	4.50	5.47	8.22	0.75	1.63	0.00	1.09
Oral	Proch	8.63	12.80	5.67	4.78	4.56	3.77	4.25	4.20
IV	Prom	8.72	13.33	2.62	10.58	0.01	0.04	0.00	0.00
Oral	Prom	15.84	39.40	7.34	7.45	6.30	6.88	5.45	5.64
Oral	Scop	114.84	113.53	68.29	110.74	22.49	20.71	18.80	24.03

*We identified some "fosaprepitant" claims in the prescription drug file even though fosaprepitant is administered intravenously. We excluded these claims from the cost analysis.
Apr: Aprepitant, Dex: Dexamethasone, Dol: Dolasetron, Dron: Dronabinol, Fos: Fosaprepitant, Gran: Granisetron, Hal: Haloperidol, Loraz: Lorazepam, Meto: Metoclopramide, NEPA: Netupitant/Palonosetron Como, Olanz: Olanzapine, Ond: Ondansetron, Palo: Palonosetron, Proch: Prochlorperazine, Prom: Promethazine, Scop: Scopolamine
IQR: Interquartile Range

4.1.2.3 Aim 1 - Medicare Supplement Population: Secondary Characterization: NK1 Fills in the Post-period

NK1 fills in the five days following first intravenous highly emetogenic chemotherapy administration (i.e., excluding day of intravenous highly emetogenic chemotherapy administration) was minimal. Of the 3,211 fills in the post-period, only 125 were for NK1 (3.9%). This translated to less than 2% of patients filling an NK1 in the period.

4.1.2.4 Aim 1 - Medicare Supplement Population: Guideline Concordance

Approximately 68% of patients filled antiemetic regimens that are considered under-use by guidelines (Figure 4.11). The most common reason for under-use was not filling an NK1 (N=89%). Interestingly, among the 39% of new chemotherapy users who filled an NK1, 80% were concordant. Of concordant strategies, 0.25% consisted of olanzapine+ palonosetron+ dexamethasone (not displayed). The most common reason for discordance among patients who filled an NK1 was lacking a dexamethasone fill. Among those who filled at least one, second-generation 5HT3A, the concordance rate was 50% versus 29% among those who filled at least one first-generation 5HT3A.

Among patients initiating anthracycline + cyclophosphamide regimens and non-surface-area-based IV HEC, guideline under-use decreased to 61% and 54%, respectively (Figure 4.12). For surface-area-based chemotherapies, under-use was high at 85% for anthracycline only regimens and 87% for cyclophosphamide therapies.

Figure 4.11 Percentage of Patients Filling Guideline Concordant Preventative Antiemetic Strategies

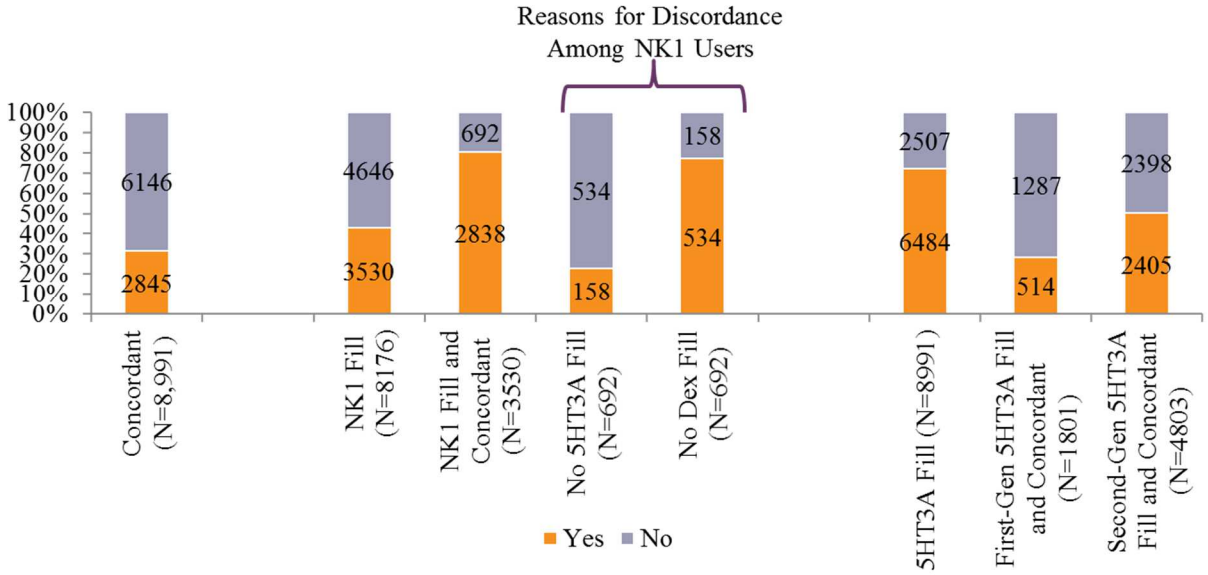
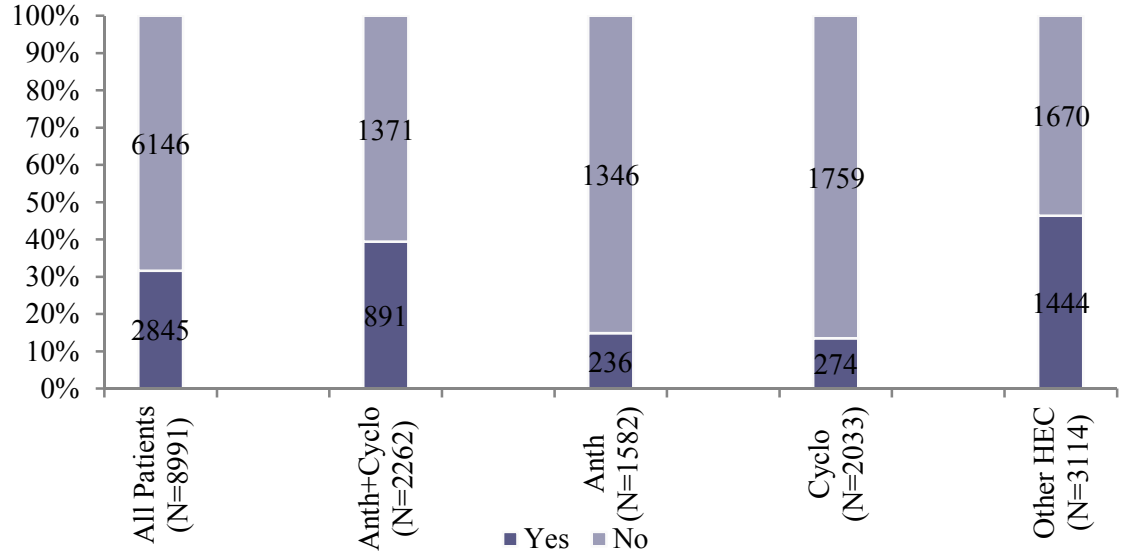


Figure 4.12 Chemotherapy Type Concordance Versus Under-use of Antiemetic Strategies by Chemotherapy Type



AC = Cyclophosphamide + Anthracycline (doxorubicin, epirubicin, idarubicin) ON THE SAME DAY
Surface Area Chemotherapies = Anthracycline and Cyclophosphamide
Other HEC: Given the limited frequencies (<1%) of carmustine, dacarbazine, mechlorethamine, streptozocin, and ifosfamide, we grouped them together with cisplatin.

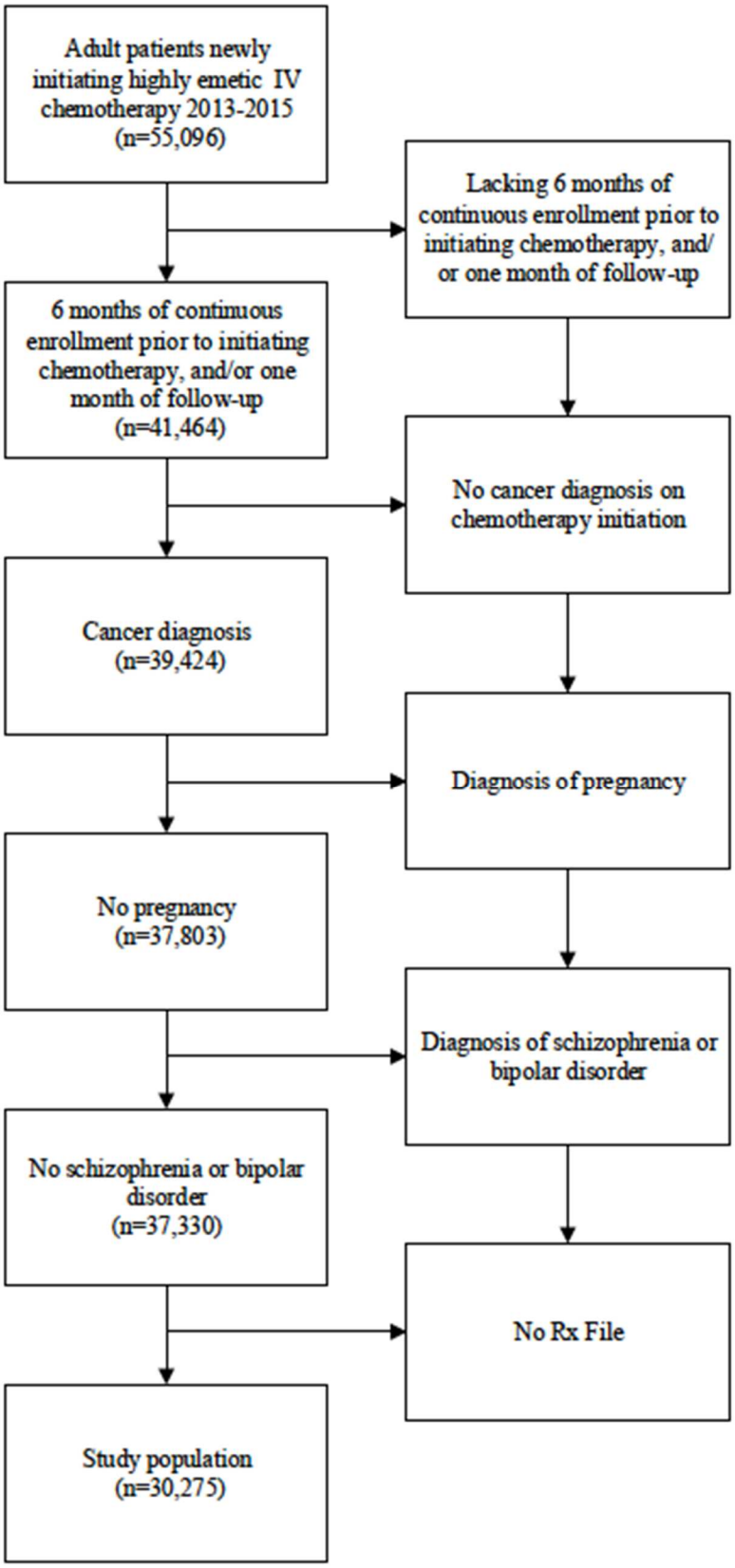
4.2 Aim 2 Results

4.2.1 Aim 2 Results - CCAE Population

4.2.1.1 Aim 2 – CCAE Population: Cohort Selection

Aim 2 used the same study cohort as Aim 1 except that patients had to initiate highly emetogenic chemotherapy on or before October 2015 (as opposed to on or before December 2015). The inclusion / exclusion criteria used to develop our CCAE study cohort is described in Figure 4.13. We identified 55,096 adult patients (age 18-64) initiating highly emetogenic chemotherapy between 2013 and 2015. Of these patients, 41,464 had the required six months of continuous enrollment prior to initiating chemotherapy and one-month follow-up. Subsequently, 39,424 patients had a cancer diagnosis on the claim associated with the highly emetogenic chemotherapy administration. We then excluded 1,591 patients for being pregnant. Finally, 7,055 patients who lacked prescription drug data were excluded. The final study population consisted of 30,275 patients.

Figure 4.13 Consort Diagram for CCAE Study Cohort Creation



4.2.1.2 Aim 2 – CCAE Population: Descriptive Statistics

We identified 30,275 patients newly initiating highly emetogenic intravenous chemotherapy between 2013 and 2015 in the commercial insurance claims. Baseline characteristics are detailed in Table 4.3. Most patients were female (69.9%) and were between the ages of 50-64 (68.3%). Among patients in the cohort 44.4% had breast cancer and 34.9% used a chemotherapy regimen consisting of an anthracycline and cyclophosphamide. Prior use of antiemetics, prior or concomitant use of IV chemotherapy, or prior or concomitant use of radiation therapy, was used by 43.1%, 15.9%, and 16.8% of the population, respectively. The average number of comorbid conditions, excluding cancer, was 0.2 (SD=0.7), with patients taking on average, 3.6 (SD=2.9) concomitant medications, excluding antiemetics, in the past 30 days. Approximately 85% of patients resided in an urban setting, with the highest proportion of patients in the southern United States (40.4%). These regional differences are expected based on the distribution of data contributors providing claims to MarketScan in the study period. Over half of patients had a PPO plan and 90.9% and 38.0% of patients had good medical benefit and prescription drug generosity, respectively (i.e., the proportion of out-of-pocket costs is less than 20% of the total healthcare cost). Chemotherapy was primarily administered in the physician office (53.6%) and outpatient hospital settings (45.2%).

