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# ASSESSING THE IMPACT OF PRESCRIPTION OPIOID USE VERSUS NO USE ON ADHERENCE TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) MAINTENANCE MEDICATIONS, COPD EXACERBATIONS AND TOTAL HEALTHCARE COSTS

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DISSERTATION

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## DEDICATION

To my parents, Ajinath and Ratnamala Kharat for always believing in me.

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My education would never be possible without my pillars of strength, my parents Drs. Ajinath and Ratnamala Kharat, my sister Aditi, and my beloved wife Kaitlin. I have successfully completed my graduate education because of my incredible family. I am grateful to have you all in my life. I am forever in your debt!

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## ABSTRACT

**OBJECTIVES:** COPD contributes significant morbidity and mortality worldwide and is currently the third leading cause of mortality in the United States. Chronic pain prevalence is high among COPD patients leading to a high rate of prescription opioid use. The potential impact of concurrent prescription opioid use on COPD maintenance medication adherence, COPD exacerbations, and total healthcare costs is not well understood. The study objectives were i) to assess the impact of prescription opioid use compared to no prescription opioid use on COPD maintenance medication adherence in 90, 180, 270, and 365-day follow-up periods, and ii) to assess the impact of long-term prescription opioid use (≥ 90 day prescription opioid supply in a one-year period) compared to no prescription opioid use on COPD maintenance medication adherence, COPD exacerbations and total healthcare costs in one-year follow-up period.

**METHODS:** Patients with COPD diagnosis were identified using ICD9-CM diagnosis codes and COPD maintenance medication prescription claims from the Truven Health MarketScan® Commercial Claims and Encounters Database from July 1, 2008 to December 31, 2009. COPD patients with prescription opioid claims were matched 1:1 to non-opioid users on baseline characteristics: age (±3 years), sex, severe and moderate COPD exacerbations, oxygen therapy use, short-acting beta$_2$-agonist use, COPD maintenance medication adherence, and asthma status. Conditional multiple logistic regression, multiple negative binomial regression and generalized linear model with a gamma distribution and log-link function were used to identify the impact of long-term prescription opioid use versus no opioid use on COPD maintenance medication adherence [defined as proportion of days covered (PDC) ≥ 0.8], COPD exacerbations, total healthcare costs in a one-year period, respectively.

**RESULTS:** A total of 5,541 matched pairs of prescription opioid versus non-opioid users were identified. After adjusting for confounders, prescription opioid use was associated with statistically significantly lower odds of being adherent to COPD maintenance medications compared to no use of prescription opioids in all the four follow-up periods. Long-term prescription opioid users (n=566) had significantly higher mean Deyo-Charlson comorbidity scores (2.4±1.8 vs 1.7±1.2, p<0.0001), presence of comorbid chronic conditions (86.6% vs 76.3%, p<0.0001) and comorbid pain conditions (93.5% vs 70.7%, p<0.0001). After adjusting for confounders, long-term prescription opioid use was associated with 0.63 times (95% CI 0.46-0.88, p<0.01) lower odds of being adherent to COPD maintenance medications; and long-term prescription opioid users had higher adjusted mean all-cause total healthcare costs $23,996 (± $1,106.22) vs $13,947 (± $512.67), $p<0.0001$], compared to non-users of prescription opioids. Long-term prescription opioid use was not statistically significantly associated with severe or total (moderate + severe) COPD exacerbations.

**CONCLUSIONS:** Concurrent long-term use of prescription opioids may significantly lower COPD maintenance medication adherence which may translate into higher total all-cause healthcare costs and requires additional investigation.

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# CHAPTER 1 INTRODUCTION

## Chronic Obstructive Pulmonary Disease burden

Chronic Obstructive Pulmonary Disease (COPD) is defined as "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases"[1]. COPD is chronic and progressive in nature and is currently treatable but irreversible[1]. COPD contributes to a significant healthcare burden around the world and the United States (US). An estimated 384 million people in 2010 had COPD representing 11.7% of the world population and the prevalence is expected to rise[1–4]. Many people may have COPD but may go undiagnosed and most may get diagnosed only at advanced stages. COPD is one of the leading causes of mortality across the world with about 6% of all deaths (3 million deaths) worldwide in 2012 being attributed to it[5]. COPD is the fourth leading cause of mortality worldwide and the third leading cause of mortality in the US[1]. Along with mortality, COPD patients also contribute significantly to the utilization of healthcare resources such as emergency room visits, hospitalization, and physician office visits[1]. According to the American Lung Association, the US spent about $49.9 billion for the management of COPD in 2010 with about $29.5 billion in direct healthcare costs[6]. According to the Centers for Disease Control and Prevention (CDC) the direct healthcare expenditures for COPD are expected to rise to US $49 billion by 2020[7]. Patients with COPD commonly experience other chronic comorbidities such as diabetes, musculoskeletal pain, and cardiovascular conditions. The presence of these conditions may make the management of COPD difficult and may contribute significantly to the utilization of healthcare services by COPD patients[8].

**Prescription opioid therapy**

Prescription opioids are commonly used to alleviate acute pain, chronic pain in terminal patients with cancer and in patients with chronic non-cancer pain (CNCP). The prevalence of CNCP among the US adult population is high (11% to 15% of the adult population), and prescription opioids are used on a wide scale for treating CNCP[9,10]. About 20% of patients with CNCP receive prescription opioids either acutely or on a long-term basis[11]. Although there is established validity for the use of prescription opioids acutely in CNCP, there is little evidence for their use on a long-term basis for CNCP[12–15]. Furthermore, the effect of either acute or long-term use of prescription opioids for CNCP on adherence to treatment for concurrent conditions, health-related quality of life, and pain-relief is still not very well understood[16]. Despite lacking evidence for effectiveness, the use of prescription opioids on a long-term basis is highly prevalent in the US population. Overall, about 11 million people in 2005 were prescribed long-term prescription opioid therapy[17].

**Adverse events associated with the use of opioids**

Prescription opioids have the potential to induce psychological addiction and have been abused on a wide scale. With the significant increase in the use of prescription opioids over the past decade the problems of opioid abuse and misuse have increased significantly, becoming a major public health concern. Prescription opioid abuse and misuse contributes to a significant healthcare and economic burden in the US. In 2009, about 1.2 million emergency room visits were associated with prescription drugs, mostly prescription opioids, compared to 1 million visits for cocaine and heroin combined[18,19]. Annually, about $20.4 billion are spent in direct and indirect costs for the treatment of opioid poisoning[20,21]. About $800 million and $1.3 billion are spent annually for emergency room visits and inpatient visits for the treatment of opioid poisoning in the US, respectively[20,21]. Opioid use is also associated with high mortality rates, and 2014 was recorded as the year with the highest number of deaths due to drug overdoses, with about 6 out of 10 deaths due to overdoses attributed to opioid abuse[20,22]. Deaths due to opioid overdoses, both prescription and illicit, have increased by four times since 1999[18]. About 30,000 deaths in 2014 were due to overdose of prescription opioids and heroin[23]. The number of deaths attributed to prescription opioids alone exceed the number of deaths due to heroin and cocaine combined[18,20].

About 8% of the US population suffers from substance abuse disorder and this rate is much higher among patients with CNCP[24–26]. Use of prescription opioids either on a long-term or short-term basis may result in patients exhibiting aberrant drug related behavior (ADRB) such as misuse, diversion, physical dependence, abuse, addiction and tolerance. The likelihood of developing ADRB among long-term opioid users is high, even short-term use (acute use) of prescription opioids significantly increases the of odds of developing ADRB[27]. Patients with CNCP using low-dose acute opioids (defined as ≤36 mg of morphine equivalent dosage) had 3.03 times (OR=3.03; 95% CI: 2.32-3.95) significantly higher odds of developing ADRB compared to non-opioid users[27]. However, among long-term, high dose prescription opioid users (defined as ≥120 mg of morphine equivalent dosage) the odds increased by 122 fold (OR=122.45; 95% CI: 72.79-205.99)[27].

Along with ADRB, the use of prescription opioids has also been reported to be associated with a range of adverse events. Use of prescription opioids on a long-term basis may have effect on a variety of hormones in both men and women. Depression has been reported as result of prescription opioid use[28]. Long-term use of prescription opioids has been associated with hyperalgesia, a condition in which use of prescription opioids leads to an increased sensitivity to pain[26,29]. Opioid induced sedation is also a common side effect of prescription opioid use[30]. One of the most commonly observed side effects associated with the use of prescription opioids is constipation. It occurs in as many as 95% of patients taking prescription opioids[31]. Although constipation may not be regarded as a serious adverse event, it may lead to morbidity, lowered health related quality of life and even mortality has been reported among some patients[26]. Respiratory depression is a serious adverse effect associated with the use of prescription opioids. One of the most common causes of deaths among illicit opioid users is respiratory depression[32].

**Medication adherence among patients with COPD**

Medication adherence is the degree to which patients follow the recommendations by their healthcare providers with regards to the timing of medication use, in the prescribed dose, and with the recommended frequency. It is defined as compliance of patients with the recommended medication dosage[33]. Medication non-adherence leads to sub-optimal control of medical conditions, increases the risks of mortality, and leads to a significant increase in healthcare costs[34–38]. About 33% to 69% of all medication-related hospitalizations have been attributed to non-adherence to medications, costing the US approximately $100 billion a year[34,36,39,40]. Good medication adherence is therefore helpful in achieving optimal clinical outcomes and in-turn lowering healthcare costs in the management of health conditions[41–43].

Patients with COPD commonly suffer from problems of poor medication adherence. Poor medication adherence to maintenance medications among COPD patients can be attributed to a number of reasons. Maintenance medications for COPD are prescribed in inhaled form using devices which may require education on proper techniques of use of inhalers. These inhaled, maintenance medications may require to be taken in multiple doses on a daily basis. Patients with COPD also commonly suffer from comorbid conditions such as diabetes, depression, cardiovascular diseases and hypertension which may add to the medication burden and lead to poor medication adherence[44,45]. In general, patients with COPD exhibit low adherence to their maintenance medications even when compared to their asthmatic counterparts[46]. About 60% of COPD patients exhibit poor adherence to COPD treatment and even more do not use their inhalers correctly[46–48].

Although COPD is a chronic progressive disorder without a cure, proper management of COPD with medication therapy helps to control the symptoms of COPD and may prolong the advancement of the disease[1,49]. Adherence to maintenance medications in patients with COPD have proven benefits in terms of economic, clinical, and humanistic outcomes. It has been shown that adherence to COPD maintenance medications helps to reduce mortality risks and the risk of severe respiratory exacerbations, leading to reduction in the number of inpatient and emergency room visits and their associated costs[50]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) treatment guidelines for managing COPD symptoms acknowledge the importance of medication adherence to maintenance medications for controlling COPD symptoms and exacerbations[1].

Many studies have been published previously that examine the clinical and economic significance of medication adherence to COPD-related maintenance medications[51–55]. There is established evidence in support of medication adherence to maintenance medications in COPD treatment[51–55]. Adherence to maintenance medications helps to control COPD symptoms and helps reduce COPD exacerbations, reduces healthcare resource utilization and costs and also reduces the risk for mortality[51–55].

**Use of prescription opioids among patients with COPD**

Prescription opioids are commonly used among patients with COPD and are proven to be effective in providing analgesia[56]. Patients with COPD commonly experience dyspnea, a feeling of shortness of breath and labored breathing associated with pain. The use of prescription opioids in the treatment of dyspnea among COPD patients is widely accepted[56,57]. Along with dyspnea, the presence of chronic pain is also widely prevalent among COPD patients. The prevalence of chronic pain is significantly higher among COPD patients compared to patients with other chronic conditions (59.8% vs 51.7%)[58]. With the high prevalence of chronic pain, the use of prescription opioids for treating pain is also highly prevalent among COPD patients[58]. When compared to patients without COPD but with another chronic illness in multivariate analyses, COPD patients had statistically significant higher odds of chronic use of prescription opioids (OR: 1.74; 95% CI: 1.57 – 1.92)[58].

With the wide use, adverse events associated with prescription opioids may also be common among patients with COPD. Respiratory depression is a major concern in patients with COPD. COPD patients who abuse or misuse prescription opioids may be at increased likelihood of respiratory depression than those without COPD. Due to the fear of respiratory depression, physicians may feel hesitant to provide prescription opioids for patients with COPD[59]. Despite the likelihood of respiratory depression, previously published controlled trials have reported prescription opioids to be safe for use in patients with COPD[56,57,60–63]. These studies however, suffered from many limitations such as small sample sizes, and systematic exclusion of patients experiencing no benefits and those who died[64]. The importance of assessing the effect of concomitant prescription opioid use on adherence to other chronic medications has been acknowledged in the past[65]. A study among type 2 diabetes patients using a large US administrative database reported that type 2 diabetes patients using prescription opioids on a long-term basis (≥90 days) had statistically significantly poorer compliance to oral antihyperglycemic agents in comparison to type 2 diabetes patients not taking long-term prescription opioids[65]. It is therefore important to understand if the use of prescription opioids has an impact on medication adherence, healthcare resource utilization and costs among COPD patients.

Vozoris N et al, 2016 conducted a study to identify the occurrence of adverse respiratory outcomes within 30 days of incident prescription opioid use among older COPD patients[64]. The study found that incident prescription opioid users were associated with a significantly higher risk for COPD and pneumonia-related emergency room visits and mortality compared to non-opioid users. Similarly, Ekstrom M and colleagues conducted a study to identify the effects of prescription opioid and benzodiazepine use on hospital admission rates and mortality rates among COPD patients from Sweden[66]. The use of prescription opioids in COPD patients had no effect on the rate of hospital admission compared to COPD patients without prescription opioids. The use of low dose prescription opioids (≤30mg of morphine equivalent dose per day) had no statistically significant effect on mortality rate, however using high dose prescription opioids (>30mg of morphine equivalent dose per day) significantly increased the mortality rate of COPD patients (hazard ratio: 1.21; 95% CI: 1.02 – 1.44)[66]. Vozoris N et al, 2017 conducted a retrospective cohort study to identify the impact of incident prescription opioid use on adverse cardiac events, among a geriatric sample of COPD patients identified using an administrative claims[67]. Incident use of prescription opioids was associated with statistically significant increased rates of ischemic heart disease-related mortality and morbidity. When stratified by the type of prescription opioid agents used, prescription opioid-only users had significantly higher hazard rates for ischemic heart disease-related emergency room visits and hospitalizations (hazard ratio 1.38; 95% CI 1.08–1.77) and mortality (hazard ratio 1.83; 95% CI 1.32–2.53) compared to users of combination prescription opioids[67].