4.2.1.3 Aim 2 – CCAE Population: Modified Poisson Regression Multivariate, Adjusted Results

Both bivariate, unadjusted and multivariable, adjusted results are found in Table 4.4; however, multivariable results are discussed in this section. Among patients initiating highly emetogenic chemotherapy in the commercial claims population, 49.6% of patients filled antiemetic regimens that did not meet guideline recommendations to prevent chemotherapy induced nausea and vomiting. Type of chemotherapy initiated was the greatest predictor of antiemetic under-use. In fact, anthracycline only, cyclophosphamide only, and carmustine regimens were at a 1.78 (95% confidence interval [CI]: 1.73-1.84, P<0.0001), 2.01 (CI: 1.73-1.84, P<0.0001), and 2.19 (CI: 2.12-2.25, P<0.0001) times the risk of underusing antiemetic regimens compared to combination anthracycline and cyclophosphamide regimens.

Table 4.3 Descriptive Statistics for the CCAE Populations (N=30,275)

		Mean (SD) or Percent
Guideline Under-use		
	Yes	49.6
Chemotherapy Setting		
	Physician Office	53.6%
	Outpatient Hospital	45.2%
	Other	1.2%
Geographical Setting		
	Rural	14.2%
	Urban	85.8%
Region		
	South	40.4%
	North Central	22.3%
	Northeast	18.3%
	West	16.9%
	Unknown	2.0%
Age		
	Younger Adult (Age 18-50)	31.7%
	Older Adult (Age 51-64)	68.3%
Gender		
	Female	69.9%
	Male	30.1%
Health Insurance Type		
	PPO	58.6%
	CDHP/HDHP	14.4%
	HMO	11.1%
	POS	7.4%
	Other	5.8%
	Missing	2.7%
Prescription Drug Generosity		
	Good Coverage (<0.2 OOP costs)	38.0%
	Fair / Poor / No Coverage / Missing (>0.19 OOP costs)	62.0%
Medical Benefit Generosity		
	Good Coverage (<0.2 OOP costs)	91.0%
	Fair / Poor / No Coverage / Missing (>0.19 OOP costs)	9.1%
Year of HEC Initiation		
	2013	38.4%
	2014	39.2%
	2015*	22.5%
Quarter of HEC Initiation		
	1	26.5%
	2	25.3%
	3	29.1%
	4	19.1%
Prior Antiemetic Use^		

	Mean (SD) or Percent
Guideline Under-use	
Yes	42.8%
No	57.3%
Prior / Concomitant IV Chemotherapy**	
Yes	15.9%
No	84.1%
Prior / Concomitant Radiation Therapy	
Yes	16.7%
No	83.3%
Number of Comorbid Conditions	
Klabunde Comorbidity Index	0.2 (0.7)
Concomitant Medication Number	
Number of unique medications, excluding antiemetics	3.6 (2.9)
Chemotherapy Type	
Anthracycline + Cyclophosphamide	34.9%
Anthracycline Only***	13.9%
Cyclophosphamide Only***	20.5%
Carmustine***	0.2%
Cisplatin and Other	30.5%
Cancer Type	
Breast	44.4%
Lymphatic	15.5%
Bronchus / Lung	7.3%
Ovary, Uterus, and Other Female Reproduction	7.8%
Urinary	2.2%
Male Genital and Other Reproduction	2.1%
Colorectal and Other GI	5.3%
Other	15.4%
Chemotherapy Setting Network	
In Network	96.5%
Out-of-Network	2.3%
Missing	1.2%

*Partial year – January 1, 2015-October 1, 2015
**Prior chemotherapy consists of exposure to any intravenously administered, non-highly emetogenic chemotherapy
***Denotes chemotherapies classified as highly emetogenic based on surface area thresholds
^Prior antiemetic use was assessed as any preventative antiemetic use between 6 months prior to IV HEC and the beginning of the look back period (i.e., 32 days)

Receiving chemotherapy in an outpatient hospital setting compared to a physician office (RR=1.44, CI: 1.33-1.55, P<0.0001) and having prior/concomitant chemotherapy therapy versus not having it (RR=1.22, CI: 1.18-1.25, P<0.0001) were the other largest predictors of antiemetic under-use.

Within the cohort of commercially insured patients, older adults compared to younger adults were at a higher risk for under-use (RR=1.07, CI: 1.05-1.10, P<0.0001), while female patients were at a lower risk (RR=0.92, CI: 0.89-0.94, P<0.0001). Additionally, patients with prior or concomitant radiation use had 1.07 (CI: 1.04-1.11, P<0.0001) times the risk of under-use compared to those without radiation exposure, while patients with prior antiemetic use were at slightly lower risk for under-use (RR: 0.97 (CI: 0.95-0.99, P=0.0057) compared to those who did not have prior antiemetic use. While the risk of underusing antiemetics increased with the number of comorbid conditions (P<0.0001), it decreased with the number of concomitant medications (P<0.0005).

The risk of under-use was 3% and 4% higher among those having more than 20% out-of-pocket costs versus having less than 20% out-of-pocket costs (RR: 1.03, CI: 1.01-1.05, P=0.0091 and RR: 1.04, CI: 1.00-1.09, P=0.0314) in the prescription drug benefit and medical benefit, respectively. There were no statistically significant differences in under-use comparing patients with CDHP/HDHP plans with those with PPO plans at alpha = 0.05; however, patients with an HMO plan were at 1.11 times the risk of antiemetic under-use (CI: 1.08-1.15, P<0.0001). Compared to 2013, under-use decreased in 2014 (P<0.0095) and 2015 (P<0.0001). Additionally, under-use was significantly lower in quarter four compared to quarter one (RR=0.95, CI: 0.92-0.98, P<0.0001).

Table 4.4 Modified Poisson Unadjusted and Adjusted Results – CCAE

		Bivariate, Unadjusted			Multivariable, Adjusted		
Variable	**Category**	**Estimate**	**CI**	**P-Value**	**Estimate**	**CI**	**P-Value**
Intercept		-	-		0.31	(0.29,0.33)	<.0001
Chemotherapy Setting	Other	1.52	(1.41,1.64)	<.0001	1.44	(1.33,1.55)	<.0001
	Hospital Outpatient	1.28	(1.25,1.31)	<.0001	1.28	(1.25,1.30)	<.0001
	Physician Office	1	REF	.	1.00	REF	.
Geographical Setting	Rural	1.01	(0.98,1.04)	0.57	1.02	(0.99,1.05)	0.27
	Urban	1	REF	.	1	(1,1)	.
Region	North Central	0.97	(0.93,1)	0.09	0.99	(0.95,1.02)	0.49
	South	1.03	(1,1.06)	0.09	1.08	(1.05,1.12)	<.0001
	Unknown	0.80	(0.72,0.88)	<.0001	0.84	(0.76,0.93)	0.0004
	West	1.15	(1.11,1.19)	<.0001	1.15	(1.12,1.20)	<.0001
	Northeast	1	REF	.	1	REF	.
Age	Older Adult	1.09	(1.06,1.12)	<.0001	1.07	(1.05,1.10)	<.0001
	Younger Adult	1	REF	.	1	REF	.
Gender	Female	0.97	(0.94,0.99)	0.0083	0.92	(0.89,0.94)	<.0001
	Male	1	REF	.	1	REF	.
Health Plan	CDHP/HDHP	0.98	(0.95,1.01)	0.24	0.99	(0.96,1.02)	0.56
	HMO	1.12	(1.08,1.16)	<.0001	1.11	(1.08,1.15)	<.0001
	Missing	1.06	(0.99,1.13)	0.11	1.06	(0.99,1.13)	0.0924
	Other	0.98	(0.93,1.03)	0.46	1	(0.95,1.05)	0.93
	POS	0.95	(0.91,1)	0.045	0.96	(0.92,1)	0.0414
	PPO	1	REF	.	1	REF	.
Medical Benefit Gener	Fair / Poor / No / Missing Coverage	0.96	(0.92,1)	0.06	1.04	(1.00,1.09)	0.0314
	Good Coverage	1	REF	.	1	REF	.
Prescription Drug Generosity	Fair / Poor / No / Missing Coverage	0.97	(0.94,0.99)	0.003	1.03	(1.01,1.05)	0.0091
	Good Coverage	1	REF	.	1	REF	.
Chemotherapy Year	2014	0.97	(0.94,0.99)	0.0095	0.97	(0.95,0.99)	0.0095
	2015	0.94	(0.92,0.97)	0.0002	0.92	(0.89,0.95)	<.0001
	2013	1	REF	.	1	REF	.
Chemotherapy Quarter	2	0.97	(0.94,1)	0.03	0.99	(0.96,1.02)	0.41
	3	0.98	(0.95,1.01)	0.16	0.99	(0.97,1.02)	0.58
	4	0.96	(0.93,0.99)	0.02	0.95	(0.92,0.98)	0.0026
	1	1	REF	.	1	REF	.
Prior/Concomitant Chemotherapy	1	1.28	(1.25,1.32)	<.0001	1.22	(1.18,1.25)	<.0001
	0	1	REF	.	1	REF	.
Prior / Concomitant Radiation	1	0.91	(0.88,0.94)	<.0001	1.07	(1.04,1.11)	<.0001
	0	1	REF	.	1	REF	.
Prior Antiemetics	1	1.11	(1.08,1.13)	<.0001	0.97	(0.95,0.99)	0.0057
	0	1	REF	.	1	REF	.

		Bivariate, Unadjusted			Multivariable, Adjusted		
Variable	**Category**	**Estimate**	**CI**	**P-Value**	**Estimate**	**CI**	**P-Value**
Chemotherapy Type	Anthracycline Only*	2	(1.93,2.06)	<.0001	1.78	(1.73,1.84)	<.0001
	Carmustine*	2.39	(2.13,2.69)	<.0001	2.01	(1.79,2.26)	<.0001
	Cyclo Only*	2.24	(2.17,2.3)	<.0001	2.19	(2.12,2.25)	<.0001
	Cisplatin and Other	1.1	(1.06,1.14)	<.0001	0.99	(0.95,1.03)	0.63
	Anthracycline + Cyclo	1	REF	.	1	REF	.
Comorbid Condition	Klabunde Index	1.09	(1.08,1.1)	<.0001	1.06	(1.04,1.07)	<.0001
Concomitant Medication	Unique medication number excluding antiemetics	0.99	(0.99,1)	0.0093	0.99	(0.99,1.00)	0.0005

*Denotes chemotherapies classified as highly emetogenic based on surface area thresholds

Patients living in the south and west,had a higher risk of antiemetic under-use compared to those living in the northeast ($p<0.0001$). There were no significant differences in risk of antiemetic under-use between patients living in rural and urban settings.

4.2.1.4 Aim 2 – CCAE Population: Sensitivity Analysis

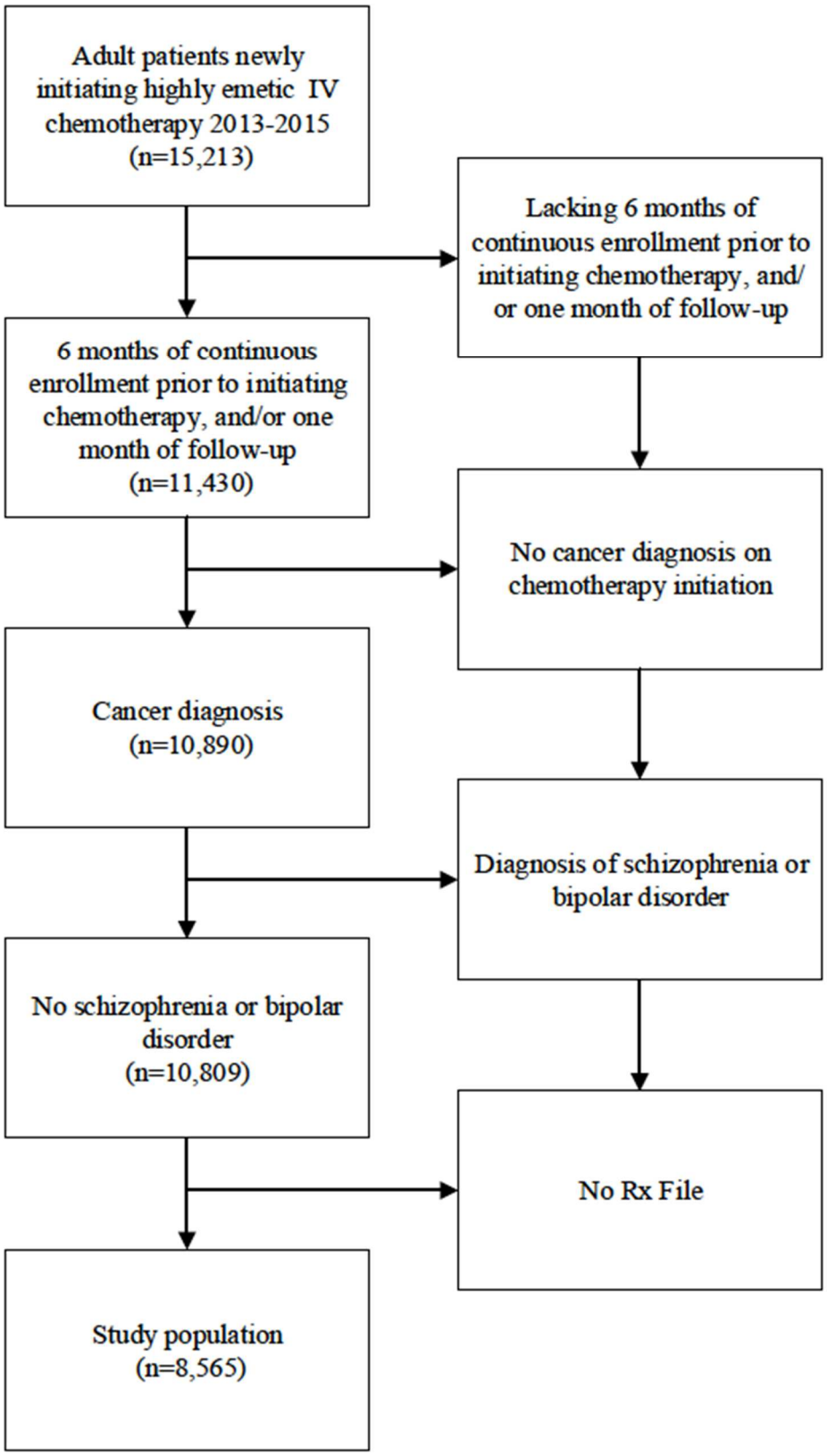
Excluding prescription drugs that cost less than $50 increased the percent of people with good prescription drug coverage to 50%. It also increased the number patients with missing prescription drug coverage from 4 to 29%. Changes in the multivariate modified poisson results using the modified prescription drug generosity measure, were minimal (not displayed).

4.2.2 Aim 2 Results – Medicare Supplement Population

4.2.2.1 Aim 2 – Medicare Supplement Population: Cohort Selection

Aim 2 used the same study cohort as Aim 1 except that patients had to initiate highly emetogenic chemotherapy on or before October 2015 (as opposed to on or before December 2015). The inclusion / exclusion criteria used to develop our Medicare Supplement study cohort is described in Figure 4.14. We identified 15,213 adult patients (aged 65 and older) initiating highly emetogenic chemotherapy between 2013 and 2015. Of these patients, 11,430 had the required six months of continuous enrollment prior to initiating chemotherapy and one-month follow-up. Subsequently, 10,890 patients had a cancer diagnosis on the claim associated with the highly emetogenic chemotherapy administration. After excluding 81 patients with a diagnosis of either schizophrenia or bipolar disorder and 2,244 patients who lacked prescription drug data the final study population consisted of 8,565 patients.

Figure 4.14 Consort Diagram for CCAE Study Cohort Creation



4.2.2.2 Aim 2 – Medicare Supplement Population: Descriptive Statistics

We identified 8,565 patients newly initiating highly emetogenic intravenous chemotherapy between 2013 and 2015 in the Medicare Supplement cohort. Baseline characteristics are detailed in Table 4.5. More than half of patients were female (58.0%) and 68.0% of patients were between the ages of 65-74, with less than 5% over the age of 85. The most common type of cancer was lymphatic cancer (28.1%) and breast cancer (24.0%), and 25.1% of patients used a chemotherapy regimen consisting of anthracycline and cyclophosphamide. Prior use of antiemetics, concomitant chemotherapy, or radiation therapy was used by 39.7%, 22.7%, and 16.3%, respectively. The average number of comorbid conditions, excluding cancer, was 0.5 (SD=0.86), with patients taking on average, 3.9 (SD=3.03) concomitant medications, excluding antiemetics, in the past 30 days. Approximately 85% of patients resided in an urban setting, with the highest proportion of patients in the north central United States (35.5%). The most common plans were PPO (41.7%) and comprehensive (40.9%), and 97.0% and 44.9% patients had good medical benefit and prescription drug generosity (i.e., the proportion of out-of-pocket costs is less than 20% of the total healthcare cost), respectively. Chemotherapy was primarily administered in the physician office (57.0%) and outpatient hospital (40.8%).

Table 4.5 Descriptive Statistics for the Medicare Supplement Populations (N=8,565)

		Mean (SD) or Percent
Guideline Under-use		
	Yes	68.4
Chemotherapy Setting		
	Physician Office	57.0%
	Outpatient Hospital	40.8%
	Other	2.2%
Geographical Setting		
	Rural	15.2%
	Urban	84.8%
Region		
	South	29.0%
	North Central	35.5%
	Northeast	20.5%
	West	14.1%
	Unknown	0.9%
Age		
	Younger Medicare Adult (65-74)	68.0%
	Middle Aged Medicare Adult (75-85)	28.5%
	Older Medicare Adult (85+)	3.5%
Gender		
	Female	58.0%
	Male	42.0%
Health Insurance Type		
	PPO	41.7%
	CDHP/HDHP	0.8%
	HMO	11.9%
	POS	4.3%
	Other	40.4%
	Missing	0.9%
Prescription Drug Generosity		
	Good Coverage (<0.2 OOP costs)	44.9%
	Fair / Poor / No Coverage / Missing (>0.19 OOP costs)	55.1%
Medical Benefit Generosity		
	Good Coverage (<0.2 OOP costs)	97.0%
	Fair / Poor / No Coverage / Missing (>0.19 OOP costs)	3.1%
Year of HEC Initiation		
	2013	42.5%
	2014	36.6%
	2015*	20.9%
Quarter of HEC Initiation		
	1	26.0%
	2	26.2%
	3	29.0%
	4	18.8%
Prior Antiemetic Use		

	Mean (SD) or Percent
Guideline Under-use	
Yes	39.7%
No	60.3%
Prior / Concomitant Chemotherapy**	
Yes	22.7%
No	77.3%
Prior / Concomitant Radiation Therapy	
Yes	16.3%
No	83.7%
Number of Comorbid Conditions	
Klabunde Comorbidity Index	0.5 (0.9)
Concomitant Medication Number	
Number of unique medications, excluding antiemetics	3.91(3.0)
Chemotherapy Type	
Anthracycline + Cyclophosphamide	25.1%
Anthracycline Only***	17.7%
Cyclophosphamide Only***	23.4%
Carmustine***	0.1%
Cisplatin and Other	33.7%
Cancer Type	
Breast	24.0%
Lymphatic	28.2%
Bronchus / Lung	11.4%
Ovary, Uterus, and Other Female Reproduction	9.3%
Urinary	6.3%
Male Genital and Other Reproduction	0.6%
Colorectal and Other GI	8.1%
Other	12.2%
Chemotherapy Setting Network	
In Network	65.8%
Out-of-Network	31.1%
Missing	3.1%

*Partial year – January 1, 2015-October 1, 2015
**Prior chemotherapy consists of exposure to any intravenously administered, non-highly emetogenic chemotherapy
***Denotes chemotherapies classified as highly emetogenic based on surface area thresholds
^Prior antiemetic use was assessed as any preventative antiemetic use between 6 months prior to IV HEC and the beginning of the look back period (i.e., 53 days)

4.2.2.3 Aim 2 – Medicare Supplement Population: Modified Poisson Regression Multivariate, Adjusted Results

Both bivariate, unadjusted and multivariable, adjusted results are found in Table 4.6; however, multivariable results are discussed in this section. Among patients initiating highly emetogenic chemotherapy in the Medicare Supplement population, 68.4% of patients filled antiemetic regimens that did not meet guideline recommendations to prevent chemotherapy induced nausea and vomiting. Receiving chemotherapy in an outpatient hospital setting compared to a physician office (RR=1.47, CI: 1.43-1.51, P<0.0001) was the greatest predictor of antiemetic under-use in this population. Patients initiating anthracycline only as well as cyclophosphamide only regimens were at 29% (RR: 1.29, CI: 1.24-1.35, P<0.0001) and 41% (RR: 1.41, CI: 1.36-1.46, P<0.0001) higher risk of underusing antiemetic regimens compared to patients initiating a combined anthracycline and cyclophosphamide regimen. However, patients initiating cisplatin and other chemotherapy regimens were 18% less likely to under-use antiemetics compared to patients initiating an anthracycline and cyclophosphamide chemotherapy regimens (CI: 0.78-0.86, P<0.0001). Additionally, adults aged 75-84 (RR=1.08, CI: 1.05-1.11, P<0.001) and over 85 (RR=1.15, CI: 1.10-1.21, P<0.0001) were at higher risk for under-use compared to Medicare beneficiaries aged 65-74.

There were no significant differences in under-use by gender as well as prior antiemetic use at alpha=0.05; though statistically significant differences occurred prior to adjustment. Patients with prior or concomitant radiation (RR=1.09, CI: 1.04-1.14, P<0.0001) as well as patients with prior/concomitant chemotherapy (RR=1.12, CI: 1.09-1.16, P<0.0001) were at increased risk of under-use compared to those without prior or concomitant radiation or chemotherapy, respectively. An increase in the number of comorbid conditions, excluding cancer, or concomitant medications, excluding antiemetics, did not significantly affect guideline concordance.

Table 4.6 Modified Poisson Unadjusted and Adjusted Results – Medicare Supplement

		Bivariate, Unadjusted			Multivariable, Adjusted		
Variable	**Category**	**Estimate**	**CI**	**P-Val**	**Estimate**	**CI**	**P-Val**
Intercept		-	-		0.48	(0.44,0.51)	<.0001
Chemotherapy Setting	Other	1.39	(1.29,1.5)	<.0001	1.23	(1.15,1.33)	<.0001
	Outpatient	1.47	(1.43,1.51)	<.0001	1.47	(1.43,1.51)	<.0001
	Physician Office	1	REF	.	1	REF	.
Geographical Setting	Rural	1.01	(0.97,1.05)	0.76	0.99	(0.95,1.02)	0.49
	Urban	1	REF	.	1	REF	.
Region	North Central	1.11	(1.06,1.15)	<.0001	1.04	(1,1.08)	0.03
	South	1.01	(0.96,1.05)	0.77	1.01	(0.97,1.06)	0.50
	Unknown	0.67	(0.52,0.87)	0.0022	0.71	(0.56,0.9)	0.0051
	West	1.12	(1.07,1.17)	<.0001	1.14	(1.09,1.19)	<.0001
	Northeast	1	REF	.	1	REF	.
Age	Middle-age Medicare Adult	1.11	(1.08,1.15)	<.0001	1.08	(1.05,1.11)	<.0001
	Older Medicare Adult	1.29	(1.22,1.36)	<.0001	1.15	(1.10,1.21)	<.0001
	Younger Medicare Adult	1	REF	.	1	REF	.
Gender	Female	1.08	(1.05,1.11)	<.0001	0.99	(0.96,1.02)	0.53
	Male	1	REF	.	1	REF	.
Health Plan	CDHP/HDHP	0.76	(0.6,0.96)	0.02	0.79	(0.64,0.98)	0.029
	HMO	1	(0.95,1.06)	0.89	0.95	(0.91,1.00)	0.048
	Missing	1.06	(0.92,1.23)	0.43	1	(0.86,1.15)	0.96
	Other	1.12	(1.08,1.15)	<.0001	1.07	(1.04,1.1)	<.0001
	POS	0.89	(0.81,0.97)	0.01	0.90	(0.83,0.98)	0.0127
	PPO	1	REF	.	1	REF	.
Medical Benefit Generosity	Fair / Poor / No / Missing Coverage	0.99	(0.91,1.08)	0.77	1.09	(1.01,1.18)	0.02
	Good Coverage	1	REF	.	1	REF	.
Prescription Drug Generosity	Fair / Poor / No / Missing Coverage	1.02	(0.99,1.05)	0.16	1.03	(1,1.05)	0.07
	Good Coverage	1	REF	.	1	REF	.
Chemotherapy Year	2014	0.98	(0.95,1.01)	0.21	0.98	(0.95,1.01)	0.14
	2015	1	(0.96,1.04)	0.93	0.96	(0.93,1)	0.03
	2013	1	REF	.	1	REF	.
Chemotherapy Quarter	2	1	(0.96,1.04)	0.88	0.99	(0.96,1.03)	0.61
	3	0.99	(0.96,1.03)	0.72	0.98	(0.95,1.02)	0.38
	4	0.97	(0.93,1.01)	0.16	0.97	(0.93,1.01)	0.18
	1	1	REF	.	1	REF	.

		Bivariate, Unadjusted			Multivariable, Adjusted		
Variable	**Category**	**Estimate**	**CI**	**P-Val**	**Estimate**	**CI**	**P-Val**
Prior / Concomitant Chemotherapy	1	1.15	(1.11,1.18)	<.0001	1.12	(1.09,1.16)	<.0001
	0	1	REF	.	1	REF	.
Prior / Concomitant Radiation	1	0.89	(0.86,0.93)	<.0001	1.09	(1.04,1.14)	<.0001
	0	1	REF	.	1	REF	.
Prior Antiemetics	1	1.08	(1.05,1.12)	<.0001	0.99	(0.96,1.02)	0.37
	0	1	REF	.	1	REF	.
Chemotherapy Type	Anthracycline Only*	1.40	(1.34,1.45)	<.0001	1.29	(1.24,1.35)	<.0001
	Carmustine*	1.37	(0.96,1.96)	0.09	1.17	(0.85,1.61)	0.35
	Cyclo Only*	1.43	(1.37,1.48)	<.0001	1.41	(1.36,1.46)	<.0001
	Cisplatin and Other	0.86	(0.82,0.9)	<.0001	0.82	(0.78,0.86)	<.0001
	Anthracycline + Cyclo	1	REF	.	1	REF	.
Comorbid Conditions	Klabunde Index	1.01	(1,1.03)	0.10	1.01	(0.99,1.02)	0.35
Concomitant Medication Number	Unique medication number excluding antiemetics	0.99	(0.99,1)	0.02	1.00	(0.99,1.00)	0.65

*Denotes chemotherapies classified as highly emetogenic based on surface area thresholds

Differences in prescription drug generosity did not have significant effects on under-use at alpha = 0.05. However, patients with more than 20% out-of-pocket costs were 1.03 times as likely to under-use antiemetics than those with less than 20% out-of-pocket costs (CI: 1.01-1.18, P=0.02). Compared to 2013, under-use was the same in 2014, but decreased in 2015 (P=0.03). Concordance did not significantly differ in quarters 2, 3, and 4 when compared to quarter 1.