**Gaps in the literature and need for the study**

Previously published studies about the prevalence of prescription opioid use among patients with COPD suggests that there is a high prevalence of prescription opioid use among COPD patients[58]. COPD patients may have higher prevalence of chronic pain compared to patients without COPD but with other chronic conditions and subsequently display a higher use of prescription opioids[58]. Despite physicians’ fear of respiratory depression due to opioid use, COPD patients still exhibit a high prevalence of both long-term and short-term use of prescription opioids[58]. Only three studies assessed and reported the impact of prescription opioid use and adverse health outcomes among COPD patients[64,66,67]. Although these studies classified prescription opioids according to high or low doses they did not assess the effect of long-term use compared to short-term use of prescription opioids on COPD-related health outcomes. These studies also found contrasting results on the effects of opioids on adverse health outcomes. Vozoris et al found prescription opioid use to be associated with increased all-cause and COPD related mortality and COPD and pneumonia-related emergency room visits[64]. The dose of prescription opioids, either low-dose or high-dose, had the same effect on the outcomes. However, Ekstorm M et al reported that only high dose prescription opioids were associated with increased mortality and low dose prescription opioids did not increase the risks of mortality among COPD patients[66]. The use of prescription opioids did not have any effect on COPD-related hospital admissions. Vozoris N et al, 2017 found that prescription opioid-only users compared to users of prescription opioids combined with non-opioid agents had significantly higher hazard rates for ischemic heart disease-related emergency room visits, hospitalizations and mortality[67].

Although the prevalence of prescription opioid use is high among COPD patients, the effects of prescription opioids in this population is not very well studied. Medication adherence is an important aspect of maintenance medication therapy among COPD patents and has been associated with significant clinical effects. None of the previously reported studies have assessed the impact of prescription opioid use on adherence to maintenance medications for COPD. Managing and controlling COPD exacerbations is an important aspect of controlling COPD symptoms. None of the previously published studies have assessed the impact of prescription opioids on COPD exacerbations. Furthermore, long-term use of prescription opioids may lead to aberrant drug related behavior among COPD patients and may have severe consequences on COPD-related medication adherence, and healthcare costs. However, no previous study has reported the impact of long-term prescription opioid use in COPD patients.

**Theoretical framework**

Healthcare behavior theories have been utilized by research studies in the past to understand and explain why individuals or a group of individuals undertake certain health behaviors[68]. For the purpose of this study, Andersen's Behavioral Model of Health Services Use was used as a theoretical framework to facilitate the analysis of the study objectives. The model was originally developed by Ronald M Andersen and has been modified since the original publication in 1968[69,70].

The model has been extensively used by previous studies to assess healthcare service utilization patterns in a multitude of disease areas and patient populations[71–75]. The model is based on the theory that factors such as predisposing factors which predispose individuals to seek care, need factors which necessitate individuals and health professionals to assess their health status, and enabling factors which provide the means to or act as barriers to access to care together contribute towards patient health behaviors and outcomes.

As per the Andersen's Behavioral Model of Health Services Use, prescription opioid use along with additional factors may affect adherence to maintenance medications for COPD and healthcare outcomes (COPD exacerbations and total healthcare costs). These predisposing, need and enabling factors comprise sociodemographic characteristics, clinical characteristics, physician characteristics, and prior utilization characteristics.

**Significance of the study**

If a significant negative association is identified between the use of prescription opioids and medication adherence to COPD-related maintenance medications and COPD exacerbations, it would suggest the need for improving the management of COPD patients concurrently taking prescription opioids to address non-adherence to maintenance therapy. Also, if our study results indicate higher healthcare costs for the management of COPD patients concurrently taking prescription opioids then proper identification and management of prescription opioid therapy along with efforts to improve COPD-related medication adherence may decrease the total healthcare costs of management of COPD. Heightened attempts to identify comorbid prescription opioid use and manage poor medication adherence to maintenance medications for COPD may lead to improved COPD outcomes such as lower rate of COPD exacerbations and healthcare costs. For COPD patients taking maintenance medications, identification of concurrent prescription opioid use might be an effective gauge of potential poor medication adherence in the future and may advocate the need for improved surveillance and management to attain optimum medication adherence.

The results from our study could facilitate designing effective interventions that may help reduce non-adherence to maintenance medications for COPD and further improving COPD-related exacerbations and healthcare costs. The healthcare resources and costs saved from these interventions could further help better allocation of limited healthcare resources among COPD patients. If the concurrent use of prescription opioids has a significant effect on adherence to maintenance medication for COPD and COPD exacerbations and total healthcare costs, then the results of the study may encourage future research to identify the impact of concurrent prescription opioid use on adherence to medications for other chronic conditions.

**Study objective:**

The objective of the study was to assess the impact of prescription opioid use compared to no prescription opioid use on COPD maintenance medication adherence, COPD exacerbations and total all-cause healthcare costs among a real-world sample of COPD patients.

**Study hypotheses and specific aims**

**Specific aim 1:**

To examine the impact of prescription opioid use compared to no prescription opioid use on adherence to COPD maintenance medications, over four different time periods, among a real-world, large sample of COPD patients after adjusting for other confounders.

**Null hypothesis 1A:**

There is no difference in adherence to COPD maintenance medications between prescription opioid users and non-users, within the first 90 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders.

**Null hypothesis 1A (sub-analysis):**

There is no difference in adherence to COPD maintenance medications between prescription opioid users (classified as having ≥30-day supply of prescription opioids and <30-day supply of prescription opioids) and non-users, within the first 90 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders.

**Null hypothesis 1B:**

There is no difference in adherence to COPD maintenance medications between prescription opioid users and non-users, within the first 180 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders.

**Null hypothesis 1B (sub-analysis):**

There is no difference in adherence to COPD maintenance medications between prescription opioid users (classified as having ≥30-day supply of prescription opioids and <30-day supply of prescription opioids) and non-users, within the first 180 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders.

**Null hypothesis 1C:**

There is no difference in adherence to COPD maintenance medications between prescription opioid users and non-users, within the first 270 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders.

**Null hypothesis 1C (sub-analysis):**

There is no difference in adherence to COPD maintenance medications between prescription opioid users (classified as having ≥30-day supply of prescription opioids and <30-day supply of prescription opioids) and non-users, within the first 270 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders.

**Null hypothesis 1D:**

There is no difference in adherence to COPD maintenance medications between prescription opioid users and non-users, within the first 365 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders.

**Null hypothesis 1D (sub-analysis):**

There is no difference in adherence to COPD maintenance medications between prescription opioid users (classified as having ≥30-day supply of prescription opioids and <30-day supply of prescription opioids) and non-users, within the first 365 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders.

**Specific aim 2:**

To examine the impact of long-term prescription opioid use (≥90-day supply in a one-year period) compared to no prescription opioid use on adherence to COPD maintenance medications among a real-world, large sample of COPD patients after adjusting for other confounders.

**Null hypothesis 2:**

There is no difference in adherence to COPD maintenance medications between long-term prescription opioid users (≥90-day supply in a one-year period) and non-users among a real-world, large sample of COPD patients after adjusting for other confounders.

**Specific aim 3:**

To examine the impact of long-term prescription opioid use (≥90-day supply in a one-year period) compared to no prescription opioid use on COPD exacerbations among a real-world, large sample of COPD patients after adjusting for other confounders.

**Null hypothesis 3A:**

There is no difference in the number of severe COPD exacerbations between long-term prescription opioid users (≥90-day supply in a one-year period) and non-users among a real-world, large sample of COPD patients after adjusting for other confounders.

**Null hypothesis 3B:**

There is no difference in the number of moderate and severe COPD exacerbations between long-term prescription opioid users (≥90-day supply in a one-year period) and non-users among a real-world, large sample of COPD patients after adjusting for other confounders.

**Specific aim 4:**

To examine the impact of long-term prescription opioid use (≥90-day supply in a one-year period) compared to no prescription opioid use on all-cause total healthcare costs (prescription medication and medical costs) among a real-world, large sample of COPD patients after adjusting for other confounders.

**Null hypothesis 4:**

There is no difference in all-cause total healthcare costs (prescription medication and medical costs) between long-term prescription opioid users (≥90-day supply in a one-year period) and non-users among a real-world, large sample of COPD patients after adjusting for other confounders.

# CHAPTER 2 LITERATURE REVIEW

This chapter provides a review of the literature associated with the various concepts of the study and is divided into numerous major sections: overview of chronic obstructive pulmonary disease (COPD), overview of prescription opioid therapy, overview of medication adherence, overview of COPD exacerbations, use of prescription opioid therapy among patients with COPD, and a comprehensive literature review of the impact of prescription opioid therapy on adherence and healthcare resource utilization among patients with COPD.

The chapter begins by providing a description of COPD along with its prevalence, healthcare and economic burden associated with COPD, methods for the diagnosis of COPD, overview of COPD exacerbations, and guidelines for the pharmacological management of patients with COPD. An overview of prescription opioid therapy in non-cancer patients and its prevalence is then presented. A discussion of the problems of opioids and prescription opioid epidemic and the economic and healthcare burden associated with the problems of prescription opioid use along with adverse effects associated with the use of prescription opioids is provided. Next, a description of medication adherence, the methods for measuring medication adherence, barriers to medication adherence, followed by a detailed description of the proportion of days covered (PDC) method for the measurement of medication adherence is presented. Further a description of the clinical significance of measuring medication adherence in general, and among patients with COPD is provided.

A detailed literature review of the impact of prescription opioid therapy on adherence to COPD maintenance medications, and the impact of prescription opioid therapy on healthcare resource utilization and costs is provided. The gaps in the literature of the impact of prescription opioid therapy on adherence to COPD maintenance medications and healthcare resource utilization and costs and drawbacks of the studies identified from the literature review is provided.

## Overview of Chronic Obstructive Pulmonary Disease (COPD)

### COPD burden

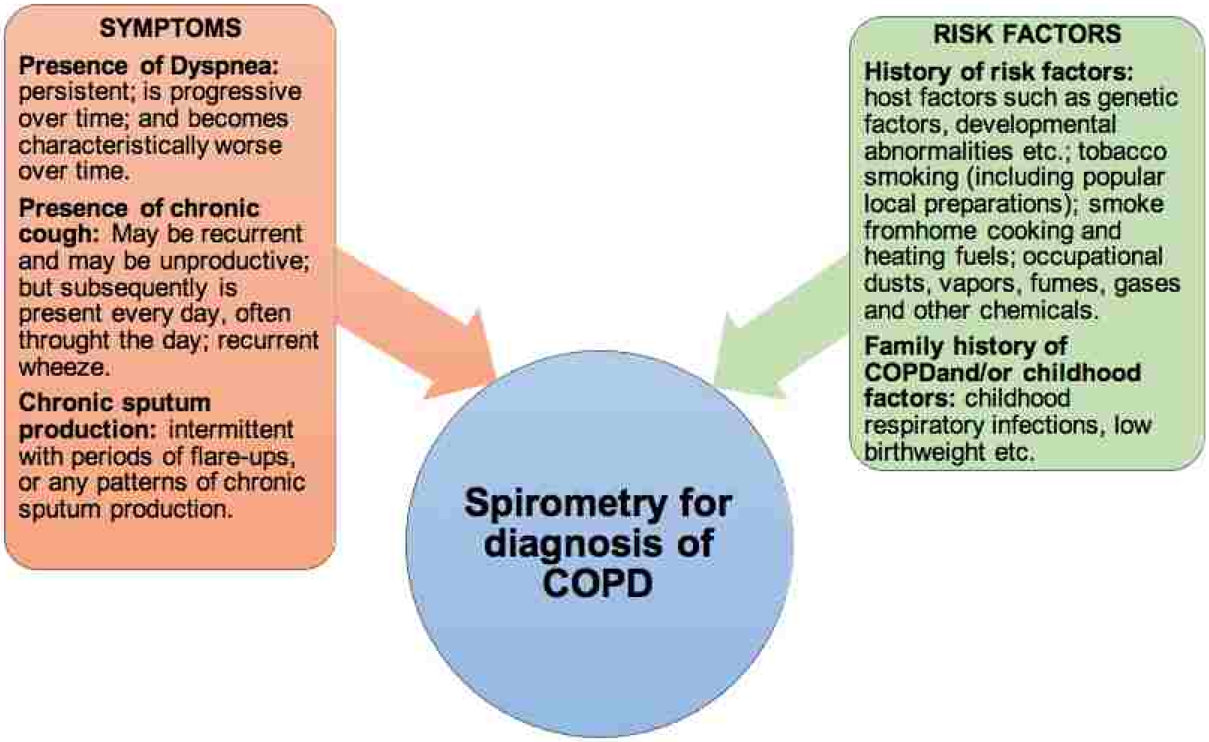
Chronic Obstructive Pulmonary Disease (COPD) is a common condition of the respiratory system and is one of the prominent contributors of mortality across the world. COPD is defined as “a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases”[1]. Emphysema and chronic bronchitis are conditions that have been used to define COPD, however they are not used in the latest updated versions of the treatment guidelines provided by Global Initiative by Chronic Obstructive Lung Disease (GOLD)[1]. COPD is characterized by chronic airflow limitation which is caused by a combination of obstructive bronchiolitis and emphysema[1]. The chronic inflammation in COPD leads to narrowing of small airways, combined with a reduction in the recoil ability of lungs which together have a negative effect on airways to remain open[1]. There are many different factors which increase the risks of developing COPD. These factors include tobacco smoking, exposure to noxious gases and particles, genetic factors, airway hyper-responsiveness, and improper development of lungs during adolescence. COPD is chronic and progressive in nature and is currently treatable but irreversible[1].

COPD contributes to a significant healthcare burden in the world and the US. It is estimated that about 384 million people in 2010 had COPD representing 11.7% of the world population[1,2]. With the increasing life expectancy of the population in the developed countries, and the rising number of smokers in the developing countries the prevalence of COPD is expected to rise[1,3,4]. About 6% (3 million deaths) of all deaths worldwide in 2012 were attributed to COPD[5]. COPD is the fourth leading cause of mortality worldwide and the third leading cause of mortality in the US[1]. Along with mortality, COPD patients also contribute significantly to the utilization of healthcare resources such as emergency room visits, hospitalization, and physician office visits. According to the American Lung Association, the US spent about $49.9 billion for the management of COPD in 2010 with about $29.5 billion in direct healthcare costs[6]. According to the Centers for Disease Control and Prevention (CDC), the direct healthcare expenditures for COPD are expected to rise to US $49 billion by 2020[7]. Patients with COPD commonly experience other chronic comorbidities such as diabetes, musculoskeletal pain, and cardiovascular conditions. The presence of these conditions may make the management of COPD difficult and may contribute significantly to the utilization of healthcare services by COPD patients[8].

**Diagnosis of COPD**

GOLD recommends the consideration for diagnosis of COPD in individuals who are greater than 40 years of age and possess any of the symptoms of COPD coupled with the risk factors such as tobacco smoking, exposure to noxious gases and particles, genetic factors, airway hyper-responsiveness, and improper development of lungs during adolescence (Figure 1.)[1].

**Figure 1. Important indicators for considering diagnosis of COPD[1]**



Spirometry testing is regarded as a reliable and most reproducible form of test for the diagnosis of COPD[1]. Although a reliable method for diagnosis of COPD, spirometry testing is not recommended as a screening tool for individuals who do not exhibit the symptoms and risk factors for COPD but rather for active case finding among individuals with the symptoms and risk factors for COPD[1].

Spirometry is a non-invasive and objective measurement of airway obstruction with a high sensitivity and a moderate specificity[76]. It is commonly performed using a device called spirometer. A spirometer helps clinicians measure the volume of air an individual can inhale and exhale. There are two measures important for the diagnosis of COPD which are calculated using a spirometer, forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_1$). The FVC is a measure of the volume of air that can be forcibly exhaled from a maximum inspiration[1]. Whereas $FEV_1$ is the volume of air that is exhaled during the first second of the calculation of FVC[1]. The ratio of these measures ($FEV_1$ / FVC) is used to diagnose COPD and is indicative of the amount of airflow limitation in an individual. Generally, the $FEV_1$ / FVC is calculated after inhalation of a short-acting bronchodilator. A $FEV_1$ / FVC value of <0.7, after administration of a short-acting bronchodilator, along with presence of COPD-related symptoms and risk factors constitutes a diagnosis of COPD in an individual[1]. The severity of airflow limitation is defined by various cut-off points in the FEV1 values (Table 1). It is important to note however, that severity of airflow limitation based on the FEV1 values alone are not predictive of future COPD exacerbations or the severity of COPD exacerbations or mortality.

**Table 1. Classification of airflow limitation in patients with COPD**

| GOLD Stage | Airflow limitation severity | Definition |
|---|---|---|
| GOLD stage 1 | Mild | $FEV_1 \geq 80\%$ predicted |
| GOLD stage 2 | Moderate | $50\% \leq FEV_1 < 80\%$ predicted |
| GOLD stage 3 | Severe | $30\% \leq FEV_1 < 50\%$ predicted |
| GOLD stage 4 | Very Severe | $FEV_1 < 30\%$ predicted |

*$FEV_1$ = forced expiratory volume in one second*

Source: GOLD[1]

**COPD exacerbations and assessing the risks for future exacerbations**

COPD patients may periodically experience sudden flare-up of their COPD symptoms which may necessitate hospitalizations[1]. These are known as COPD exacerbations and are defined as "acute worsening of respiratory symptoms that result in additional therapy"[1]. Patients with COPD may experience various symptoms during exacerbations such as, dyspnea, wheezing, irregular breathing, anxiety, cough, changes in skin or nail color, difficulty in sleeping and eating, headaches in the mornings, inflammation of legs or ankles, and inability to speak[77,78]. Assessment of COPD exacerbations is very important as it has been regarded as a strong predictor of future exacerbations[79].

COPD exacerbations may be classified as mild, moderate or severe[1]. Mild COPD exacerbation may likely be controlled using only short-acting bronchodilators[1]. A moderate COPD exacerbation may require treatment using a short-acting bronchodilator with a combination of antibiotics and may even require an oral corticosteroid[1]. A severe COPD exacerbation on the other hand may require an emergency room visit or an inpatient hospitalization and may sometimes be associated with acute respiratory failure[1].

**Management of COPD**

Treatment for stable COPD is based on an assessment of patient's symptoms and their likelihood of experiencing future exacerbations. Although COPD cannot be reversed the objectives of COPD treatment are twofold, decrease COPD symptoms, and lessen the risks for future exacerbations. For optimal management of COPD, a combination of both pharmacological and non-pharmacological strategies are undertaken. Patients with COPD need to be provided proper education on optimal management of their symptoms and reducing their risk factors which include lifestyle modification along with a healthy diet and physical exercise. Patients with COPD need to be regularly monitored for their symptoms, exacerbations, medication adherence and presence of adverse events which need to be managed as well.

One of the most common problems with COPD patients is cigarette smoking. It is important that patients with COPD quit smoking, and therefore patients should be provided counseling to encourage them to quit. If necessary, medications and smoking cessation interventions should be delivered. Patients should also be encouraged to take necessary steps to reduce the risks from indoor and outdoor pollutants. COPD patients are also recommended by the Centers for Disease Control and Prevention (CDC) to receive pneumococcal vaccination, although meta-analysis studies among COPD patients have found no benefit from pneumococcal vaccination in terms of reduction of inpatient and emergency room visits or reduction in the rates of pneumonia[80]. COPD patients are recommended to have an annual influenza vaccination, which unlike pneumococcal vaccination has found to be associated with reduction in COPD exacerbation rates[81]. Pulmonary rehabilitation among severe COPD stages may also prove beneficial in improving exercise tolerance, and reducing dyspnea[82].

Along with lifestyle modification, patients with COPD are prescribed pharmacological therapy which is crucial in the management of COPD. The various agents used in the treatment of COPD are listed in Table 2.

**Table 2. Medications in the treatment of COPD**

| Drug class | Drugs in the class |
|---|---|
| Beta$_2$-agonist | **Short-acting**<br>Fenoterol<br>Levalbuterol<br>Salbutamol (albuterol)<br>Terbutaline<br>**Long-acting**<br>Arformoterol<br>Formoterol<br>Indacaterol<br>Olodaterol<br>Salmeterol |
| Anticholinergics | **Short-acting**<br>Ipratropium bromide<br>Oxitropium bromide<br>**Long-acting**<br>Aclidinium bromide<br>Glycopyrronium bromide<br>Tiotropium<br>Umeclidinium |
| Combination of short-acting beta$_2$-agonist and anticholinergic in one device | Fenoterol/Ipratropium<br>Salbutamol/Ipratropium |
| Combination of long-acting beta$_2$-agonist and anticholinergic in one device | Formoterol/Aclidinium<br>Formoterol/Glycopyrronium<br>Indacaterol/Glycopyrronium<br>Vilanterol/Umeclidinium<br>Olodaterol/Tiotropium |
| Methylxanthines | Aminophylline<br>Theophylline |
| Combination of long-acting beta$_2$-agonist and corticosteroids in one device | Formoterol/Beclomethasone<br>Formoterol/Budesonide<br>Salmeterol/Fluticasone<br>Vilanterol/Fluticasone furoate |
| Phosphodiesterase-4 inhibitors | Roflumilast |

Source: GOLD[1]

GOLD recommends that the choice of medications in the management of COPD should rely on patients' symptoms and risk of future exacerbations. They have created an ABCD assessment tool to simplify healthcare providers in choosing the various medications (Table 3)[1]. Based on the ABCD assessment tool, GOLD provides an algorithm for treatment of COPD patients as described in Table 4[1].

In summary, COPD is a common respiratory condition and is the fourth leading cause of mortality worldwide[1]. It is associated with a significant health care burden with about 12% of the world population suffering from COPD and leading to about US $50 billion in healthcare spending, annually[1,2,6]. It is generally diagnosed using spirometry in people above 40 years of age and possessing symptoms of COPD coupled with risk factors for COPD such as exposure to smoke, particulate matter, or having a family history of COPD. Patients with COPD commonly experience exacerbations which may require an emergency room visit or inpatient hospitalization. Having a COPD exacerbation is regarded as the strongest predictor of future exacerbations[79]. Patients with COPD are commonly prescribed inhaled bronchodilators which help in controlling the symptoms of COPD and reduce the likelihood of future exacerbations[1].

**Overview of prescription opioid therapy**

**Opioid epidemic**

The use of prescription opioids has increased drastically in the past few years with nearly three-fold increase in sales of prescription opioids in the US in 2015 compared to 1999 and nearly four times the amount sold in Europe in 2015[18,83,84]. Prescription opioids are commonly used to alleviate acute pain, chronic pain in terminal patients with cancer and in patients with chronic non-cancer pain (CNCP). Although the

**Table 3. ABCD assessment tool by GOLD**

| ABCD classification | Spirometric evaluation | Exacerbation history | mMRC | CAT |
|---|---|---|---|---|
| A | GOLD stage 1 | ≤1 exacerbation not leading to hospital admission | 0 – 1 | <10 |
| B | GOLD stage 2 | ≤1 exacerbation not leading to hospital admission | ≥2 | ≥10 |
| C | GOLD stage 3 | ≥2 exacerbations or ≥1 exacerbation leading to hospital admission | 0 – 1 | <10 |
| D | GOLD stage 4 | ≥2 exacerbations or ≥1 exacerbation leading to hospital admission | ≥2 | ≥10 |

*mMRC = modified Medical Research Council Dyspnea Scale*
*CAT = COPD Assessment Test*
Source: GOLD[1]

**Table 4. COPD treatment algorithm**

| Group | GOLD recommendation for pharmacological therapy |
|---|---|
| A | • Patients should be prescribed either a short-acting or long-acting bronchodilator.<br>• Symptoms should be evaluated and therapy should be continued if adequate symptoms relief is achieved.<br>• If symptomatic benefits not achieved, therapy should be stopped and alternative class of bronchodilator should be prescribed. |
| B | • Long-acting bronchodilators are preferred over short-acting.<br>• Choice of long-acting bronchodilator is based on symptom relief of individual patients.<br>• If patients have persistent breathless on monotherapy with long-acting bronchodilator, dual-therapy with bronchodilators is recommended.<br>• If severe breathlessness if present, patients can be directly initiated with dual-therapy with bronchodilators. |
| C | • Initial therapy with long-acting bronchodilator.<br>• LAMA preferred over LABA for initial therapy.<br>• If patients experience persistent exacerbations, then LABA/LAMA or LABA/ICS combination therapy is recommended.<br>• LABA/LAMA combination is preferred over LABA/ICS. |
| D | • Initiate combination therapy with LABA/LAMA or LABA/ICS.<br>• LABA/LAMA combination is preferred over LABA/ICS.<br>• If patients continue to experience exacerbations, then choose either: LABA/LAMA/ICS, or LABA/ICS.<br>• If patients with LABA/LAMA/ICS still continue to experience exacerbations then choose either: add roflumilast, add macrolide, or stop ICS. |

*LAMA = long-acting muscarinic agent*
*LABA = long-acting beta$_2$ agonist*
*ICS = inhaled corticosteroid*
Source: GOLD[1]

use of prescription opioids in cancer and short-term use in acute pain and CNCP is effective, their use however on a long-term basis for CNCP is widely debated[12–15]. Opioids in general have the potential to induce psychological addiction and have been abused on a wide scale. Opioid abuse and misuse contributes to a significant healthcare and economic burden in the US. Prescription opioid abuse has become a major public health concern in the past years.

With the rising rates of prescribing of prescription opioids, comes the rise in mortality due to prescription opioid abuse and overdoses. Prescription opioid abuse is considered an epidemic, and 2014 was recorded as the year with the highest number of deaths due to drug overdoses with about 6 out of 10 deaths due to overdoses attributed to opioid abuse[20,22]. Deaths due to opioid overdoses, both prescription and illicit, have increased by four times since 1999[18]. About 30,000 deaths in 2014 were due to overdose of prescription opioids and heroin[23]. About 78 deaths daily are due to opioid overdoes in the US[85]. The number of deaths attributed to prescription opioids alone exceed those due to heroin and cocaine combined[18,20].

According to Birnbaum H et al, prescription opioid abuse contributes to a significant economic burden, not just on the US healthcare system ($25 billion) but also the US justice system ($5.1 billion) including correctional facilities and police costs, workplace burden ($25.6 billion) including lost employment and lost earnings from premature death, and society ($55.7)[86]. In 2009, about 1.2 million emergency room visits were associated with prescription drugs, mostly prescription opioids, compared to 1 million visits for cocaine and heroin combined[18,19]. About $20.4 billion are spent in direct and indirect costs attributed annually in the treatment of opioid poisoning[20,21].

About $800 million and $1.3 billion are spent annually for emergency room visits and inpatient visits for the treatment of opioid poisoning in the US, respectively[20,21]. Average treatment costs per event for prescription opioid poisoning is higher compared to heroin poisoning which may be attributed to the longer half-life of prescription opioids (varies by drug) compared to heroin (15 to 30 minutes) requiring longer monitoring time[21].

**Prescription opioid therapy in the treatment of chronic non-cancer pain**

It is estimated that about 11% to 15% of the adult US population has chronic pain on a daily basis[9,10]. Prescription opioids are commonly used for the treatment of CNCP. CNCP is defined as pain typically lasting more than 3 months which may result from an injury, inflammation or an underlying condition or an unknown cause[87,88]. About 20% of patients with CNCP receive prescription opioids, either acutely or on a long-term basis[11].

There is established validity for the use of prescription opioids acutely in CNCP[14,15]. However, there is little evidence for their use on a long-term basis for CNCP[12,13]. The effect of long-term use of prescription opioids for CNCP on adherence to treatment for comorbid conditions, health-related quality of life, and pain-relief is still not very well understood[16]. A Cochrane literature review of studies assessing safety, efficacy and effectiveness of long-term prescription opioid use in CNCP patients reported that there was very limited evidence for clinically meaningful amount of alleviation of pain associated with long-term use of prescription opioids for CNCP[13]. The study found that prescription opioid use was only effective in a small group of patients with no history of substance abuse[13]. Many of the participants from previously published studies discontinued their prescription opioid treatment due to opioid-related side effects or inadequate pain relief[13]. The review also reported that long-term use of prescription opioids for CNCP had inconclusive evidence for improvement on functioning or quality of life. Despite lacking evidence for effectiveness, the use of prescription opioids among CNCP patients on a long-term basis is highly prevalent in the US population. About 11 million people in 2005 were prescribed long-term prescription opioid therapy for CNCP[17].