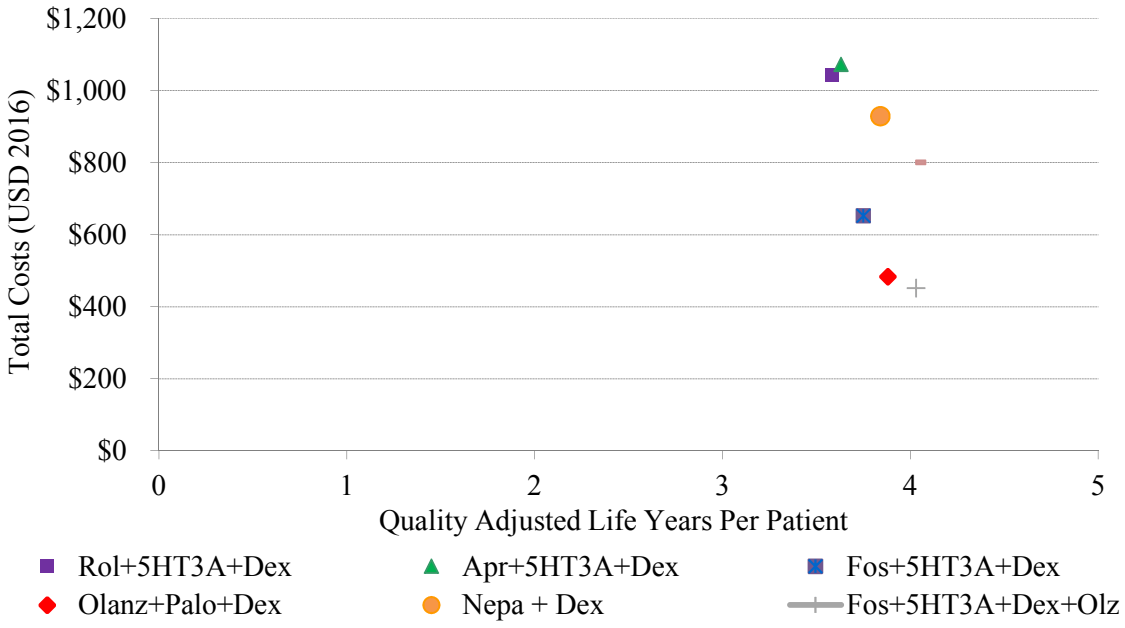
Patients living in the north central (p=0.03) or western (p<0.0001) United States had a higher risk of antiemetic under-use compared to those living in the northeast. There were no significant differences in risk of antiemetic under-use between patients living in a rural and urban setting.

4.3 Aim 3 Results

4.3.1 Base Case Results

The purpose of aim 3 was to evaluate the trade-offs in cost, clinical, and quality-of-life outcomes across the guideline-concordant antiemetic strategies in patients initiating highly emetogenic chemotherapy. Specifically, we conducted a cost-utility analysis using a Markov Model. After ranking by cost and applying dominance principles sequentially, we found that from the perspective of the US healthcare system, the use of olanzapine + fosaprepitant + 5HT3A + dexamethasone among patients initiating highly emetogenic chemotherapy had the lowest total costs ($452) and highest total benefit (4.03 QALD) (Figure 4.15,Table 4.7). As such, this strategy dominated all other strategies. Olanzapine + fosaprepitant + 5HT3A + dexamethasone had the third lowest treatment acquisition costs ($310). Aprepitant + 5HT3A + dexamethasone had the highest total costs ($1,073) and rolapitant + 5HT3A + dexamethasone had the lowest total benefit (3.58 QALD). Olanzapine + palonosetron + dexamethasone had the lowest treatment acquisition cost ($242), and the second lowest total costs ($484) and second highest total benefit (3.88 QALD). Findings were similar from the societal perspective.

Figure 4.15 Cost Effectiveness Plane Depicting Base Case Results for Antiemetic Strategies Used to Prevent CINV in Patients Initiating Highly Emetogenic (US Healthcare System Perspective



4.3.2 Sensitivity Analyses

We conducted sensitivity analyses from the perspective of the US healthcare system for the three lowest total cost strategies (i.e., olanzapine + fosaprepitant + 5HT3A + dexamethasone, olanzapine + palonosetron + dexamethasone, and fosaprepitant + 5HT3A + dexamethasone) because they are closest in total costs. The probabilistic sensitivity analyses consisting of 1,000 trials are displayed in the scatter plots in (Figure 4.16). Olanzapine + palonosetron + dexamethasone was less effective than fosaprepitant + 5HT3A + dexamethasone + olanzapine in 99.9% of simulations, was dominated in 56.5% of simulations, dominates in .1% of simulations, and was cost effective in 37.5% of simulations at a willingness to pay threshold of $50,000/QALY (Figure 4.16A). In 79.9% and 50.0% of simulations, fosaprepitant + 5HT3A + dexamethasone was dominated by olanzapine + fosaprepitant + 5HT3A + dexamethasone (Figure 4.16B) and olanzapine + palonosetron + dexamethasone (Figure 4.16C) strategies, respectively. In 7.9% and 0% of simulations, fosaprepitant + 5HT3A + dexamethasone dominates olanzapine + fosaprepitant + 5HT3A + dexamethasone (Figure 4.16B) and olanzapine + palonosetron + dexamethasone (Figure 4.16C) strategies, respectively. Compared to olanzapine + fosaprepitant + 5HT3A + dexamethasone (Figure 4.16B) and olanzapine + palonosetron + dexamethasone (Figure 4.16C) strategies, fosaprepitant + 5HT3A + dexamethasone was cost-effective at a willingness to pay threshold of $50,000/QALY in .1% and 19.0% of simulations, respectively. Figure 4.17 depicts the probability of these comparisons being cost effective at willingness to pay thresholds ranging from $0-$250,000.

Using one-way sensitivity analysis (Figure 4.18), cost of 5HT3A used, cost of palonosetron, cost of fosaprepitant, and cost of CINV event were the inputs to which the ICER was most sensitive when comparing olanzapine + palonosetron + dexamethasone with olanzapine + fosaprepitant + 5HT3A + dexamethasone (Figure 4.18A). In contrast, when comparing olanzapine + fosaprepitant + 5HT3A + dexamethasone to fosaprepitant + 5HT3A + dexamethasone, the analysis was most sensitive to complete protection, complete response, and incomplete response utility values as well as CINV event costs (Figure 4.18B). When comparing olanzapine + palonosetron + dexamethasone with fosaprepitant + 5HT3A +

dexamethasone (Figure 4.18C), the 5HT3A costs and effectiveness of fosaprepitant + 5HT3A + dexamethasone +olanzapine were the input parameters to which the analysis was most sensitive.

After conducting a scenario analysis excluding all strategies containing olanzapine in the base case, fosaprepitant+5HT3A+dexamethasone had the lowest total costs ($653). Netupitant/palonosetron combination + dexamethasone offers an advantage of 0.09 QALDs at an additional cost of $276 over five days over fosaprepitant + 5HT3A + dexamethasone resulting in an ICER of $3,064/QALD. To convert this ICER to one using QALYs, we multiplied the ICER in QALDs by 365.25. We found that this ICER was not cost-effective at a willingness-to-pay threshold of $50,000/QALY, $100,000/QALY, or $200,000/QALY (Table 4.8). Aprepitant + 5HT3A + dexamethasone and rolapitant + 5HT3A + dexamethasone were both dominated by the two previous strategies, as they had a higher total cost and offered less benefit.

Table 4.7 Base Case Results Comparing Antiemetic Strategies from the US Healthcare System and Societal Perspectives (2016 US Dollars)

TREATMENT ACQUISITION COSTS (15, 18)	
Treatment Strategy	**Costs (USD 2016)**
Olanz+Palo+Dex	242.39
Fos+5HT3A+Dex	310.09
Fos+5HT3A+Dex+Olz	320.09
Rol+5HT3A+Dex	620.59
Nepa + Dex	635.59
Apr+5HT3A+Dex	659.09
Apr+5HT3A+Dex+Olz	669.09

US HEALTHCARE PERSPECTIVE						
	1-person (5 Days)					
Treatment Strategy	**Total Costs**	**QALD**	**Incremental Cost**	**Incremental QALD**	**ICER (Cost/ QALD)**	**ICER (Cost/ QALY)**
Fos+5HT3A+Dex+Olz	$452	4.03				
Olanz+Palo+Dex	$484	3.88	$32	-0.15	Dominated	Dominated
Fos+5HT3A+Dex	$653	3.75	$201	-0.28	Dominated	Dominated
Apr+5HT3A+Dex+Olz	$801	4.03	$349	0.00	Dominated	Dominated
Nepa + Dex	$929	3.84	$477	-0.19	Dominated	Dominated
Rol+5HT3A+Dex	$1,044	3.58	$592	-0.45	Dominated	Dominated
Apr+5HT3A+Dex	$1,073	3.63	$621	-0.40	Dominated	Dominated

US SOCIETAL PERSPECTIVE						
	1-person (5 Days)					
Treatment Strategy	**Total Costs**	**QALD**	**Incremental Cost**	**Incremental QALD**	**ICER (Cost/ QALD)**	**ICER (Cost/ QALY)**
Fos+5HT3A+Dex+Olz	$477	4.03				
Olanz+Palo+Dex	$529	3.88	$52	-0.15	Dominated	Dominated
Fos+5HT3A+Dex	$717	3.75	$240	-0.28	Dominated	Dominated
Apr+5HT3A+Dex+Olz	$826	4.03	$349	0.00	Dominated	Dominated
Nepa + Dex	$984	3.84	$507	-0.19	Dominated	Dominated
Rol+5HT3A+Dex	$1,123	3.58	$646	-0.45	Dominated	Dominated
Apr+5HT3A+Dex	$1,151	3.63	$674	-0.40	Dominated	Dominated

Figure 4.16 Probabilistic Sensitivity Analyses – ICER Scatterplot

Figure 4.16A Cost Effectiveness Scatterplot of Fos+5HT3A+Dex+Olanz (Ref) vs. Olanz+Palo+Dex

Figure 4.16B Cost Effectiveness Scatterplot of Fos+5HT3A+Dex+Olanz (Ref) vs. Fos+5HT3A+Dex

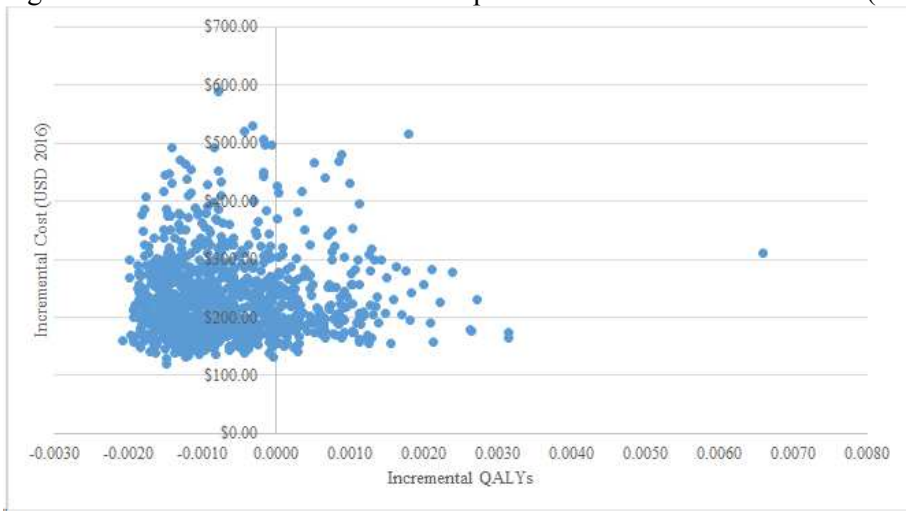


Figure 4.16C Cost Effectiveness Scatterplot of Olanz+Palo+Dex (Ref) vs. Fos+5HT3A+Dex

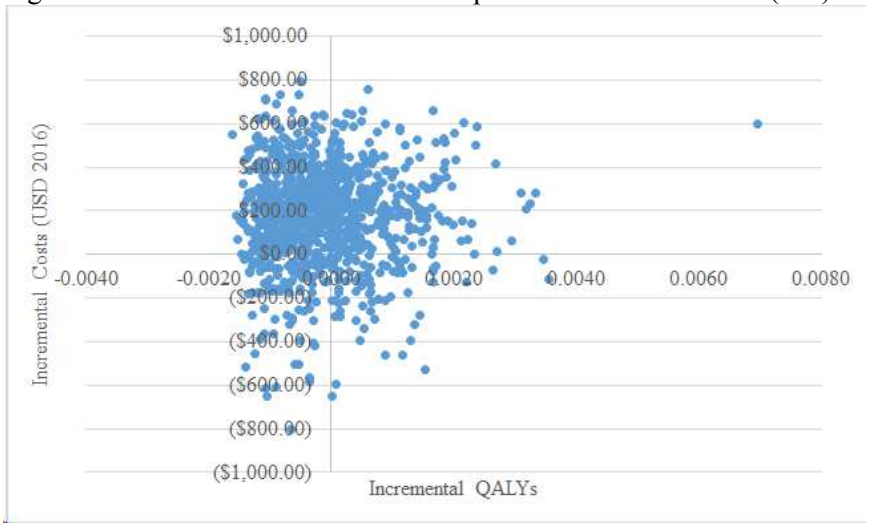


Figure 4.17 Cost Effectiveness Acceptability Curves for Olanz + Palo + Dex vs. Fos + 5HT3A+ Dex + Olanz, and Fos + 5HT3A + Dex + Olanz