**Risks of developing long-term use from an acute use of prescription opioid**

Previously published evidence suggests that as low as 8 days of acute use of prescription opioids has the likelihood of developing long-term use when measured over 1 to 3 years. Shah and colleagues used a 10% random sample from the 2006 – 2015 IMS Lifelink + database to identify commercially insured adult patients who had used a prescription opioid[89]. Included patients were required to be prescription opioid-naïve with a 6-month pre-period of no evidence of prescription opioid use. Patients with cancer and evidence of opioid abuse diagnosis were excluded. They measured the time to discontinuation of prescription opioids. The study found that the number of days of doses in the first prescription fill is a significant predictor of long-term use of prescription opioids. Patients who had just 8 days of supply of the first prescription opioid fill had a rate of long-term use (1 year of use) of 13.5% compared to 6% among people having only 1-day supply. This rate increased considerably to 29.9% when the first fill of prescription opioid was for 31 days. About 1 in 7 patients who had a refill of a prescription opioid (or a second fill) were using prescription opioid one year later. Results from the study suggest that a transition from acute use to a long-term use may happen in just 3 days of prescription opioid use. Similarly, a study conducted by Deyo

RA and colleagues in 2017 among prescription opioid-naïve patients residing in Oregon reported that patients refilling their opioid prescription had 2.25 (95% CI, 2.17-2.33) times higher likelihood of developing chronic long-term use compared to patients having only one fill of prescription opioids[90].

**Guidelines for prescription opioid therapy for chronic non-cancer pain**

Although prescription opioid use is highly prevalent in the US population, there seems no uniform consensus among clinicians in prescribing opioid therapy[91]. The Centers for Disease Control and Prevention (CDC) in 2016 published evidence based guidelines in order to assist clinicians to appropriately prescribe opioids for patients with CNCP[92]. It is important to note that the CDC acknowledges the lack of evidence for long-term prescription opioid use in CNCP, "In summary, evidence on long-term opioid therapy for chronic pain outside of end-of-life care remains limited, with insufficient evidence to determine long-term benefits versus no opioid therapy, though evidence suggests risk for serious harms that appears to be dose-dependent"[92]. The CDC guideline provides recommendations in three different areas of opioid prescribing: when to initiate and continue opioids in CNCP; selection of opioids, duration, dosage, follow-up and discontinuation; and assessing the risks and harms of opioid prescribing[92].

**Initiating and continuing prescription opioids in CNCP:**

CDC recommends the use of non-pharmacological therapy (such as exercise therapy, cognitive behavior therapy, etc.) and non-opioid pharmacological therapy (such nonsteroidal anti-inflammatory drugs, acetaminophen) in patients with CNCP[92]. Prescription opioid therapy should only be considered if the anticipated benefits (for both pain and functioning) of prescription opioid therapy outweigh the risks[92].

Prescription opioids when initiated should be used in conjunction with non-pharmacological and non-opioid pharmacological therapy[92]. Clinicians should discuss treatment goals along with the risks and benefits of treatment with patients before starting prescription opioid therapy[92].

**Selection of prescription opioids, duration, dosage, follow-up and discontinuation:**

Patients should generally start with immediate-release prescription opioids instead of long-acting prescription opioids[92]. Prescription opioid therapy should be initiated with the lowest effective dose and generally patients should not be prescribed doses ≥90 mg of morphine equivalent dose per day[92]. Patients should be prescribed only required doses, no additional doses should be prescribed[92]. After initiating a prescription opioid therapy, patients should be monitored within 1 to 4 weeks to assess the effectiveness of the therapy and increase the dosage as needed. Clinicians should regularly monitor dosage (every 3 months) to assess the benefits and harms of the therapy[92]. If the clinicians decide that the risk of the prescription opioid therapy outweighs the benefits than they should taper the therapy and lower the dosage or taper the therapy and discontinue the therapy[92].

**Assessing the risks and harms of opioid prescribing:**

Clinicians should regularly monitor patients on prescription opioid therapy for CNCP. Factors such as previous history of overdose and substance abuse, concurrent benzodiazepine administration, and prescription opioid doses ≥50 mg of morphine equivalent dose per day may increase the patients' likelihood of having an opioid overdose[92]. When such factors are present, clinicians should consider offering naloxone to patients. Before prescribing an opioid, clinicians should consider a patients' history of substance abuse and concurrent receipt of opioids from other sources and receipt of other medications which could lead to serious adverse events[92]. Clinicians should also regularly monitor such data every 3 months along with the use of other drugs and use of illicit drugs by urine testing while the patient is on prescription opioid therapy[92]. If possible, benzodiazepines should not be prescribed concurrently with prescription opioids[92].

**Aberrant Drug Related Behavior**

About 8% of the US population suffers from substance abuse disorder, and this rate is much higher among patients with CNCP[24–26]. Use of prescription opioids may result in patients exhibiting aberrant drug related behavior (ADRB) such as misuse, diversion, physical dependence, abuse, addiction and tolerance. The likelihood of developing ADRB among long-term prescription opioid users is high, even the use of acute prescription opioids significantly increases of odds of developing ADRB[27]. Patients with CNCP using low-dose acute prescription opioids (defined as ≤36 mg of morphine equivalent dosage) had 3.03 times (OR=3.03; 95% CI: 2.32-3.95) significantly higher odds of developing ADRB (abuse and dependence) compared to non-opioid users[27]. However, among long-term, high dose prescription opioid users (defined as ≥120 mg of morphine equivalent dosage) the odds of developing ADRB increased significantly by 122 folds (OR=122.45; 95% CI: 72.79-205.99)[27].

**Tolerance**

Use of prescription opioids may lead to development of tolerance to opioid medications. A tolerance to an opioid prescription is developed when increasing doses of prescription opioids are required over time to generate the original degree of therapeutic effect[93]. For example, a patient may be prescribed a short-acting prescription opioid and later during the treatment may require increasing dosage of the short-acting prescription opioid to achieve the same therapeutic effect of the initial dosage of the short-acting prescription opioid. Subsequently, the same patient might even be prescribed a long-acting prescription opioid to achieve the therapeutic effect of the original dosage of the short-acting prescription opioid.

Tolerance to prescription opioids is not necessarily misuse, or addiction to prescription opioids. Patients who are tolerant may still be adherent to their physician's prescribing guideline. In short, tolerance occurs when opioids are prescribed over a long-term basis. As patients who develop tolerance for opioids are prescribed higher doses of opioids, their odds for accidental overdoses are increased.

**Physical Dependence**

Like tolerance, use of prescription opioids may lead to physical dependence on opioid medications. Physical dependence is a manifestation of withdrawal symptoms and is revealed when a specific drug class like opioids are reduced in dosage, abruptly stopped, or when an antagonist if prescribed. Patients who are physically dependent are not necessarily addicted or abusing the drug.

**Addiction**

Addiction occurs when use of prescription opioids leads to a "chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences"[94]. When addicted, a person displays an inability to refrain from using opioids, or control cravings leading to a compulsive drug seeking behavior[95]. A person with addiction may display the following characteristics: inability to abstain from opioid use; cravings for opioid medications; impaired behavioral control; diminished ability to recognize problems with behavior and interpersonal relationships; and lack of or poor emotional response[96].

If opioid addiction in not treated a person can progress to illegally obtaining and using heroin[97]. According to Jones M et al, about 4 out of every 5 heroin users progressed to heroin after use of prescription opioids[97]. In a 2014 survey of heroin users by Cicero J and colleagues over 90% of respondents reported switching to heroin because it was cheaper and more readily available than prescription opioids[98]. If not managed, addiction to prescription opioids can progress to greater cravings and may lead to premature death or disability[95].

**Diversion**

Section 309 of the Uniform Controlled Substances Act of 1994 defines diversion as “the transfer of a controlled substance from a lawful to an unlawful channel of distribution or use”[99]. For example, a patient receiving a prescription opioid may share, or sell their medications with their family members or friends. Patients may also purchase prescription opioids from non-medical sources such as friends, family members, or through internet websites which do not require a prescription for purchase. Diversion may also involve theft from hospitals, pharmacies or from patients.

**Misuse**

Misuse of prescription opioids is their use that is not as directed or instructed by physicians or health care providers[100]. Misuse may or may not necessarily be intentional or may not necessarily result in harm. For example, a patient may misuse opioid prescription by increasing the dosage of the medication either forgetfully or intentionally due to physical dependence or tolerance to achieve a higher therapeutic effect. Patients may also hoard their opioid prescriptions during periods of reduced symptoms for use as and when needed[100].

**Abuse**

Abuse is the intentional use of an opioid medication for non-medical reasons such a recreational use, or altering one's state of consciousness such as achieving a state of "high"[101].

**Side effects associated with the use of opioids**

Along with aberrant drug related behavior, the use of prescription opioids has also been reported to be associated with certain side effects such as hyperalgesia, sedation, constipation, respiratory depression, depression etc.

**Hormonal effects**

Use of prescription opioids on a long-term basis may have effect on a variety of hormones in both men and women. Men and women who take prescription opioids on a long term-basis may show reduced levels of testosterone leading to problems with sexual dysfunction, and decreased physical energy[26,28,102–104]. Depression has also been reported as a result of prescription opioid use[28]. In women, taking prescription opioids on a long-term basis has also been associated with reduced estrogen levels which may have an impact on osteoporosis in geriatric patients[28,104]. Non-spinal fractures were reported by Ensrud K et al among a sample of older women taking prescription opioids[104].

**Hyperalgesia**

Long-term use of prescription opioids has also been associated with hyperalgesia, a condition in which use of prescription opioids leads to an increased sensitivity to pain[26,29]. Patients taking prescription opioids to manage chronic pain may find themselves unexpectedly having a higher sensitivity to pain with an increasing use of prescription opioids[26,105]. A study by Chu L et al reported that patients treated for chronic back pain reported developing hyperalgesia within just a month of using morphine[106].

**Opioid-induced sedation and sleep disturbances**

Opioid induced sedation is also a common side effect of opioid use[30]. Although patients can eventually develop tolerance for sedation, increasing the dosage of prescription opioids may lead to sedation which in turn has been proposed to affect medication adherence and reduce patients' quality of life[26]. Conversely, studies have also shown that patients taking prescription opioids may also experience reduced sleep and increased sleep disturbances[107].

**Opioid-induced constipation**

One of the most common side effects associated with the use of prescription opioids is constipation. It occurs in as many as 95% of patients taking prescription opioids[31]. Although constipation may not be regarded as a serious adverse event associated with prescription opioids the chronic nature of constipation in opioid users makes it difficult to develop tolerance towards it[26]. Constipation may lead to dose lowering of prescription opioids which may in turn lead to decreased analgesic effects of opioids, and may sometimes lead to complete cessation of therapy[26]. Constipation may also lead to morbidity and mortality and lowered health related quality of life among patients[26]. Opioid-induced constipation may not improve on its own and requires adequate treatment and monitoring[108].

**Opioid-induced respiratory depression**

Respiratory depression is a serious adverse effect associated with the use of opioids. One of the most common causes of deaths among illicit opioid users is respiratory depression[32]. Although the proportion of patients who die due to respiratory depression among prescription drug users is low, the large number of patients using opioid prescriptions makes it an important healthcare concern[109]. Concerns for respiratory depression may lead to under-treatment of pain[109].

Respiratory depression is a major concern in patients with respiratory conditions such as COPD. Patients with COPD commonly experience dyspnea, a feeling of shortness of breath and labored breathing associated with pain. The use of prescription opioids in the treatment of dyspnea among COPD patients is widely accepted[56,57]. However, COPD patients prescribed opioids need to be appropriately monitored. COPD patients who abuse or misuse opioids may be at increased likelihood of respiratory depression than those without COPD.

In summary, prescription opioids are commonly used for the treatment of CNCP. Although prescription opioids are recommended for acute use in patients with CNCP, their use on a long-term basis is widely debated with a systematic literature review study reporting little to no improvement in pain-relief or health-related quality of life among long-term users of prescription opioids with CNCP[12–15]. Even the CDC acknowledges the lack of evidence for long-term prescription opioid use in CNCP. Patients using prescription opioids even on acute basis may lead to using them on a long-term basis[89, 90]. For example, evidence from a previously published study suggests that as low as 8 days of acute use of prescription opioids has the likelihood of developing long-term use of 1 to 3 years[89]. Use of prescription opioids may result in patients exhibiting ADRB[27]. The use of prescription opioids has also been reported to be associated with side effects such as hyperalgesia, sedation, constipation, respiratory depression, depression etc[26].

**Overview of medication adherence**

Medication adherence is the ability of patients to follow the recommendations by their healthcare providers with regards to the timing of medication use, in the prescribed dose, and with the recommended frequency. It is defined as compliance of patients with the recommended medication dosage[33].

Adherence is commonly reported in the form of a “percentage of prescribed doses actually taken by the patient over a specified period”[110]. Generally, patients with acute condition are more likely to be adherent to their medication regimen than patients diagnosed with chronic conditions[111]

As compared to real world settings, the average medication adherence rates in randomized controlled trials (RCTs) is significantly higher due to selection of patients and attention received by the patients. In spite of this, medication adherence rates of only 40% to 80% are achieved by RCT participants with severe medical conditions[112–114]. There is however, no set standard for an optimum medication adherence rate. A medication adherence rate of 80% is commonly observed in published RCTs and observational studies, whereas other RCTs consider rates of 95% to be necessary for optimum adherence (RCTs with patients diagnosed with human immunodeficiency virus).

Medication non-adherence may lead to sub-optimal control of medical conditions, increase the risks of mortality, and may lead to a significant increase in healthcare costs[34–38]. About 33% to 69% of all medication-related hospitalizations have been attributed to non-adherence to medications, costing the US approximately $100 billion a year[34,36,39,40]. Good medication adherence is therefore helpful in leading to better clinical and economic outcomes in the management of health conditions[41–43]. With the increasing importance of proper management of patients and improving medication adherence, the World Health Organization has compiled guidelines for healthcare professionals and policymakers to enhance medication adherence strategies and interventions[111].

Several previous studies have tried to understand the reasons that contribute to non-adherence to medications among patients. The following are some of the common barriers to medication non-adherence among patients: presence of comorbid conditions, severity of the disease, presence of depression, low perceived health status, high number of medications, complexity of medication regimen, low health literacy, high cost of medications, side effects of medications, poor patient-provider relationship, and polypharmacy[115–119]. To improve medication adherence of patients, all the potential barriers to medication adherence need to be addressed.

There are several different methods of measuring medication adherence which can be classified into two categories: direct and indirect methods of measurement.

Medication adherence can be measured either directly through addition of biological markers to drug formulations, measurement of amount of drug or metabolite in urine or blood, or directly observed therapy. Indirect methods of measurement include patient interviews, patient diaries, prescription refill rate, electronic monitoring, assessing clinical outcomes, and assessing physiological indictors such as heart rates.[33,110,114].

The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) formed the ISPOR Medication Compliance and Persistence Special Interests group (SIG) with the goal to stimulate research in issues related to medication adherence, persistence, and implications of health outcomes[120]. Accordingly, the ISPOR SIG group developed a checklist for appropriately conducting medication adherence studies.

**Proportion of days covered (PDC)**

Proportion of days covered (PDC) is a validated method of measuring medication adherence that is used in studies involving pharmacy refill data, and is a recommended technique for assessing medication adherence by the ISPOR SIG[33,120]. Use of PDC for the measurement of medication adherence is also consistent with recommendations of the Pharmacy Quality Alliance (PQA) and the National Quality Forum (NQF), which support the use of PDC as the preferred method to assess medication adherence[121]. The Centers for Medicaid and Medicare Services (CMS) uses medication adherence to using PDC as one of the measures for assessing quality and performance and assigning star ratings for Medicare Part C and D plans[122]. Recent studies on adherence to COPD maintenance medications have also used PDC as the primary measure of medication adherence[51,52].

PDC is an indirect measure to assess medication adherence that has been used with increasing frequency[123–126]. “The PDC is calculated as the number of days with drug on hand divided by the number of day in the specified time interval”[120]. The PDC is generally represented in the form of a percentage.

$$\text{PDC} = \frac{\text{total number of days with drug on hand}}{\text{total number of days in the time interval}} \times 100$$

Similar to PDC, medication possession ratio (MPR) is also an indirect method commonly utilized to assess medication adherence[127]. The MPR is the ratio of the dispensed “days’ supply divided by the number of days before the patient discontinues the medication”[127]. The MPR however, calculates medication adherence only when the patient has the drug on hand, PDC on the other hand assess adherence over an entire specified time period. The PDC also has an advantage over the use of MPR when patients are prescribed multiple medications at a time. Patients with COPD prescribed maintenance medications may undergo different patterns of maintenance medication use. When multiple maintenance medication use patterns are present, MPR may cause double counting and overestimate the actual medication adherence. Contrarily, while assessing medication adherence using PDC, filled prescriptions are assessed such as to avoid double-counting in the numerator.

**Significance of medication adherence in COPD treatment**

Patients who have chronic conditions and require therapy on a long-term basis have lower adherence than patients with acute conditions[111]. Patients with COPD may also suffer from problems of poor medication adherence because of the number of medications concurrently prescribed for controlling the symptoms. Maintenance medications for COPD are usually prescribed in inhaled form using devices which may require education on proper techniques of use of inhalers. These inhaled, maintenance medications may be taken in multiple doses on a daily basis. Patients with COPD may also commonly suffer from comorbid conditions such as diabetes, depression, cardiovascular diseases and hypertension which may add to the medication burden and lead to poor medication adherence[44,45]. In general, patients with COPD are poorly adherent to their maintenance medications even when compared to their asthmatic counterparts[46]. About 60% of COPD patients exhibit poor adherence to COPD treatment and even more do not use their inhalers correctly[46–48].

COPD is a progressive disorder without a cure, however proper management of COPD with medication therapy helps to control the symptoms of COPD and may prolong the advancement of the disease[1,49]. Adherence to maintenance medications in patients with COPD have proven benefits in terms of economic, clinical, and humanistic outcomes. It has been shown that adherence to COPD maintenance medications helps to reduce mortality risk and the risk of severe respiratory exacerbations, which may in turn lead to reduction in the number of inpatient and emergency room visits and their associated costs[50]. Invariably, the GOLD guidelines emphasize adherence to COPD-related maintenance medications for achieving control of COPD symptoms and exacerbations[1].

Many studies have been published previously that examined the clinical and economic significance of medication adherence to COPD-related maintenance medications. Eaddy and colleagues conducted a literature review of studies published from 1974 to 2008, to assess the impact of medication adherence in chronic conditions and its impact on clinical and economic outcomes[53]. In the review, studies conducted in patients with COPD and asthma were grouped together. They reported that past studies have sufficiently shown that medication adherence among COPD and asthma patients has a significant positive impact on clinical outcomes. Furthermore, they found that medication adherence was significantly associated with lower healthcare resource utilization and costs among patients with COPD or asthma.

Simoni-Wastila L et al, 2012 assessed a sample of Medicare beneficiaries diagnosed with COPD using the 2006-2007, 5% random sample of Medicare beneficiaries[51]. They calculated medication adherence (using PDC) and persistence to maintenance medications for COPD for 18 months among 33,816 COPD patients satisfying the study inclusion criteria. They found that both high medication adherence (PDC ≥ 80%) and persistence (greater than 280 days on maintenance medications) were statistically significantly associated with lower all-cause hospitalization and all-cause Medicare costs.

Toy E and colleagues assessed the impact of medication adherence (using PDC) to COPD-related maintenance medications on all-cause healthcare resource utilization[52]. They followed a sample of 55,076 COPD patients for 12 months after index date (date of first fill of a COPD-related maintenance medication) using a large administrative dataset from 1999 to 2006. They found that medication adherence to maintenance medications was significantly associated with healthcare resource utilization and costs. Every 5% increase in medication adherence on the PDC scale was associated with a 2.5%, 1.8% and $300,00 decrease in all-cause inpatient visits, emergency room visits, and annual costs, respectively.

Halpern et al conducted a study using a large administrative database among 4,537 COPD patients initiating maintenance medications tiotropium or fluticasone and salmeterol combination between December 2004 and December 2005[54]. They reported that patients who were adherent (MPR ≥ 80%), had lower respiratory-related medical and inpatient costs by 37.1% (95% CI 0.43-0.91) and 53.4% (95% CI 0.30-0.72), respectively.

Vestbo J et al, 2009 analyzed data for 6,112 patients with COPD who participated in the Towards a Revolution in COPD Health (TORCH) study, a double-blind randomized controlled trial[55]. They assessed medication adherence for patients prescribed either fluticasone propionate and salmeterol combination or each drug individually. They found that patients who had "good adherence" (defined as adherence of greater than 80% to study medications) had statistically significantly lower odds of 3-year mortality compared to patients who had poor adherence to study medications. Patients with good adherence, as compared to patients with poor adherence, also had significantly lower hospital admissions after controlling for other factors.

In summary, previously published studies have provided evidence highlighting the importance of medication adherence to maintenance medications in COPD treatment. Good medication adherence helps to control COPD symptoms and helps reduce COPD exacerbations, reduce healthcare resource utilization and costs, and reduces the risk for mortality.

**Use of prescription opioids among COPD patients**

A significantly higher number of patients with COPD experience chronic pain compared to patients with other chronic health conditions[58]. With the high prevalence of chronic pain, the use of prescription opioids for treating pain is also highly prevalent (55.8%) among COPD patients[58]. Prescription opioids are commonly used in treating pain in COPD patients and are proven to be effective in providing analgesia[56].

Patients with COPD may experience dyspnea, a feeling of shortness of breath and labored breathing associated with pain. The use of prescription opioids in the treatment of dyspnea among COPD patients is widely accepted[56,57]. Along with dyspnea, prescription opioids are also used in COPD patients for other frequently occurring conditions such as insomnia and musculoskeletal pain[128,129]. The GOLD guidelines also support cautious use of prescription opioids among COPD patients[1].

With their wide use, adverse events associated with prescription opioids may also be common in COPD patients. Respiratory depression is a major concern in patients with COPD. COPD patients who abuse or misuse opioids may be at increased likelihood of respiratory depression than those without COPD. Due to the fear of respiratory depression, physicians may feel hesitant to provide prescription opioids for patients with COPD[59]. Despite the likelihood of respiratory depression, previous published controlled trials have reported prescription opioids to be safe for use in patients with COPD[56,57,60–63]. These studies however, suffered from many limitations such as small sample sizes, and systematic exclusion of patients experiencing no benefits and those who died[64]. With the high prevalence of prescription opioid use, it is important to understand how prescription opioids affect COPD patients' healthcare resource utilization and costs and medication adherence to maintenance medications.

**Prevalence and the effects of prescription opioid use in COPD patients and healthcare outcomes**

Roberts M and colleagues used 2006 to 2010 data from a managed care plan from southwest region in the US to assess the prevalence of chronic pain among COPD patients[58]. COPD patients (n=7,952) above 40 years of age were matched in a 1:2 ratio to a similar sample of patients without COPD (n=15,904) but having a diagnosis of another chronic health condition. The prevalence of chronic pain was higher in COPD patients compared to the matched group of non-COPD patients (59.8% vs 51.7%). When compared to patients without COPD but with another chronic illness in multivariate analyses, COPD patients had higher odds of having chronic pain, and overall use of chronic pain-related medication, and statistically significant higher odds of chronic use of short and long acting prescription opioids (OR: 1.74; 95% CI: 1.57 – 1.92). The findings from the study suggest that COPD patients have a high prevalence of chronic pain and consequently have a high prevalence of opioid medications compared to patients with other chronic conditions.

Vozoris N et al, 2015 conducted a study using an administrative claims database from Ontario, Canada to estimate the prevalence of prescription opioid use among older COPD patients[130]. They identified physician-diagnosed COPD patients from 04/01/2003 to 03/31/2012 using a validated algorithm. Only incident prescription opioid users were included in study, defined as patients without a receipt of prescription opioid use for 12-months before the first prescription opioid fill. Included patients were followed for 12 months from the first prescription opioid fill to assess patterns of opioid use. The study included a total of 123,316 COPD patients of which about 60% received an opioid prescription during the study period, representing a high prevalence of incident prescription opioid use among older COPD patients. Among COPD patients enrolled in long-term care, about 20% received a greater than 30-day supply of prescription opioids, 35 to 43% had second dispensing of prescription opioids, 24.2% had early refills, and about 9% had concurrently received multiple prescription opioids.

Cicero T and colleagues conducted a study using a sample of privately insured patients from a large administrative claims database from the Midwest region[131]. Their objective was to describe the prevalence of chronic and acute prescription opioid use among pain patients and to identify the presence of comorbid conditions among prescription opioid users. They identified a total of 3,726 chronic prescription opioid users (defined as having >180 days of supply for opioids in a year) and 37,108 acute prescription opioid users (defined as having <10 days of supply for opioids a year), and 337,366 non-opioid users. About 4.5% of the entire study sample had a diagnosis of COPD however COPD patients represented over 6% of all prescription opioid users. The prevalence of prescription opioid use among COPD patients was high, about 15% of all COPD patients in the study were prescription opioid users with about 3% of all COPD patients being chronic prescription opioid users. Of all the chronic prescription opioid users in the study, 12.7% had a diagnosis of COPD. Cicero T et al reported that although chronic prescription opioid users represented only 0.65% of the entire study population they had significantly higher all-cause healthcare resource utilization, compared to acute and non-users, and filed over 5% of all medical claims. Chronic prescription opioid users, compared to acute and non-opioid users, had significantly higher number of emergency room and outpatient visits, longer inpatients hospital visits, visited higher number of physicians, and had higher comorbid health condition diagnoses, including COPD.

Vozoris N et al, 2016 conducted a study to identify the effects of prescription opioid use on adverse respiratory outcomes among older COPD patients[64]. They used a validated algorithm to identify physician-diagnosed COPD patients from 04/01/2007 to 03/31/2012, using an administrative claims database from Ontario, Canada. A cohort of COPD patients with incident prescription opioid use (n=89,224), with evidence of no prescription opioid use in 12-months pre-period, was matched to a controlled group of COPD patients having an incident fill for any medication (n=41,930), with no fill for the same medication in the 12-months pre-period using inverse probability of treatment weighting using propensity score technique. Their objectives were to identify the occurrence of adverse respiratory outcomes within 30 days of incident prescription opioid use. Adverse respiratory outcomes were defined as COPD or pneumonia-related outpatient respiratory exacerbation, hospitalization, or an intensive care unit (ICU) admission during a hospitalization for COPD or pneumonia, and COPD and all-cause mortality. The authors reported that incident prescription opioid users, regardless of opioid dose, were associated with a significantly higher risk for COPD and pneumonia-related emergency room visits (hazard ratio (HR) 1.14, 95% CI: 1.00–1.29) and mortality (HR 2.16, 95% CI: 1.61–2.88) and all-cause mortality (HR 1.76, 95% CI 1.57–1.98). The significant results persisted even after adjusting for the use of low dose (⩽30 mg morphine equivalent dose per day) and high dose prescription opioids (>30 mg morphine equivalent dose per day). No differences were found for hospitalizations and

ICU admissions between the two groups. The objectives of the study were to only assess the risk of incident prescription opioid use, and the authors therefore did not assess the effect of long-term prescription opioid use. It is possible that long-term prescription opioid use may be associated with higher adverse events than incident use, however this was beyond the scope of the study.

Ekstrom M and colleagues conducted a study to identify the effects of prescription opioid and benzodiazepine use on hospital admission rates and mortality rates among COPD patients[66]. They used a Swedish national registry to identify severe COPD patients, above 45 years of age and starting long-term oxygen therapy between 2005 and 2009. Patients were classified based on their baseline prescription opioid use, irrespective of whether the dose changed in the follow-up period, as low dose prescription opioids (⩽30 mg morphine equivalent dose per day) and high dose prescription opioids (>30 mg morphine equivalent dose per day). In the adjusted analysis, the use of prescription opioids in COPD patients had no effect on the rate of hospital admission compared to COPD patients without prescription opioids, this effect persisted even when accounted for the use of low dose or high dose of prescription opioids. For mortality rates, use of low dose prescription opioids had no statistically significant effect on mortality rate, however using high dose prescription opioids significantly increased the mortality rate of COPD patients (hazard ratio: 1.21; 95% CI: 1.02 – 1.44). There was a linear dose response relationship with increased mortality for increased opioids doses (increments of 0.1 mg morphine equivalent dose per day). The finding of lack of association between low-dose prescription opioids and mortality among COPD patients in the Ekstrom M et al study contradicts the findings from the

Vozoris N et al, that use of even low-dose prescription opioids were associated with increased COPD-related and all-cause mortality[64].