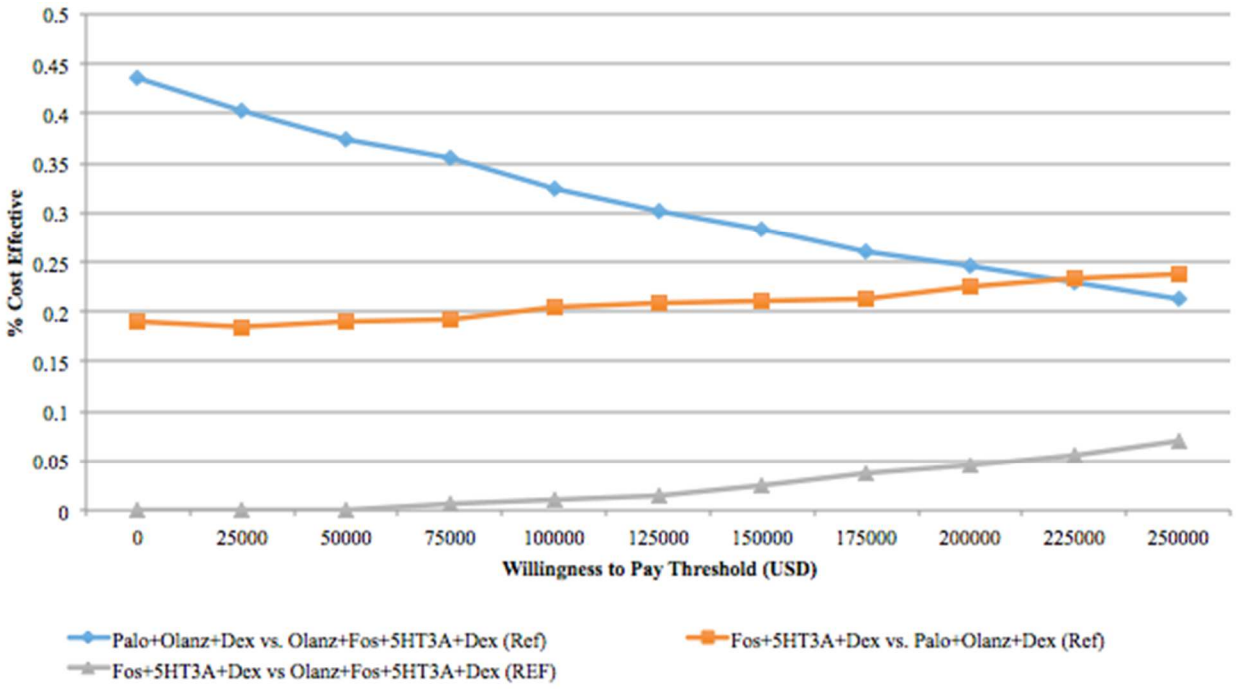


Figure 4.18 One Way Sensitivity ICER (Cost (USD 2016) /QALY) Analysis – Tornado Diagram (Top 5 Variables)

Figure 4.18A. Change in ICER: Fos +5HT3A+Dex+Olanz (Ref) vs. Olanz+Palo+Dex

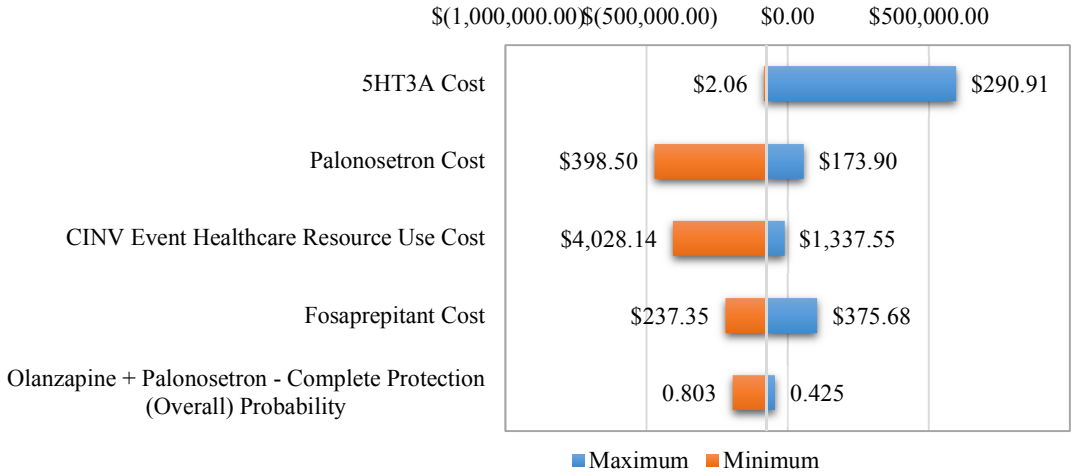


Figure 4.18B Change in ICER: Fos+5HT3A+Dex+Olanz (Ref) vs. Fos+5HT3A+Dex

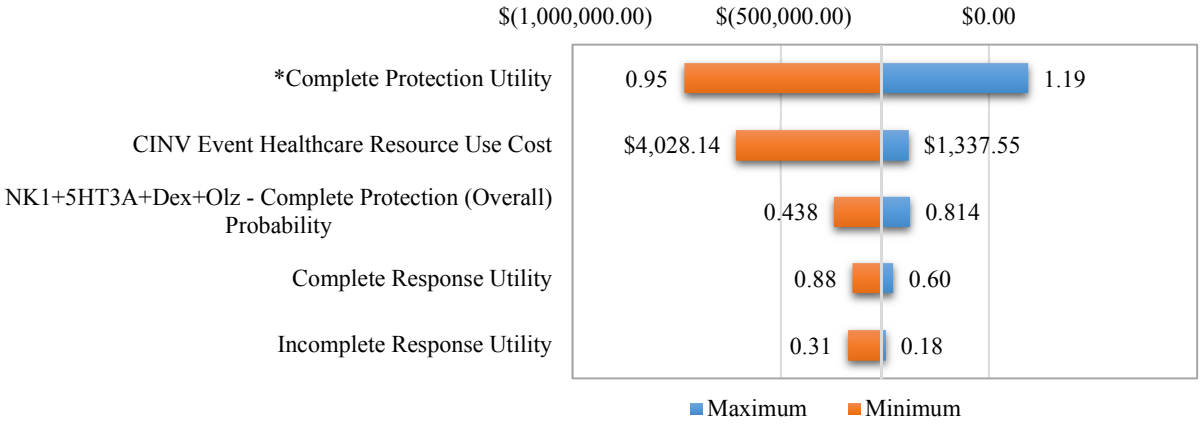


Figure 4.18C Change in ICER: Olanz+Palo+Dex (Ref) vs. Fos+5HT3A+Dex

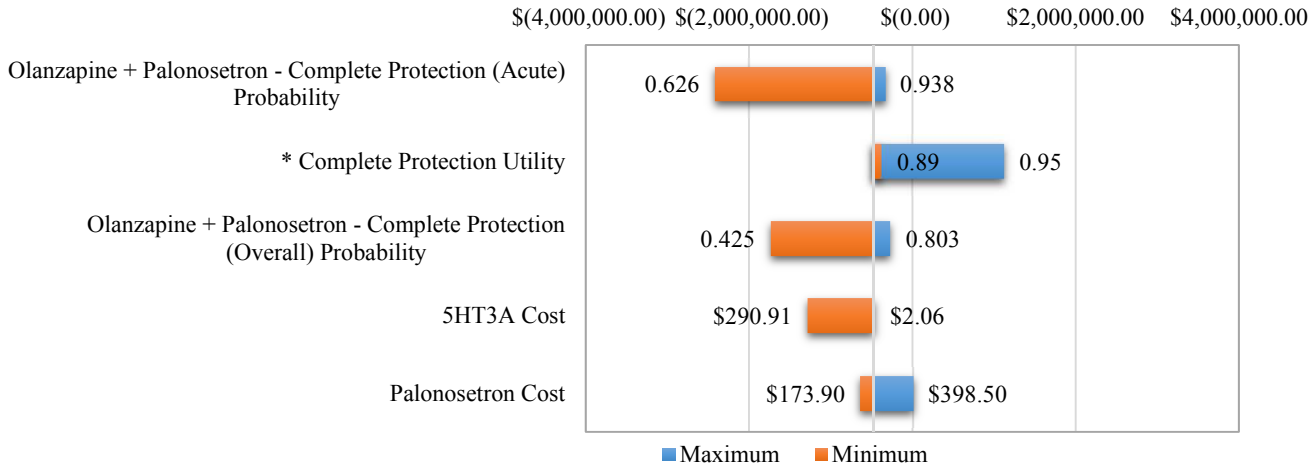


Table 4.8 Scenario Analysis Excluding Olanzapine Strategies

1-person (5 Days)						
Treatment Strategy	**Total Costs**	**QALD**	**Incremental Cost**	**Incremental QALD**	**Cost/QALD**	**Cost/QALY**
Fos+5HT3A+Dex	$653	3.75				
Nepa + Dex	$929	3.84	$276	0.09	$3,065	$1,119,074
Rol+5HT3A+Dex	$1,044	3.58	$115	-0.26	Dominated	Dominated
Apr+5HT3A+Dex	$1,073	3.63	$144	-0.21	Dominated	Dominated

CHAPTER 5: DISCUSSION

5.1 Dissertation Objectives Recap

Patients initiating highly emetogenic chemotherapy are at a 90% risk of chemotherapy-induced nausea and vomiting (CINV). Antiemetic drugs are highly effective in preventing CINV, and thus improve quality of life and generate cost savings by reducing the need for CINV-related health services.(1-4) Despite the fact that guideline-concordant antiemetic prescribing is estimated to prevent CINV in as high as 80% of CINV patients, evidence suggests that use of ASCO and NCCN guideline-concordant antiemetic regimens by patients initiating highly emetogenic chemotherapy are low. Furthermore, there are several CINV preventative treatment regimens that are considered guideline-concordant that are associated with a wide range of costs. However, there is no clearly preferred treatment strategy. The purpose of this dissertation was to characterize antiemetic use; identify predictors of antiemetic under-use; and evaluate the trade-offs in cost, clinical, and quality of life outcomes across the guideline-concordant regimens available for use among patients who initiate highly emetogenic chemotherapy. Aim 1 used descriptive statistics to describe antiemetic prescribing patterns, including antiemetic under-use, in patients with cancer initiating highly emetogenic chemotherapy using the IBM Watson's/Truven's MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits data. Aim 2 used a modified Poisson regression to identify predictors (i.e., environmental, predisposing, enabling, and need) of antiemetic under-use in these same data. Aim 3 assessed the health and economic impacts of guideline-concordant antiemetic strategies through a cost-utility analysis in order to prioritize them.

5.2 Summary/Discussion

5.2.1 Summary / Discussion – Aim 1

The primary purpose of Aim 1 was to describe what types of antiemetic regimens are being used and to assess the proportion of antiemetic under-use in patients with cancer who are initiating highly emetogenic, intravenous chemotherapy. Our final study population consisted of 31,923 and 8,991 patients initiating highly emetogenic chemotherapy between 2013-2015 in the CCAE population and Medicare Supplement population, respectively. Antiemetic fills in the Medicare Supplement population were lower than the Commercial Claims population with 97% of patients in the Commercial Claims population filling at least one antiemetic, compared to 93% in the Medicare Supplement population. This aligns with prior US studies in which patients initiating highly emetogenic chemotherapy filled at least one antiemetic more than 80% of the time, indicative of provider understanding that patients initiating emetogenic chemotherapy should be prescribed an antiemetic strategy to prevent CINV, though the specifics of the antiemetic strategy may be lacking.(22, 30) While patients both in the Medicare Supplement and CCAE populations had 3 median unique antiemetic fills, the proportion of patients that filled 2 unique antiemetics was higher in the Medicare Supplement population and that filled 4 unique antiemetics was higher in the CCAE population. Coupling this with the finding that the Medicare Supplement population had a lower percentage filling rescue antiemetics in the pre-period suggests that younger patients are receiving more aggressive supportive care. This may be because patients under the age of 50 are at a higher risk of CINV events as well as younger patients are treated more aggressively in oncology than older patients (e.g., receiving more chemotherapy/radiation therapy or adjuvant therapy).(74, 211-213) Most preventative antiemetics were intravenously administered with minimal median out-of-pocket costs and an interquartile range of less than $6 for filled products. This is likely the result of 1) generous coverage of cancer care in these populations and 2) patients having reached out-of-pocket maximums given the high cost of cancer care in the CCAE population. Median out-of-pocket costs for filled oral antiemetics were generally higher than for intravenously administered antiemetics. It will be important to

monitor total cost and out-of-pocket costs of antiemetics as insurance benefits continue to shift toward greater use of deductibles and co-insurance.