Vozoris N et al, 2017 conducted a retrospective cohort study to identify the impact of incident prescription opioid use on adverse cardiac events[67]. The study was conducted among a geriatric sample of COPD patients identified using an administrative claims database from Ontario, Canada between April 2008 to April 2013. The COPD patients were either residents of long-term care facilities or non-institutionalized community dwellers. The study cohort included COPD patients with incident prescription opioid use and the control group were COPD patients without evidence of a prescription opioid fill. Study objectives were to identify the occurrence of adverse cardiac events, defined as mortality, emergency room visits, and inpatient hospitalization associated with ischemic heart disease and cardiac failure, within 30 days of incident prescription opioid use[67]. Incident use of prescription opioid was associated with statistically significant increased rates of ischemic heart disease-related mortality and morbidity among COPD patients residing in long-term care facilities. Contrarily, among community dwelling COPD patients, incident prescription opioid use was not significantly associated with adverse cardiac events. This insignificant association could be attributed to the fact that about 90% of COPD patients used a combination of an opioid agent (combined with non-opioid agents such as non-steroidal anti-inflammatory agents) compared to just 10% using potent opioid-only agents such as fentanyl and hydromorphone. Hence, when stratified by the type of prescription opioid agents used, prescription opioid-only user had significantly higher hazard rates for ischemic heart disease-related emergency room visits and hospitalizations (hazard ratio 1.38; 95% CI

1.08–1.77) and mortality (hazard ratio 1.83; 95% CI 1.32–2.53) compared to users of combination prescription opioids.

In summary, previously published studies about the prevalence of prescription opioid use among patients with COPD suggests a high prevalence of prescription opioid use among COPD patients[58,131]. COPD patients may have higher prevalence of chronic pain compared to patients without COPD but with other chronic conditions and subsequently display a higher use of prescription opioids[58]. Despite physicians' fear of respiratory depression due to prescription opioid use, COPD patients still exhibit a high prevalence of both long-term and short-term use of prescription opioids. Only three studies assessed the effect of prescription opioid use on adverse health outcomes among COPD patients[64,66,67]. Although these studies classified prescription opioids according to high or low doses they did not assess the impact of length of prescription opioid use either long-term use or short-term use of prescription opioids on COPD-related health outcomes. These studies also found contrasting results on the effects of prescription opioids on adverse health outcomes. Vozoris et al found opioid use to be associated with increased all-cause and COPD related mortality and COPD and pneumonia-related emergency room visits[64]. The dose of prescription opioids, either low-dose or high-dose, had the same effect on the outcomes. Contrarily, Ekstorm M et al reported that increased mortality was associated with only high dose prescription opioids, whereas  low dose prescription opioids did not increase the risks of mortality among COPD patients[66]. Vozoris N et al, 2017 found that prescription opioid-only users compared to users of prescription opioids combined with non-opioid agents had significantly higher hazard rates for ischemic heart disease-related emergency room visits, hospitalizations and mortality[67].

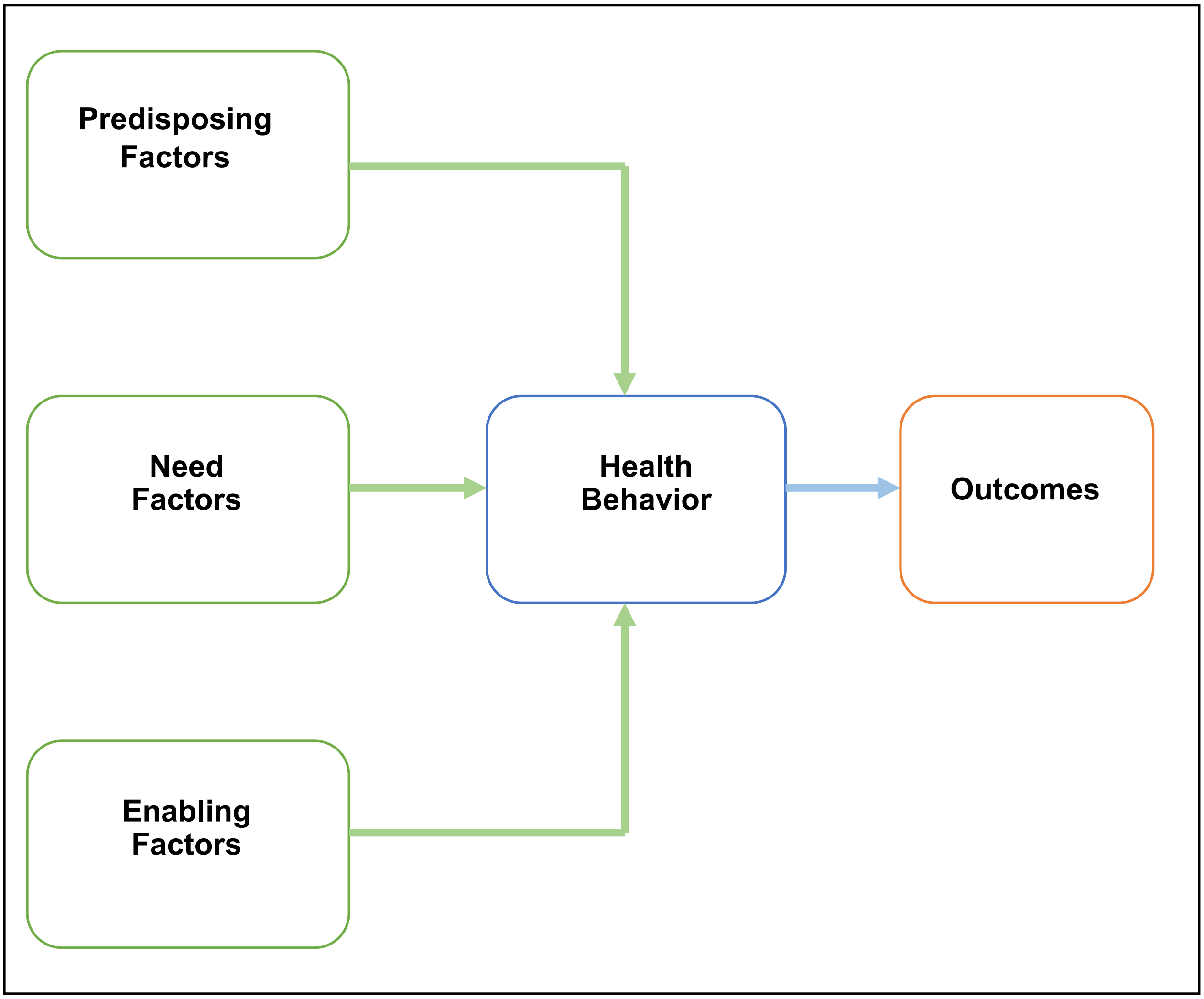
Although the prevalence of prescription opioid use is high among COPD patients, the effects of prescription opioids on COPD outcomes in this population is not very well studied. Medication adherence is an important aspect of maintenance medication therapy among COPD patents and has been associated with significant clinical and economic outcomes. None of the previous studies have assessed the impact of prescription opioid use on adherence to maintenance medications for COPD. Managing and controlling COPD exacerbations is an important aspect of controlling COPD symptoms. None of the previously published studies have assessed the impact of prescription opioids on COPD exacerbations. Furthermore, long-term prescription opioids may lead to aberrant drug related behavior among COPD patients and may have severe consequences on COPD-related medication adherence and COPD-related healthcare resource utilization and costs. However, no study in the past has the assessed the effect of long-term prescription opioid use in COPD patients.

**Theoretical Framework**

The Andersen's Behavioral Model of Health Services Use was used as a theoretical framework to facilitate the analyses of the study objectives. The model was originally developed by Ronald M Andersen and has been modified since the original publication in 1968[69,70]. The model has been extensively used by previous studies to assess healthcare service utilization patterns in a multitude of disease areas and patient populations[71–75]. The model is based on the theory that factors such as predisposing factors which predispose individuals to seek care, need factors which necessitate individuals and health professionals to assess their health status, and enabling factors which provide the means to or act as barriers to access to care together contribute towards patient health behaviors outcomes. The model, as depicted in Figure 2, predicts the influence of different factors on individual's predisposition or predisposing factors, ability or enabling factors and need to access the available resources that eventually result in patients' health behavior and eventually outcome such as healthcare service utilization[69,70].

Predisposing factors already exist in individuals or group of individuals prior to them having the disease condition. These factors indicate the tendency of the individuals towards utilization of healthcare services and they include socio-demographic characteristics such patient age, gender, race, education level, and values towards health and illness.[187,188].

**Figure 2. Andersen's Behavioral Model of Health Services Use**




*Source: Andersen (1995)[70]

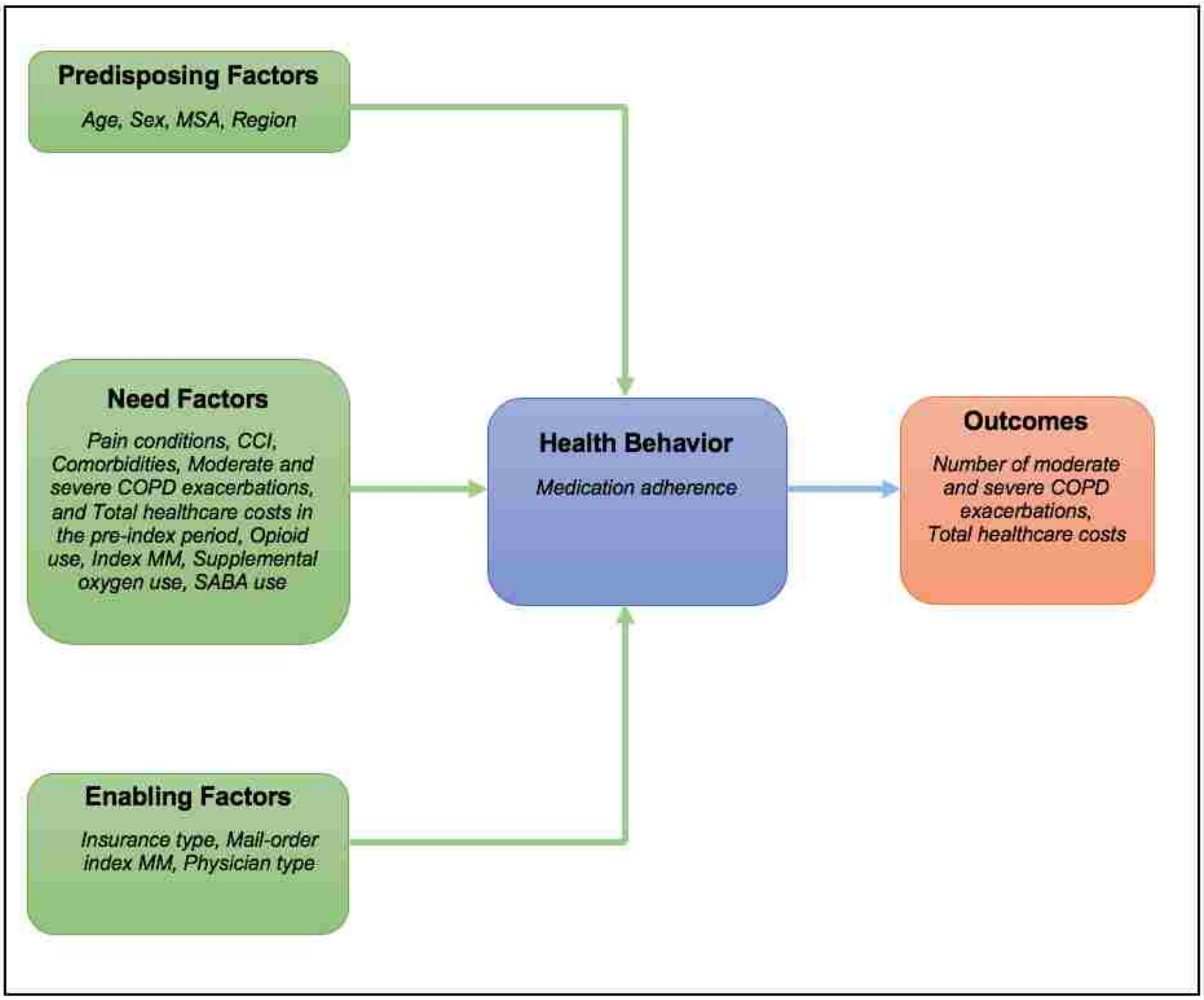
Enabling factors are the means available to an individual to be able to utilize healthcare services. These factors include accessibility to services, access to care, insurance status, source of care and income level[69,70].

Need factors are comprised of factors that include self-perception of individuals about their health status and the evaluation of the individual's healthcare provider: perceived health status, severity of disease, number of physician visits, presence of comorbidities and quality of life[69,70].

Health behavior describes the behavior that individuals undertake due to the influence of predisposing, need and enabling factors. Outcomes are comprised of utilization of healthcare resources and the associated costs of the use.

Andersen's Behavioral Model of Health Services Use presents a complete theoretical framework of numerous factors influencing healthcare services utilization. The model serves as a guide for the choice of variables which may impact adherence to COPD-related maintenance medications and COPD exacerbations and healthcare costs among COPD patients. In the proposed study, predisposing, need, and enabling factors together affect a patient's health behavior, which is their ability to either adhere or not to adhere to their maintenance medication regimen for COPD. The impact of the factors on medication adherence eventually will affect the individual's outcome, which is COPD exacerbations and total healthcare costs. The health behavior variables in this study are COPD-related maintenance medication adherence that will influence COPD-related exacerbations (both moderate and severe exacerbations) and total healthcare costs (prescription medication and medical costs) (Figure 3.).

**Figure 3. The impact of prescription opioid use on COPD maintenance medication adherence, COPD exacerbations and COPD-related total healthcare costs using Andersen's Behavioral Model of Health Services Use**




* CCI, Deyo-Charlson comorbidity index; IP, inpatient; ER, emergency room; OP, outpatient; MM, maintenance medication; SABA, short-acting beta agonist; MSA, metropolitan statistical area.

Prescription opioid use along with additional factors may affect adherence to maintenance medications for COPD and healthcare outcomes (COPD-related healthcare resource utilization and costs). Predisposing, need and enabling factors comprised of sociodemographic characteristics, clinical characteristics, physician characteristics, and prior utilization characteristics may also affect adherence. Although the model enlists a range of factors to consider to better explain healthcare utilization, some factors may not be measurable considering the retrospective claims nature of the data used to conduct the analyses.

A disparity in access to care between the prescription opioid user and non-user groups of COPD patients can be due to a stronger effect of enabling and predisposing factors on COPD-related medications, COPD exacerbations, and total costs compared to need factors[132]. On the other hand the stronger influence of need factors compared to enabling and predisposing factors on total healthcare costs can signify equal access to care[132].