More than 80% of CCAE patients and 70% of Medicare Supplement patients filled at least one 5HT3A and dexamethasone. Additionally, there was minimal uptake of new NK1 products NEPA and rolapitant, which is not surprising given the low proportion of patients filling at least one NK1 to begin with (58% and 39% in the commercial and Medicare populations, respectively). However, these proportions are higher than those in a study conducted between 2006-2008 that found only 11% of patients were filled NK1s.(30) Despite olanzapine being recommended for preventative use since 2012 in the NCCN guidelines and its low costs, limited olanzapine fills were seen in the pre-period. We hypothesize a few reasons for this. First, providers may have concerns about the safety of olanzapine, which include significant cardio-metabolic events and a black box warning for death in elderly patients with dementia-related psychosis, despite the short duration of use and evidence demonstrating that adverse event rates with olanzapine strategies were similar to the comparator arm.(28) Additional high-quality studies supporting the tolerability of olanzapine for use in this clinical context may alleviate this issue. Second, because this indication for olanzapine is not FDA-approved, manufacturers are unable to market this indication to providers, so dissemination of evidence of olanzapine's use for CINV prevention is limited compared to that of other antiemetic products, which have an FDA-approved indication.(214) Third, there is a limited evidence base for olanzapine use prior to 2016 – early studies had study design issues including small sample size and uneven patient characteristic distribution between the comparators.(125) Given the new randomized controlled evidence published in 2016, as well as olanzapine's incorporation into the ASCO guidelines in 2017, higher uptake is anticipated in the future.(18, 28)

Under-use of guideline-concordant antiemetic fills is high at 49% and 68% in the commercial claims and Medicare supplement populations, respectively. These results align with a prior study that found that 56.4% of breast cancer patients on AC therapy were concordant in the commercial claims population in 2013.(45) Another US study estimated guideline-concordance to be 91% on day 1 in a

practice group in the southeast; however, these providers used an EMR system embedded with a standardized antiemetic protocol.(22) We found that the most common reason for discordance is a lack of NK1, and under-use of NK1s was higher in the Medicare supplement population (89%) versus the commercial claims population (85%). This aligns with prior studies that estimate that a lack of an NK1 constitutes 51%-80% of the reasons for discordances.(22, 31, 39, 45, 46) The high under-use of NK1s is surprising given that they have been in the guidelines since 2006. This highlights an opportunity for further provider education as there is a robust evidence base supporting the superiority of NK1s over 5HT3As for achieving clinical outcomes and reducing downstream economic impacts.

One potential reason for low NK1 fills is treatment acquisition cost, as they are the most expensive class of antiemetics. While median out-of-pocket costs for NK1s in both populations is nominal among those who filled these products, it could still be hypothesized that while providers are prescribing NK1s patients did not fill them because of the high out-of-pocket costs. We are unable to discern the costs of drugs that were not filled because claims were only filled for filled drugs. Conversely, patients in both populations are more likely to fill expensive, second-generation 5HT3A (palonosetron) versus cheaper, first-generation 5HT3As (as low as $1.10 / treatment cycle). Intravenous palonosetron costs $229 (2016 USD) / treatment cycle, just slightly less expensive than the cheapest NK1, intravenous fosaprepitant at $299 (2016 USD) / treatment cycle.(18) Notably, guidelines do not prioritize 5HT3As, and palonosetron is more expensive than first-generation 5HT3As (e.g., oral ondansetron costs $1.10 (2016 USD) / treatment cycle and oral granisetron costs $3.13 (2016 USD) / treatment cycle). This suggests that the high costs of NK1s are not the only reason for their limited uptake. Another notable finding is that the proportion of patients that used at least one second-generation palonosetron fill was more than 20% higher than those who filled at least one first-generation 5HT3A among both populations This suggests that patients who are receiving palonosetron have providers who may be more knowledgeable of the current antiemetic treatment landscape, which may be the result of manufacturer marketing. The lack of NK1 prescribing among palonosetron prescribers may be confusion with

moderately emetogenic chemotherapy recommendations, where palonosetron is the preferred 5HT3A, and along with only dexamethasone is considered guideline concordant.

Concordance increases by about 10% in both populations when assessing anthracycline + cyclophosphamide-regimens and non-surface-area based regimens, which are strictly highly emetogenic chemotherapy regimens. High under-use in the anthracycline and cyclophosphamide only populations is expected given than claims-based data sources (as the ones used in this study) do not provide dosage levels for infused products and patients may be receiving doses that are considered moderately emetogenic chemotherapy versus highly emetogenic chemotherapy. To the extent that this is the case, we would over-estimate antiemetic under-use in these populations.

5.2.2 Summary / Discussion – Aim 2

The purpose of Aim 2 was to identify predictors of antiemetic under-use as opposed to guideline-concordant use in patients with cancer who are initiating highly emetogenic, intravenous chemotherapy. Our final study population consisted of 30,275 and 8,565 patients initiating highly emetogenic chemotherapy between January 1, 2013-October 1, 2015 in the CCAE population and Medicare Supplement population, respectively. While the data sources for this study represent two different populations – under age 65 (CCAE) and age 65 and over (Medicare Supplement), there were some similarities in the predictors of antiemetic under-use. Compared to receiving chemotherapy in the physician office setting, patients receiving chemotherapy in an outpatient hospital setting were at a 28% ($p<0.0001$) and 48% ($p<0.0001$) higher risk of under-use in the CCAE and Medicare Supplement populations, respectively. This might be the result of increased patient-centered care in a community care setting compared to that of a hospital-based outpatient clinic, which is not measured in this data. Additionally, prior studies have shown that cancer costs are higher in the outpatient hospital setting than the physician's office, which may lead to higher out-of-pocket costs for the patient and prevent patients from using antiemetics.(154-156) However, our study found that patients with good medical benefit out-of-pocket coverage (patients paid less than 20% of medical spending out-of-pocket) were slightly more likely fill concordant antiemetics than those without good coverage (RR=1.04 ($p<0.05$) and RR=1.09

($P<0.05$) in the CCAE and Medicare Supplement populations, respectively). Good prescription drug coverage also improved guideline concordance, but the effect size was small (although statistically significant), and smaller than medical benefit coverage in both populations. This suggests that coverage generosity has a limited effect on receiving guideline-concordant prescribing, though medical benefit generosity plays a bigger role than prescription drug benefit generosity in this particular evaluation. Importantly, this is likely due to the fact that commercially insured patients with cancer reach their out-of-pocket maximums and subsequently have relatively low to no out-of-pocket financial responsibilities

Type of chemotherapy received was among the greatest predictors of under-use with patients receiving anthracycline and cyclophosphamide combination regimens less likely to under-use compared to anthracycline-only and cyclophosphamide-only regimens. A limitation of this dataset is that it does not include information on surface area-based dosing, which defines whether these two types of regimens are considered highly emetogenic or moderately emetic. This is contributing to the high under-use proportion; however, it is likely that because of the surface area-based dosing variation under-use may still be more likely in this population due to provider confusion as to when surface area-based chemotherapies are considered highly emetogenic versus moderately emetogenic. Reasons why patients with prior or concomitant chemotherapy or radiation therapy were more likely to under-use antiemetics in both populations may include past experience, competing demands, and challenges with coordination of health care services. The effects of prior experience are mixed with prior studies finding that patients with prior nausea and vomiting are less likely to receive guideline-concordant antiemetic regimens, but patients undergoing later cycles of chemotherapy are more likely to receive guideline-concordant antiemetic regimens.(34, 36, 43) Finally, under-use tended to slightly decrease over time in our three-year study period in both the CCAE and Medicare Supplement populations, potentially highlighting natural provider guideline diffusion. This aligns with a prior study by MacGregor-Chavez that found that year of treatment was associated with guideline adherence in both of these populations.(45)

Although there were some similarities between commercially insured and Medicare-insured cohorts regarding predictors of antiemetic under-use, there were also several important differences. It is

important to identify how under-use factors differ across the two populations to develop targeted interventions. Importantly, antiemetic under-use rates were 49.6% and 68.6% during 2012-2015 in the CCAE and Medicare Supplement populations, respectively. Differences in under-use may be due to younger patients receiving more aggressive supportive care than older patients. Furthermore, we found variation within age by payer with younger CCAE patients and Medicare supplement patients having significantly lower risks of under-use than older patients in both populations. While the evidence base is mixed, younger patients generally were more likely to receive the guideline-concordant antiemetics compared to older patient in prior studies.(4, 32, 34, 39, 43, 74) Because the Medicare supplement population is older, it is not surprising that we found that they have higher measured comorbidity (0.50 vs. 0.22 comorbid conditions, in addition to their cancer diagnoses) and use more medications (3.91 vs. 3.59). An increase in the number of comorbid conditions increases the risk of under-use among patients in the CCAE population, but there is no difference in the Medicare Supplement. This suggests that disease burden affects antiemetic use among CCAE patients, but that perhaps because Medicare patients have generally higher levels of comorbidity and medication use, they are not affected by these factors. While men were more likely to under-use antiemetics in the CCAE population, there were no significant differences by gender in the Medicare supplement population. This aligns with prior studies that found that women were more likely to receive guideline-concordant antiemetic products and breakthrough therapy compared to men across CINV risk as well as in high CINV-risk chemotherapy.(32, 34, 39) Additionally, use of prior antiemetics slightly decreased the risk of under-use in the CCAE population, but did not have an effect in the supplement population. In contrast to the CCAE population where there was no effect, patients using regimens consisting of cisplatin and other types of chemotherapy were less likely to under-use antiemetics compared to patients initiating anthracycline and cyclophosphamide regimens.

5.2.3 Summary / Discussion – Aim 3

The purpose of aim 3 was to evaluate the trade-offs in cost, clinical, and quality-of-life outcomes across the guideline-concordant antiemetic strategies in patients initiating highly emetogenic chemotherapy. Specifically, we conducted a cost-utility analysis using a Markov model to prioritize antiemetic strategies, which have a wide range of costs and no clinical preference. From the perspectives of both the US healthcare system and society, olanzapine + fosaprepitant + 5HT3A + dexamethasone was the most efficient strategy in the base-case cost utility analysis. All other strategies were dominated in the base case meaning that they provided lower quality-adjusted life days at higher costs.. Notably, olanzapine + palonosetron + dexamethasone had the lowest treatment acquisition cost and second lowest total costs. Compared with olanzapine + fosaprepitant + 5HT3A + dexamethasone, olanzapine + palonosetron + dexamethasone was less effective in 99.9% of simulations, was dominated in 56.5% of simulations, and was cost effective in 37.5 % of simulations at a wiliness to pay threshold of $50,000/QALY.

While some strategies offer incremental benefits, the total effectiveness of all strategies is similar with the total QALDs for each treatment ranging from 3.63 QALD – 4.03 QALD. This aligns with some meta-analyses that have found that products in the NK1 class offer similar effectiveness to each other except for rolapitant.(117, 118) As such, it may be appropriate to utilize a cost-minimization approach and revert to using the treatment with the lowest acquisition cost, which should be monitored over time as drug prices will likely change over time. In this case, olanzapine + palonosetron + dexamethasone is the most efficient strategy in our analysis. Furthermore, the cost input variables including 5HT3A, NK1, and palonosetron were among the most sensitive inputs when comparing olanzapine + palonosetron + dexamethasone with olanzapine + fosaprepitant + 5HT3A + dexamethasone, highlighting the influence of cost estimates in this model.

In addition to treatment acquisition costs, prescribers may consider factors related to medication adherence when selecting an antiemetic strategy such as frequency of administration, route of administration, and out-of-pocket costs. Aprepitant is not only the most expensive NK1, but also it must

be taken on days 2 and 3 in contrast to the other NK1s, which only have to be taken on day one.(18, 20) Additionally, intravenous NK1 (i.e., fosaprepitant) may be given in conjunction with the intravenous chemotherapy administration rather than requiring the patient to obtain the oral antiemetic before the chemotherapy infusion appointment. This may be more convenient for the patient and may reduce costs for patients with less generous prescription drug insurance. Furthermore, Aim 2 results showed medical benefit coverage of antiemetics, under which the intravenous NK1 would be covered, is typically more generous than prescription drug benefit coverage of antiemetics under which oral NK1s would likely be covered. Finally, there is no evidence prioritizing the many 5HT3A options, which range in cost from $1.10 to $468.00. While aim 1 results showed that the more expensive, second-generation 5HT3A, palonosetron, was filled more frequently than were first-generation 5HT3As, we recommend that unless a patient has a contraindication, lower-cost 5HT3As (generic, first-generation intravenous products) should be prioritized.

In scenario analyses, we removed olanzapine-based strategies from considerations for several reasons. First, while promising, the evidence base for olanzapine use is limited and there may be some hesitation by clinicians to prescribe an antipsychotic for this purpose given the significant side effects of this product (albeit a short duration). Furthermore, while NCCN guidelines dictated evidence strong enough to support its inclusion, the studies supporting olanzapine + palonosetron + dexamethasone remain controversial in the clinical community due to study design issues including small sample size, lack of blinding, lack of stratification by CINV risk, and unbalanced patient characteristics.(125) Second, relevant cost-effectiveness studies conducted in Italy and the UK did not include olanzapine-based strategies in their analyses.(143, 144) Both of these studies found that NEPA dominated aprepitant and fosaprepitant-based strategies in patients initiating highly emetogenic chemotherapy. Our scenario analysis supported that NEPA dominated rolapitant and aprepitant-based strategies. However, while it conferred an additional benefit when compared with fosaprepitant, NEPA was not cost-effective in our analysis. Differences observed between this study and those from international settings may be due to differing costs both from treatment acquisition as well as care in Italy and the UK versus the US. Notably

the treatment acquisition costs of all products were more expensive in the US. For example, the treatment acquisition cost of NEPA in the US ($632 (2016 USD)) was several times that in the UK ($223 (2016 USD)) UK and Italy ($100 (2016 USD)).(18, 143, 144)

It is important to discuss the generalizability of these results. First, the results of the analysis presented here are only applicable to the first highly emetogenic chemotherapy cycle. As guidelines dictate, prescribers should use outcomes based on the first cycle to inform future antiemetic use. Second, because patients with cancer who are commercially insured often reach their out-of-pockets maximums, the results from the US healthcare perspective may be applicable to the US commercial payer perspective. This is further supported by the fact that the main difference between the healthcare and commercial payer perspectives are the costs of the healthcare resource use associated with each health state, which would be modeled by reducing the total costs by a standardized percentage. This would not alter the ICER. Third, to the best of our knowledge there is not a commonly accepted willingness to pay threshold for QALD. As a result, we converted our primary outcome QALD to QALY to assess cost-effectiveness. However, decision-makers should reflect on the implications of extrapolating the QALD in this manner when considering their resources and constraints.

5.3 Limitations

5.3.1 Aim 1 Limitations

First, as is inherent with claims database studies, we were only able to capture information on healthcare encounters and prescription drug fills that were submitted to insurance for payment, thus generating a claim. This neither entirely captures what a provider may have prescribed nor is it indicative of what a patient actually took, when precisely they took it, or its intended use. Additionally, antiemetics given as samples will not be captured. Second, steroids are an inexpensive component of antiemetic regimens and expert opinion suggests that claims may not be filed by providers for these drugs when given during a visit in which the chemotherapy infusion is administered, leading to under-reporting of steroid use. Third, we did not have access to body mass information or precise drug dosing information. We assumed that patients using antiemetics that have varying emetogenic risk based on quantity per body

surface area were at high risk for CINV. This could potentially over-estimate guideline discordance if these patients were appropriately using antiemetics based on receiving a moderately emetogenic chemotherapy does for their size. To address this limitation, we stratified results by regimens that are highly emetogenic based on combination or body mass / dose versus always emetogenic. Fourth, the total price of the drugs used to calculate total and out-of-pocket costs was based on the transaction price between the manufactures and the payer listed in MarketScan, which does not reflect rebates and discounts received by payers and thus may overestimate the cost to payers for antiemetics. However, because rebates and discount are not typically shared with the patients, we anticipated out-of-pocket estimates to be accurate. Fifth, the preventative antiemetic look-back period chosen a priori based on expert opinion incorporated a minimum rate of antiemetic use in the measure, which increases the risk of capturing antiemetics not intended for CINV prevention. To address this, we limited the look-back period calculation to only preventative antiemetic drugs. However, this may still underestimate the proportion of patients who underused antiemetics. Similarly, patients with prior non-highly emetogenic chemotherapy or radiation therapy may have been using antiemetics captured in the look-back period in conjunction with those treatments versus the intravenously administered highly emetogenic chemotherapy treatment. Finally, our data had limited overlap following the approval of the netupitant-palonosetron combination in late 2014 and rolapitant in late 2015.(1) Additionally, while studies supporting the use of olanzapine as a prophylactic antiemetic were published as early as 2011, NCCN included it as a recommendation only in 2014, ASCO highlighted it as a highly promising therapy in 2015, and the largest trial to date was published in 2016, again providing limited overlap with our study period.(27, 52, 84)

5.3.2 Aim 2 Limitations

In addition to the limitations outlined in section 5.3.1 regarding retrospective data and antiemetic measurement, three other limitations should be noted. First, we were unable to measure prescriber level characteristics including physician awareness of current guidelines. This limited our ability to disentangle physician-drivers of treatment choice such as lack of knowledge versus provider preference for treatment strategy. Second, we did not have data on facility level characteristics such as whether an automated

electronic medical record prescribing system existed. Having an automated prescribing system largely eliminates the role of physician choice in standard order sets, unless s/he overrode the default antiemetic option. Third, we were unable to measure the effect of patient-level engagement or preferences on antiemetic use.

5.3.3 Aim 3 Limitations

There are several limitations related to uncertainty that our probabilistic sensitivity analysis aimed to address by modeling a range of input values. First, there were several challenges with the trial data used as clinical inputs. Characteristic of randomized clinical trials, the outcomes did not reflect the real world use of the products, as patients may not have adhered to their regimens.(215) We also had to compute complete protection rates for olanzapine-based strategies because the trials did not capture this outcome. Additionally, because the only trial assessing the effectiveness of olanzapine in the presence of NK1 had much lower effectiveness outcomes for the NK1 without an olanzapine arm, we computed base case complete response rates based on the relative risk. Second, we assumed that patients either remained in the same health state or transitioned to a worse health state by using linear interpolation between the acute phase and overall phase to calculate transition probabilities for each day in the delayed phase. While this assumption and approach is used in the most recent cost-effectiveness studies modeling antiemetic use, in the real world patients may transition into a better health state. In addition, because trials measured days 2-5 as a single delayed state, we did not have access to day level health states. Notably, this approach is more accurate that older models where days 2-5 were treated as a single period and patients would remain in the same health state in all four days of the delayed phase.(56-58) Given that the utilities and costs associated with each health state are the same regardless of which day the state is experienced, the distribution of days in each health state may not be relevant (e.g., experiencing incomplete response consecutively on days 4 and 5 is the same as experiencing incomplete response on days 2 and 5).

While there are several indirect costs associated with CINV such as transportation costs to access the healthcare system and caregiver costs, the only indirect cost information identified in the literature was related to productivity. Finally, treatment acquisition costs were based on price information available

in the 2017 ASCO antiemetic guideline, which used the following sources: UpToDate.com (dosing schedules), Medicare Part B Average Sales Price (ASP) Data (intravenously administered Medicare Part D Plan Finder Data (orally administered products). While ASP data incorporate discounts and rebates, the Plan Finder Data represent the cost to the consumer, which may not reflect true acquisition costs to plans. Additionally, the literature used to identify cost inputs were based on claims studies, which only include information on nausea and vomiting events that were severe enough for hospitalizations, so rescue medication use on its own was not captured.(8, 9) As such, we used the sum of the median costs for olanzapine and ondansetron as a proxy for rescue medication use.

5.4 Conclusion and Future Research

In the US, the increased attention on value-based care, including alternative payment models and outcomes-based contracting are incentivizing stakeholders to emphasize high-quality, evidence-based care, which includes guideline adherence. Oncology especially is an area of interest given the high costs associated with cancer care, projected to total $173B in 2020.(60) Prior studies have shown that promoting value-based cancer treatment and supportive care is effective in reducing cancer-associated spending.(216) This project focuses on antiemetic under-use in patients initiating highly emetogenic chemotherapy. Preventing CINV through guideline-concordant antiemetic prescribing has been shown to reduce downstream costs and improve quality of life as well as potentially improve future chemotherapy adherence.(1, 3, 4, 11-13, 67, 68)

While there are several antiemetic strategies that have robust evidence supporting their effectiveness, their use and the factors that affect use are not well understood in the United States. Studies examining antiemetic under-use have largely taken place outside of the United States with the exception of two small studies. The first aim of this study contributes to the understanding of antiemetic use by examining it in a large claims population reflective of the Commercial Claims and Medicare Supplement population. This is the largest study examining under-use in the United States to the best of our knowledge. Alarmingly, under-use of guideline-concordant antiemetic fills is high at 49% and 68% in the commercial claims and Medicare supplement populations, respectively. While more than 75% of patients

are filling 5HT3As and dexamethasone, we found that NK1 product fills were low and olanzapine fills were negligible despite NK1s being in guidelines since 2006 and olanzapine being in NCCN guidelines since 2014 (and effectiveness data available since 2011). Additionally, more expensive palonosetron was more frequently prescribed than low-cost first-generation 5HT3As in both populations, despite having similar effectiveness in the presence of NK1s.

In our second aim, we assessed the effects of environmental, predisposing, enabling, and need factors on under-use in the same claims data as Aim 1. Type of chemotherapy received was among the strongest predictors of under-use, with patients receiving anthracycline and cyclophosphamide combination regimens less likely to under-use compared to anthracycline-only and cyclophosphamide-only regimens. However, this is expected given anthracycline-only and cyclophosphamide-only regimens are considered highly emetogenic only when given at certain doses based on body-surface area thresholds. The next greatest predictor of under-use was the setting in which chemotherapy was administered. Compared to receiving chemotherapy in the physician office setting, patients receiving chemotherapy in an outpatient hospital setting were at 28% and 48% higher risk of under-use in the CCAE and Medicare Supplement populations, respectively. As a result, we recommend prioritizing interventions targeting under-use in the outpatient hospital setting over the physician outpatient setting.

Of note, it is hypothesized that out-of-pocket costs may prevent patients from filling guideline-concordant prescribing treatment strategies, especially given that NK1s are expensive, though this had not been previously studied. Our analysis found that medical benefit generosity and prescription drug generosity has limited impact on under-use in both populations. Additionally, given the high cost of cancer care, patients may be reaching out-of-pocket maximums in the CCAE population, so out-of-pocket costs and insurance generosity may be moot. Aim 1 cost results that found patients in both populations had a median out-of-pocket costs for $0 for all intravenously administered antiemetic products (covered by the medical benefit) support this.

While not measured in Aim 2 because we did not have the data, the role of the provider in antiemetic use is important to consider. Whether guideline discordant prescribing is due to a gap in

provider knowledge or provider accountability is unknown. If it is the former, provider education by professional societies, patient advocacy groups, payers, and manufacturers is necessary. If it is the latter, one solution is the development of a validated appropriate antiemetic prescribing measure for patients initiating highly emetogenic chemotherapy that is implemented into commercial plan quality programs and the CMS Merit-Based Incentive Payment System. Notably, ASCO's Quality Oncology Practice Initiative program does include an antiemetic measure for patients initiating highly emetogenic and moderately emetogenic chemotherapy under its symptom/toxicity management module.(217) However, it requires only that providers prescribe a 5HT3A and dexamethasone for patients initiating highly emetogenic chemotherapy, in contradiction with guidelines that also recommend an NK1. It also does not allow for olanzapine-based strategies to be considered as a concordant strategy that fulfills the measure, which in fact we found to be the most cost-efficient strategy. This highlights the importance of quality initiatives correctly incorporating guideline recommendations into their measures as over 8,000 oncologists are registered for QOPI across the United States.(218)

Future studies should assess the uptake of newer antiemetic products and regimens in patients initiating highly emetogenic chemotherapy with more recent claims data to understand their fill trends. Using other data sources such as electronic medical records that include antiemetic prescribing data or patient diaries that include data on what antiemetics patients actually took could help triangulate occurrences of care failure and address them. Additionally, understanding the real world outcomes (i.e., CINV events and their associated healthcare resource) and subsequent activities (e.g., future antiemetic prescribing and chemotherapy adherence) associated with antiemetic under-use will support the value of appropriate prescribing. Though challenging to conduct in claims data given the lack of specificity in identifying chemotherapy-induced nausea and vomiting events, this may be possible in other data sources such as electronic health record data or registry data.

As mentioned earlier, there are several CINV preventative treatment regimens that are considered guideline-concordant for patients initiating highly emetogenic chemotherapy, with no clearly preferred treatment strategy. Given the wide variability in costs for these regimens, assessing cost effectiveness

across the regimens is one way to prioritize products, which we did in Aim 3. Notably, this is the first cost-effectiveness analysis to compare all NK1 strategies and olanzapine strategies. Ultimately, we found that from the US healthcare system perspective and societal perspective, olanzapine + fosaprepitant + 5HT3A + dexamethasone dominated all other strategies in the base-case. We also conducted a scenario analysis from the US healthcare perspective removing olanzapine strategies given clinical and evidentiary concerns and found that that NEPA dominated rolapitant- and aprepitant-based strategies. While it conferred an additional benefit when compared with fosaprepitant+5HT3A+dexamethasone, NEPA was not cost-effective. Given the limited incremental benefit across strategies (the max difference is .86 QALD), it may be appropriate to utilize a cost-minimization approach and revert to using the treatment with the lowest acquisition cost, which would be, olanzapine + palonosetron + dexamethasone.

We recommend that guidelines and prescribers consider the cost of antiemetics to prioritize strategies. When using an NK1 strategy, especially given that there are no differences in 5HT3A effectiveness, there is no reason to prescribe palonosetron over less expensive first-generation 5HT3As (both oral and intravenous). Additionally, given that total cost of intravenous antiemetic products is generally lower than oral products (in addition to our earlier findings that intravenous products had lower out-of-pocket costs to patients), intravenous products should be used over oral products unless the patient is contraindicated or unable to tolerate it.

While we conducted sensitivity analyses, more research on the real world effectiveness of these various strategies and indirect cost information is necessary to inform clinical inputs. Future studies should also assess this model from the commercial payer, Medicare, and Medicaid perspectives. Reimbursement policies and product prices along with patient needs are different across these populations. Additionally it is important to assess the effects of these antiemetic products in preventing anticipatory or refractory nausea and vomiting in future cycles is critical given the paucity of knowledge in this area.

APPENDIX 1: ANTIEMETIC COST TABLE METHODOLOGY (CHAPTER 2, TABLE 2.4)

This cost table was leveraged from the 2017 ASCO guidelines.(18) The following sources of data were used to compile this table UpToDate (dosing schedules), pricing for oral products (Medicare Part D Plan Finder), pricing for intravenously administered products (Medicare Part B Sales Price Data). Please refer to the guidelines for the full methodology.