Andersen's Behavioral Model of Health Services Use is a widely used model to understand factors that have an influence on the utilization of healthcare services by individuals. The choice of the variables in the study was determined by the various components of the Andersen's Behavioral Model of Health Services Use. Controlling for the various predisposing, enabling, and need factors in the model helps us understand the impact prescription opioid use may have on adherence to maintenance medications for COPD and COPD exacerbations and total healthcare costs.

**Significance and need for the study**

If a significant negative association is identified between the use of prescription opioids and medication adherence to COPD-related maintenance medications and COPD-exacerbations, it would suggest for improving the management of COPD patients to address non-adherence to maintenance therapy. Also, if our study results indicate higher healthcare costs for the management of COPD patients concurrently taking prescription opioids then proper identification and management of prescription opioid therapy along with efforts to improve COPD-related adherence may decrease the total healthcare costs of management of COPD.

Increased efforts to identify comorbid prescription opioid use and manage poor adherence to maintenance medications for COPD may lead to improved COPD outcomes such as lower rate of COPD exacerbations and lower total healthcare costs. For COPD patients taking maintenance medications, identification of concurrent prescription opioid use might be an effective gauge of potential poor medication adherence in the future and may advocate for improved surveillance and management to attain optimum medication adherence. The results from our study could facilitate designing effective interventions that would help reduce non-adherence to maintenance medications for COPD and thus improving COPD exacerbations and total healthcare costs and further lead to better allocation of limited healthcare resources among COPD patients. If concurrent use of prescription opioids has a significant association on adherence to maintenance medication for COPD and COPD exacerbations and total healthcare costs, then the results of the study may encourage future research to identify the effects of concurrent prescription opioid use on adherence to medications for other chronic conditions.

# CHAPTER 3 METHODS

This chapter is a description of the methods utilized to execute the numerous specific aims of the study. The chapter starts with a detailed description of the study research design and the study population. Next, a description of the study database timeline is provided followed by a detailed description of the study inclusion and exclusion criteria. A description of the study's independent and dependent variables is provided followed by the statistical techniques used to analyze the study objective by specific aims. Finally, the chapter provides a section on estimation of the required sample size for the study, followed by the potential study limitations, institutional review board approval, and the timeline for conducting the study.

**Research Design**

A retrospective, cross-sectional study design was utilized to examine the impact of prescription opioid use on adherence to maintenance medications for COPD, COPD exacerbations and total healthcare costs among COPD patients. Patients using maintenance medications for COPD were identified from the 2008 to 2010, Truven MarketScan Commercial Claims and Encounters Database. Patients using maintenance medications for COPD were identified in the 12-month index period. A 6-month pre-index period without an opioid prescription was used to determine inclusion of only prescription opioid naïve patients. Adherence to maintenance medications for COPD and COPD-related severe and moderate exacerbations and total, all-cause healthcare costs were assessed in the 12-month post-index period. Patients were required to be continuously enrolled in the dataset in both the pre- and post-index periods for a total of 24 months.

**Study population**

This study utilized the Truven Health MarketScan Commercial Claims and Encounters Database which is comprised of patients aged 40 to 64 years old. The National, Heart, Lung, and Blood Institute reports that COPD generally occurs in adults 40 years old and above[78]. The Truven Health MarketScan Commercial Claims Database only includes patients below the age of 65. Therefore, our inclusion criteriion was restricted to ages 40 to 64.

The Truven Health MarketScan Commercial Claims and Encounters Databases is the largest administrative claims database in the US with 143 million unique patients in total since 1996. Nearly half of all US private healthcare insurance plans are represented in the MarketScan databases. The MarketScan Commercial Claims and Encounters Databases reflect patients' real-world treatment costs and patterns as they proceed through the healthcare system. The dataset includes information on active employees, early retirees, and their dependents insured by employer-sponsored plans[133]. The MarketScan database contains information on outpatient and inpatient visits, prescription drugs, and costs of services[133].

In one full average data year, MarketScan database contains information on 50 million unique patients. The dataset has a large number of patients and can provide a US nationally representative sample with employer-provided health insurance[133]. The MarketScan database offers information on healthcare provided in "all settings including, physician office visits, hospitalizations, and retail and mail-order and specialty pharmacies"[133]. The MarketScan database allows for longitudinal information on patients for multiple years. As the database is sourced from large employers it allows for tracking of patients across multiple health plans. This is useful as patients often change health plans and this allows for information on patients who have the potential to lack information due to this change. Sample elements collected in the MarketScan database are listed in Table 5.

**Study dataset timeline**

Data used in the study consisted of data available in the Truven Health MarketScan Commercial Claims and Encounters Data for the time period, January 1, 2008 to December 31, 2010. The study data was classified into three specific time periods: pre-index period, index period, and post-index period. The study dataset timeline is depicted in Figure 4. Study dataset timeline

**Index period**

The period from July 1, 2008 to December 31, 2009 was categorized as the index period. This period was used to identify COPD patients with a prescription fill for COPD-related maintenance medications and additionally a fill for prescription opioids for the exposed group.

**Index date**

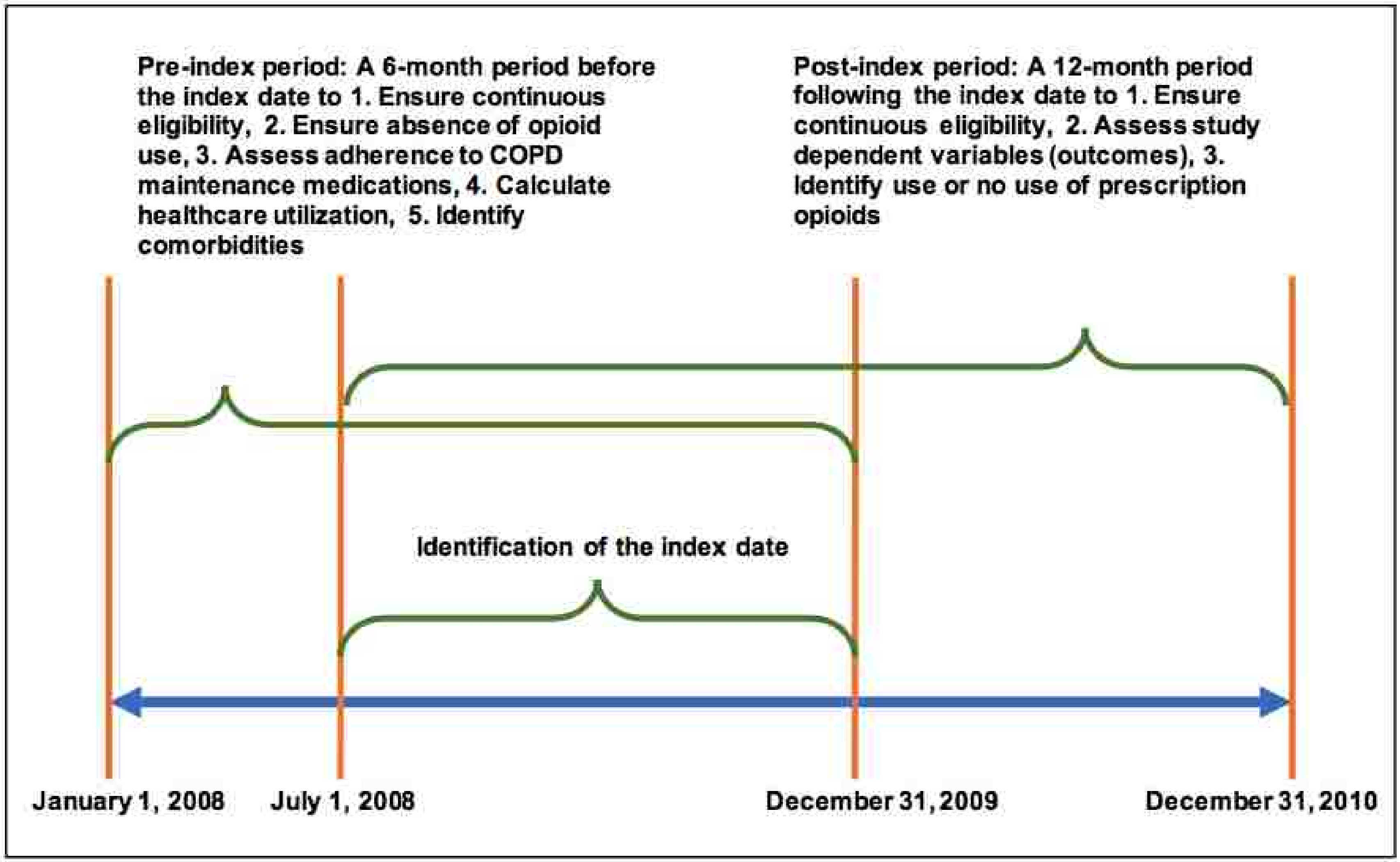
The first fill of a prescription opioid and maintenance medication during the index period was identified for COPD patients. The date of the first fill of a prescription opioid was marked as the index date for the exposed group (prescription opioid users) and the first prescription fill of a maintenance medication as the index date for the control (non-opioid users).

**Table 5. Sample data elements collected in the MarketScan Commercial Claims database**

| Demographic characteristics | Medical information | Health plan features | Financial information | Drug information | Enrollment information |
|---|---|---|---|---|---|
| Patient ID | | | | | |
| Age | Admission date and type | Coordination of benefits amount | Total payments | Generic product ID | Date of enrollment |
| Gender | Principal diagnosis code | Deductible amount | Net payments | Average wholesale price | Member days |
| Employment status (hourly, etc) | Discharge status | Copayment amount | Payments to physician | Prescription drug payment | Date of disenrollment |
| Relationship of patient to beneficiary | Major diagnostic category | Plan type | Payments to hospital | Therapeutic class | |
| Geographic location (state, zip code) | Principal procedure code | | Payments – total admission | Days supplied | |
| | Secondary diagnosis codes (up to 14) | | | National drug code | |
| | Secondary procedure codes (up to 14) | | | Refill number | |
| | DRG | | | Therapeutic group | |
| | Length of stay | | | | |
| | Place of service | | | | |
| | Provider ID | | | | |

*Adapted from Hansen LG and Chang S, 2012[133]

**Figure 4. Study dataset timeline**



**Pre-index period**

After the identification of the index date within the index period, a period of 6 months preceding the index date was categorized as the pre-index period. This 6-month per-index period is important for several reasons:

1. The pre-index period was used to ensure continuous eligibility of patients with COPD in the dataset;

2. This pre-index period was used to ensure that patients with COPD do not have the presence of prescription opioid fill before the index date;

3. During the pre-index period, adherence to COPD maintenance medications before the start of a prescription opioid therapy was assessed;

4. The pre-index period was also the period during which COPD exacerbation were identified;

5. Presence of other comorbid chronic conditions was also assessed during the pre-index period.

**Post-index period**

Post-index period was classified as a period of 12 months following the index date among patients with COPD. It was used to ensure continuous eligibility of the patients in the dataset. A 12-month post-index period helps maintain uniform length of follow-up for each patient in the study. Healthcare outcomes for the study such as medication adherence to COPD maintenance medication, COPD exacerbations, and total, all-cause healthcare costs were assessed during this period. Use of prescription opioids either long-term or short-term were also be identified in the post-index period.

**Inclusion and exclusion criteria**

**Criteria for the identification of COPD**

The study population with COPD was identified from healthcare claims using the ICD-9-CM diagnoses codes. Patients with COPD were identified on the basis of ICD-9-CM diagnosis codes corresponding to COPD (Table 6.). The study population comprised patients diagnosed with COPD and having a minimum of two prescription claims for COPD maintenance medications. Evidence of maintenance medication use was identified using national drug codes (NDC). NDCs are 11-digit codes that are unique to each medication approved by the US FDA. The numbers in an NDC can be used to identify the drug manufacturer, the specific dosage and strength of the medication, and the package size and form. The specific NDC codes for inhaled, long-acting bronchodilators (maintenance medications) for COPD, approved during the study period, were used to identify patient's maintenance medication use status. The following criteria for the identification for COPD patients was used:

1. At least one inpatient hospitalization claim for COPD in the primary or secondary diagnosis position and a minimum of two prescription claims for maintenance medications for COPD.
2. At least two emergency room visit claim for COPD in the primary or secondary diagnosis position and a minimum of two prescription claims for maintenance medications for COPD.
3. At least two outpatient provider visit claim for COPD in the primary or secondary diagnosis position and a minimum of two prescription claims for maintenance medications for COPD.

**Study inclusion criteria**

1. Patients with a diagnosis of COPD were included in the study. The aforementioned criteria were employed to identify the presence of COPD. Only patients having evidence of COPD maintenance medication (as described above) use were included in the study.
2. The identified patients with COPD were required to have continuous enrollment in the database in the pre-index and post-index periods (6 months before and 12 months after the index date).
3. Only patients aged 40 to 64 years old at the index date were included.
4. Prescription opioid users were also required to have a COPD maintenance medication on-hand when initiating a prescription opioid therapy.

**Study exclusion criteria**

1. Patients who do not have continuous eligibility in the dataset 6 months before and 12 months after the index date were excluded from the study.
2. Patients with diagnosis of any cancer, HIV and AIDS (Table 6.) were excluded from the study as the use of prescription opioid therapy in these patients is markedly different than in patients without these conditions.
3. COPD maintenance medication use may differ among COPD patients with certain respiratory comorbidities compared to COPD patients without these comorbidities[134,135]. Hence COPD patients with the following comorbid conditions were excluded: asbestosis, sarcoidosis, pulmonary tuberculosis, fibrosis due to tuberculosis, cystic fibrosis, pulmonary fibrosis, pneumoconiosis, bronchiectasis, and alpha-1 antitrypsin (Table 6.).

4. Only prescription opioid naïve patients were included. A 6-month pre-index period without an opioid prescription was used to ensure that only patients who are drug-naïve for prescription opioids are included.
5. Patients who start prescription opioid therapy before starting COPD maintenance medications were excluded.
6. COPD patients who have claims for prescription opioids specifically methadone and buprenorphine were excluded. Methadone and buprenorphine are used as opioid maintenance therapy for the treatment of opioid addiction and are therefore different than prescription opioid therapy for the treatment of CNCP.

**Study variables**

**Independent Variables**

Table 7. provides a list of all the independent variables that were used in the analyses of the specific aims. The independent variables are representative of sociodemographic characteristics, clinical characteristics, prior utilization characteristics, COPD severity, and physician characteristics.