APPENDIX 2: EUROPEAN AND ASIAN STUDIES (CHAPTER 2, SECTION 2.2.2)

European Studies

A prospective cohort study in 1996 with approximately 1,200 consecutive Italian cancer patients, 96.1% received some sort of antiemetic therapy for acute prophylaxis regardless of CINV risk of the chemotherapy.(23) All patients on highly emetogenic chemotherapy received some type of antiemetics. Nearly all patients received 5HT3A monotherapy or in combination with a corticosteroid. In contrast, ~36% received antiemetics for delayed CINV, with patients initiating cisplatin-based therapy having the highest proportion. While 38.8% of patients were prescribed rescue treatment across CINV-risk, only 16.8% filled the prescription. While the study cohort included both new and prior initiators of chemotherapy (92%), there was no significant difference in the antiemetics used.(23)

Chinese Studies

Zong 2016 published the largest study examining antiemetic prescribing using the China Health Insurance Research Association (CHIRA) Database consisting of over 14,000 patients initiating moderately or highly emetogenic chemotherapy between 2008-2012, when NK1s were not approved in China.(32) This study found that 89.5% of patients received antiemetics for prevention of acute CINV, 71.5% for delayed CINV, and 9.0% for breakthrough CINV. Among patients using antiemetics to prevent acute CINV, 6.3%, 93.3%, and 0.4% used single, multiple, and herbal/alternative regimens, respectively. Product use for preventing CINV in the delayed phase was similar. Nearly 60% of patients initiating highly emetogenic chemotherapy received three-class regimens in both the acute and delayed phases, with the most common three-class regimen consisting of a 5HT3A+corticosteroid, and either antihistamine or benzoylamide. (32) Additionally, 26.5% and 25.5% of patient initiating highly emetogenic chemotherapy initiated four-class regimen in the acute phase and delayed phase respectively. Notably, 5HT3As (97.4% and 97.5%) were prescribed to a higher proportion of patients initiating highly emetogenic chemotherapy than corticosteroids (85.5% and 84.2%) in the acute and delayed phases, respectively.(32) Another large retrospective study that took place between 2005-2011 consisting of more than 2,500 Japanese patients

found that antiemetic use increased over time, up 95% in 2011 among highly emetogenic chemotherapy users.(33) Additionally, NK1 use increased to 60% in 2011 use in highly emetogenic chemotherapy users after 37.0% use after its approval in 2009. (33) A retrospective, distributed research network study in Japan also found that the 96% of patients initiating highly emetogenic chemotherapy received at least one antiemetic in the acute phase but overall compliance was only 9.4%.(34) Also, while the NK1 use in the delayed phase was increasing, the corticosteroid use was low. (34)

A pan-Asia and Australia prospective study using a combination of electronic medical record data and self-reported data from 2011-2012 found that all patients but 1 out of 318 initiated highly emetogenic chemotherapy received an antiemetic for preventing acute CINV with 96% receiving a 5HT3A and 85% receiving a corticosteroid.(35) On average, patients in the highly emetogenic group were prescribed 3.2 (1.1) and 1.9 (1.1) unique antiemetic drugs in the acute and delayed phases. (35) Another prospective observational study in Singapore using data from 2006-2011found that 90% of patients initiating highly emetogenic chemotherapy (N=361) were prescribed 5HT3A + corticosteroid regimen in the delayed phase versus an aprepitant + dexamethasone regimen, though adherence was only 58%.(36) Additionally they found the rate of dexamethasone prescribing was low. (36) A third prospective observational study found that over 70% of Japanese patients initiating highly emetogenic chemotherapy were using a three-class regimen consisting of dexamethasone, 5HT3A, and aprepitant. (37)

APPENDIX 3: AIM 1 METHODS AND RESULTS APPENDIX FIGURES AND TABLES

Table A.1 Distribution of Preventative Antiemetic Filled in the 6 Months Prior to First IV Chemotherapy Administration in the CCAE Population (IVAntiBefore = Number of Days Before IV HEC)

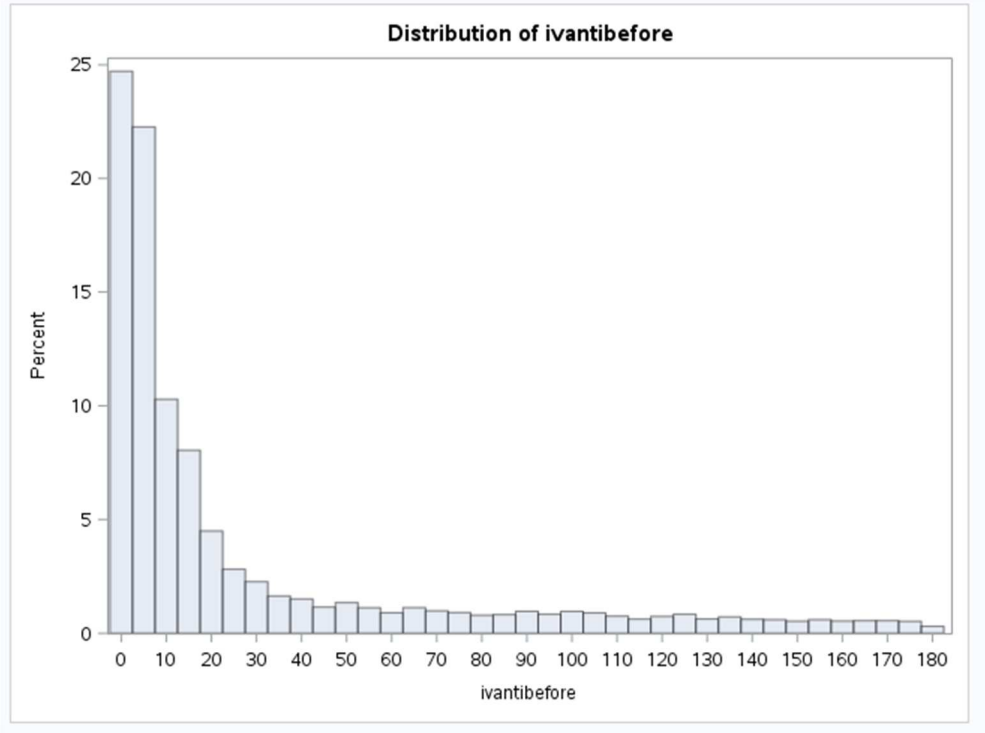


Table A.2 Distribution of Preventative Antiemetic Filled in the 6 Months Prior to First IV Chemotherapy Administration in the Medicare Supplement Population (IVAntiBefore = Number of Days Before IV HEC)

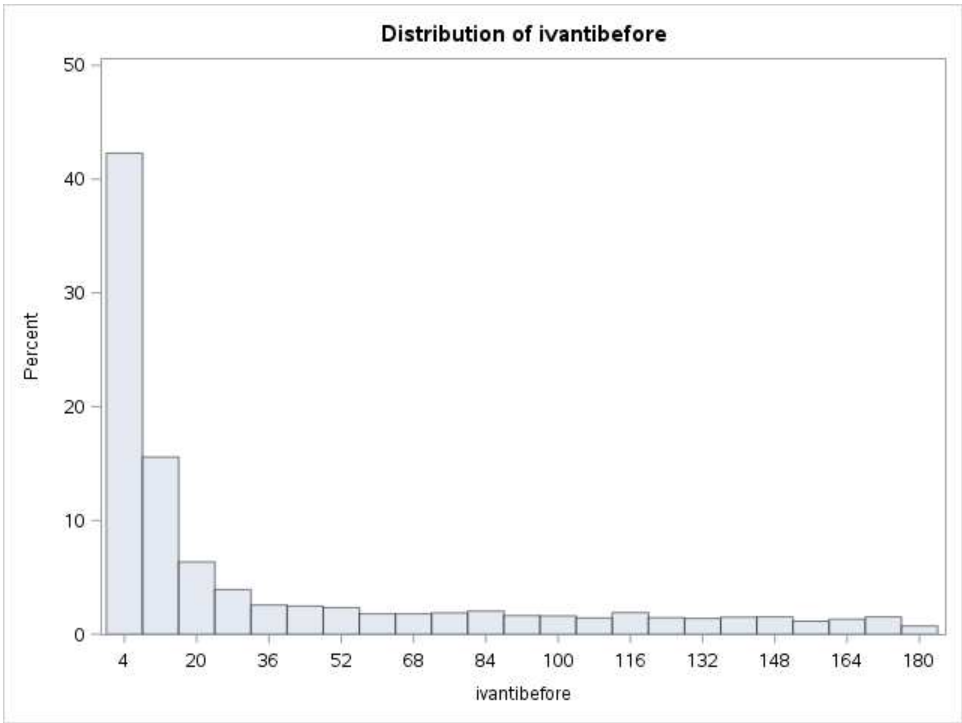


Figure A.1 Number of Antiemetics Filled by Class CCAE Population (N=31,923 Patients)

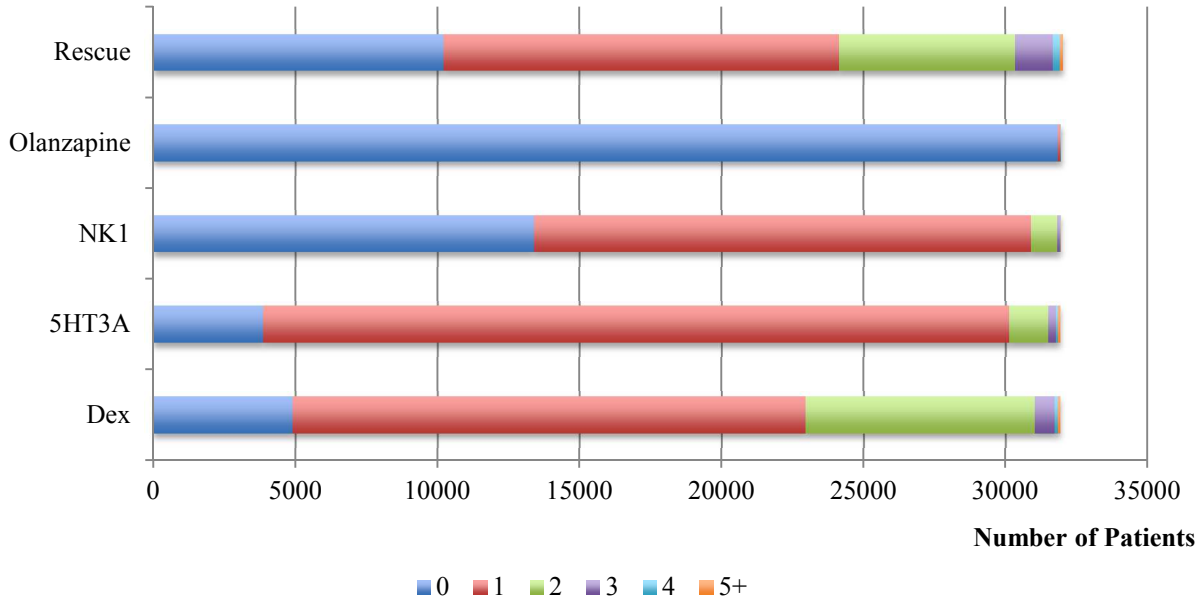
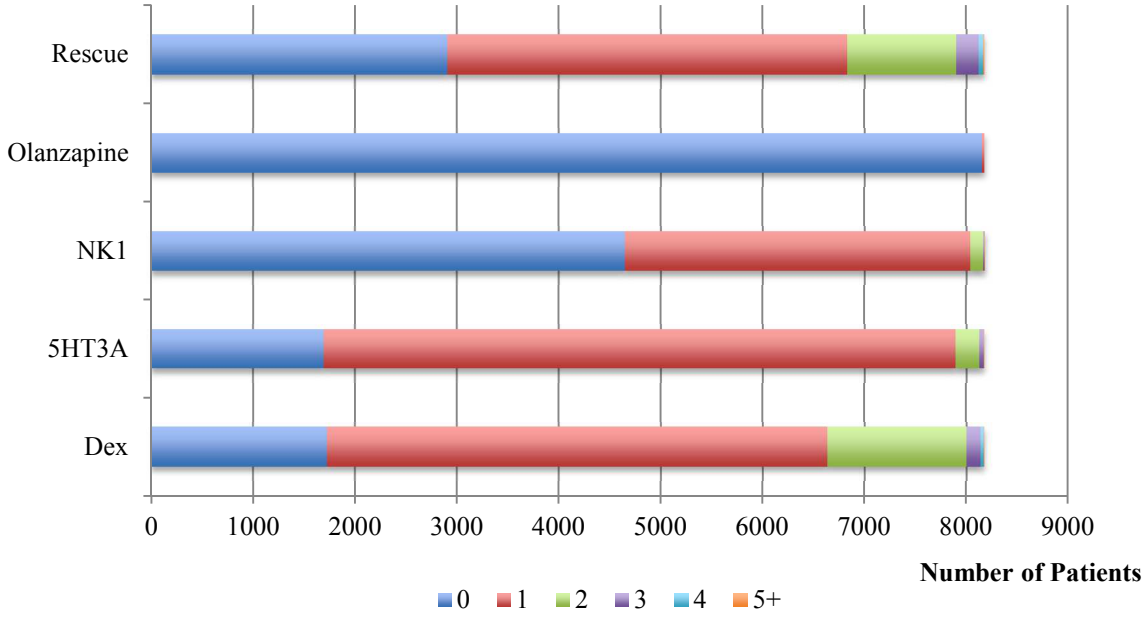


Figure A.2 Number of Antiemetics Filled by Class Medicare Supplement Population (N=8,991 Patients)



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