The selection of variables is based on the proposed theoretical framework, the Andersen’s Behavioral Model of Health Services Use. Variables were categorized into three groups: predisposing factors, enabling factors, and need factors. Predisposing factors include sociodemographic variables. Enabling factors include economic

**Table 6. Conditions satisfying the inclusion and exclusion criteria and their corresponding ICD-9CM diagnosis codes**

| Condition | Corresponding ICD-9CM diagnosis codes |
|---|---|
| Included condition | |
| COPD | 491.x, 492.x, or 496 |
| Excluded conditions | |
| Cancer conditions | 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 170, 171, 172, 173, 174, 175, 176, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239 |
| HIV/AIDS | 042.xx, 079.53, 279.10, 279.19, 795.71, 995.8x |
| Asbestosis | 501 |
| Sarcoidosis | 135 |
| Pulmonary tuberculosis | 011 |
| Fibrosis due to tuberculosis | 011.40 |
| Cystic fibrosis | 277.00 |
| Pulmonary fibrosis | 513.31 |
| Pneumoconiosis | 505 |
| Bronchieostasis | 494.0, 494.1 |
| Alpha-1 antitrypsin | 273.4 |

**Table 7. Study independent variables**

| Variable | Operational Definition | Factors as per Andersen's Behavioral Model |
|---|---|---|
| **Sociodemographic characteristics** | | |
| Sex | Dichotomized as:<br>Male<br>Female | Predisposing factor |
| Age | Categorized as:<br>40 to 49 years<br>50 to 59 years<br>≥60 years | Predisposing factor |
| Metropolitan Statistical Area | Dichotomized as:<br>Urban<br>Rural | Predisposing factor |
| Region | Categorized as:<br>Northeast<br>North Central<br>South<br>West | Predisposing factor |
| Insurance Plan Type | Categorized as:<br>Preferred provider organization (PPO)<br>Health maintenance organization (HMO)<br>Other | Enabling factor |
| **Clinical characteristics** | | |
| Prescription opioid use (Specific Aim 1) | Characterized as:<br>Non-user<br>User | Need factor |
| Prescription opioid use (Specific aim 1 – sub-group analysis) | Characterized as:<br><30-day supply in the follow-up period | Need factor |

| Variable | Operational Definition | Factors as per Andersen's Behavioral Model |
|---|---|---|
| | ≥30-day supply in the follow-up period | |
| Prescription opioid user (Specific Aims 2 to 4) | Dichotomized as:<br><br>Non-user<br>Long-term user | Need factor |
| Deyo-Charlson Comorbidity Index | Continuous variable indicating Deyo-Charlson Comorbidity score in the pre-index period | Need factor |
| Pain conditions | Categorized as:<br>Back pain<br>Neck pain<br>Arthritis/Joint pain<br>Headache/Migraine<br>Dyspnea | Need factor |
| Number of pain conditions | Categorized as:<br><br>0<br>1<br>≥2 | Need factor |
| Type of index maintenance medication | Categorized as:<br><br>ICS+LABA<br>LAMA+LABA or LAMA+ICS<br>ICS+LABA+LAMA<br>ICS or LABA or LAMA | Need factor |
| Mail-order index maintenance medication prescription | Dichotomized as:<br><br>Yes<br>No | Enabling factor |
| Co-morbid conditions | Categorized as:<br>Asthma | Need factor |

| Variable | Operational Definition | Factors as per Andersen's Behavioral Model |
|---|---|---|
| | Cardiovascular disease<br>Chronic kidney disease<br>Depression<br>Diabetes<br>Osteoporosis<br>Anemia | |
| Number of comorbid conditions | Categorized as:<br><br>0<br>1<br>≥2 | Need factor |
| Adherence to COPD-maintenance medications in the pre-index period | Dichotomized as:<br><br>Adherent if PDC ≥ 80%<br>Non-adherent if PDC < 80% | Need factor |
| **COPD severity indicators** | | |
| Supplemental oxygen use in the pre-index period | Dichotomized as:<br><br>Yes<br>No | Need factor |
| SABA use in the pre-index period | Dichotomized as:<br><br>Yes<br>No | Need factor |
| COPD-related severe exacerbations in the pre-index period | Dichotomized as:<br><br>0<br>≥1 | Need factor |
| COPD-related moderate | Dichotomized as: | Need factor |

| Variable | Operational Definition | Factors as per Andersen's Behavioral Model |
|---|---|---|
| exacerbations in the pre-index period | 0<br>≥1 | |
| **Physician characteristics** | | |
| Pulmonologist visit in the pre-index period | Categorized as:<br>Yes<br>No | Enabling factor |
| **Prior utilization characteristics** | | |
| Total all-cause healthcare costs in the pre-index period | Continuous variable representing total all-cause healthcare costs (medical costs + prescription costs) in the pre-index period | Need factor |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.

variables and variables related to access to healthcare. Need factors include variables related to the severity of the disease.

**Predisposing factors:**

Demographic variables in this study include patient’s age, sex, and region of residence and metropolitan statistical area. Patient’s age was calculated as the difference between year of birth and the year of the study index date.

**Enabling factors:**

The enabling variables in the study include type of insurance plan the patient is enrolled in, visit to a pulmonologist in the pre-index period, and whether the index maintenance medication is a mail-order prescription. The type of health insurance plan the patient was enrolled in was categorized as health maintenance organization (HMO), preferred provider organization (PPO) and other plan types which included point of service (POS), comprehensive, preferred of service (POS) with capitation, consumer-driven health plan (CDHP), high-deductible health plan (HDHP).

**Need factors:**

Severity of the disease constitute the need factors in the Andersen model. As the MarketScan Commercial Claims and Encounters Data doesn’t record clinical variables for severity, the study includes proxy measures for severity such as having moderate and severe COPD exacerbations  in the pre-index period, total all-cause healthcare expenditures in the pre-index period, presence of chronic comorbidities and pain conditions in the pre-index along with comorbidity index measured by the Deyo-Charlson comorbidity index, the type of index maintenance medication, the use of short-acting beta agonist in the pre-index, and also the use of supplemental oxygen.

Since outcomes in the post-index period may be influenced by several variables in the pre-index period, these variables were adjusted for while conducting data analyses. Patients with low or high medication adherence or higher or lower healthcare costs in the pre-index period could also lead to high or low medication adherence or higher or lower total healthcare costs in the post-index period, respectively. Having a history of COPD exacerbations has been considered as a strong predictor of having COPD exacerbations in the future[79]. Hence, variables related to COPD severe and moderate exacerbations, medication adherence, total healthcare costs in the pre-index period were adjusted for in multiple regression analyses.

Charlson's comorbidity index identifies the comorbid conditions in patients and applies weights to those conditions depending on the disease severity. The weight assigned to a comorbid condition depends on its relationship with mortality. In 1987, Charlson developed a comorbidity index based on 17 comorbidities. The comorbid conditions included in the Charlson's index are reported in Table 8. The Charlson index assigns weights of 1, 2, 3 or 6 to these comorbid conditions based on their severity (Table 8.). The diseases that have a higher impact on mortality have higher weights as opposed to conditions that have a lower impact. All the weights for all the 17 comorbidities are totaled for each patient to calculate the index severity score. The Deyo modification of the Charlson index has been adapted for its use in administrative claims databases[136]. This study uses the Deyo modification of the Charlson index.

**Table 8. ICD-9CM codes for medical conditions included in the Deyo-Charlson comorbidity index and their corresponding weights**

| Medical Condition | ICD-9 CM Code |
|---|---|
| **Conditions with a weight of 1** | |
| Cerebrovascular disease | 430-433, 435 |
| Congestive heart failure | 398, 402, 428 |
| Dementia | 290, 291, 294 |
| Mild liver disease | 571, 573 |
| Myocardial infarction | 410, 412 |
| Peripheral vascular disease | 440-447 |
| Rheumatologic disease | 710, 714, 725 |
| Ulcer disease | 531-534 |
| **Conditions with a weight of 2** | |
| Hemiplegia | 342, 434, 436, 437 |
| Moderate or severe renal disease | 403, 404, 580-586 |
| Any tumor | 140-195 |
| Diabetes | 250 |
| Leukemia | 204-208 |
| Lymphoma | 200, 202, 203 |
| **Conditions with a weight of 3** | |
| Moderate or severe liver disease | 070, 570, 572 |
| **Conditions with a weight of 6** | |
| Acquired immune deficiency syndrome (AIDS) | 042-044 |
| Metastatic solid tumor | 196-199 |

**Dependent Variables**

Table 9 provides a list of all the dependent variables assessed in the study along with their operational definitions and are presented by each specific aim in the study.

**Operational definition of study outcome for Specific Aims 1 and 2**

Specific Aim 1 examines the impact of prescription opioid use compared to no opioid use on adherence to controller mediations for COPD among a real-world, large sample of COPD patients after adjusting for other confounders. The outcome measured in Specific Aim 1 was medication adherence.

For the calculation of medication adherence to COPD maintenance medications using proportion of days covered (PDC), a technique developed by Choudhry NK et al, 2009 and recommended by the Pharmacy Quality Alliance (PQA)[121,137] was used. The interval-based technique using the proportion of days during which the patients had at least one of their medications available to them is useful when calculating medication adherence in a scenario where patients with chronic conditions such as COPD have multiple classes of maintenance medications being concurrently prescribed. Using medication possession ratio (MPR) in such a scenario may overestimate medication adherence to controller medications, and assessing adherence using PDC to only the index prescription as done by previous studies may underestimate the actual medication adherence[127]. Therefore, the interval-based technique for calculation of PDC was utilized in the study.

**Table 9. Outcomes assessed in the study (dependent variables)**

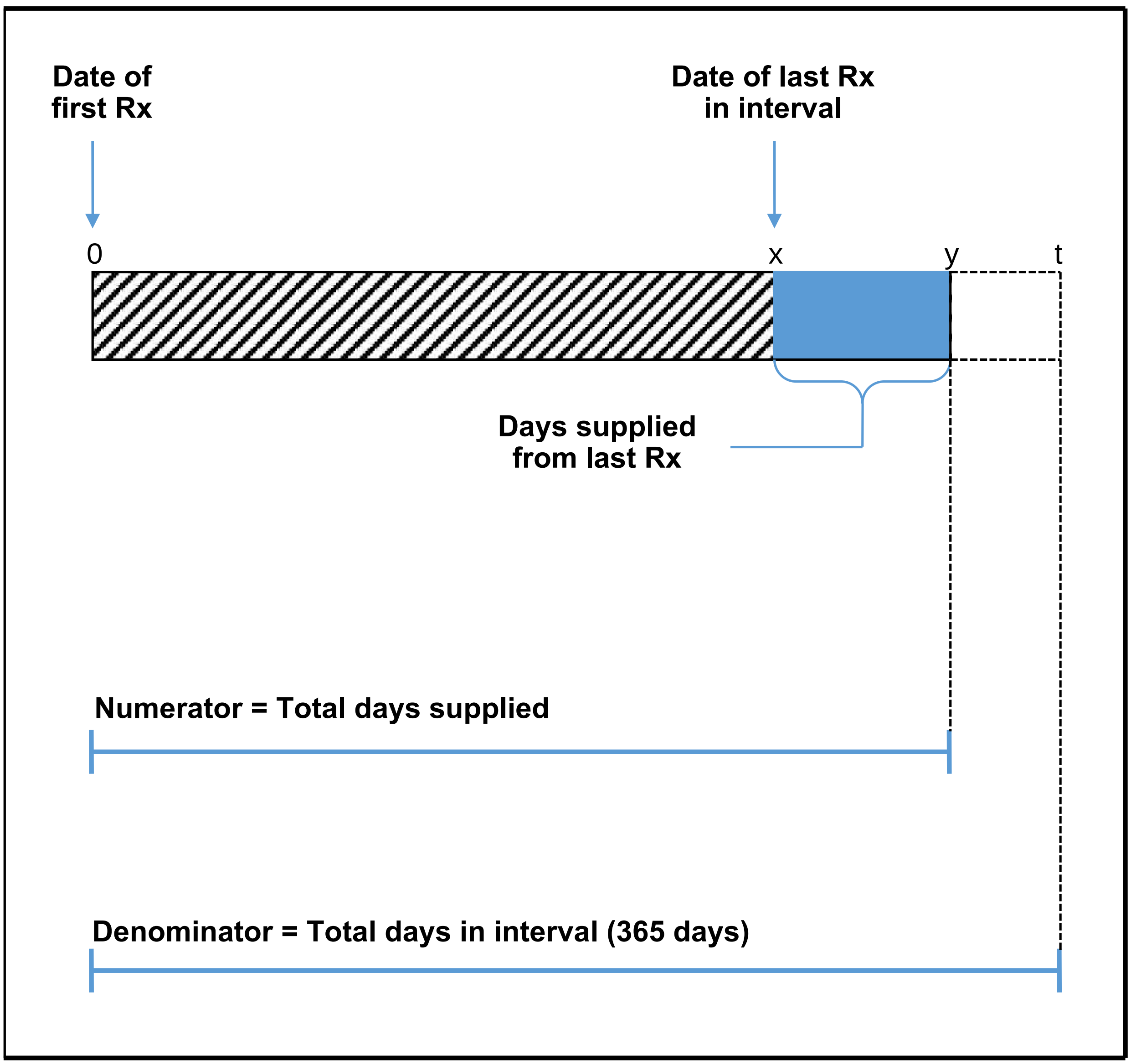
| Variable | Operational definition |
|---|---|
| **Specific Aim 1** | |
| Medication adherence measured using proportion of days covered (PDC) | Dichotomized as:<br><br>Adherent if PDC ≥ 80%<br>Non-adherent if PDC < 80% |
| **Specific Aim 2** | |
| Medication adherence measured using proportion of days covered (PDC) | Dichotomized as:<br><br>Adherent if PDC ≥ 80%<br>Non-adherent if PDC < 80% |
| **Specific Aim 3** | |
| Severe COPD exacerbations | Count variable – number of post-index severe COPD exacerbations |
| Moderate and severe COPD exacerbations | Count variable – number of post-index severe and moderate COPD exacerbations |
| **Specific Aim 4** | |
| Total medical costs | Continuous variable – post-index all-cause drug costs + medical costs (USD, 2010) |

The following steps adapted from Naik R et al, 2011[138] were utilized in the calculation of PDC as a measure of medication adherence:

For the numerator in the PDC equation, the number of days during which patients had at least one of their prescribed COPD long-acting maintenance medications available to them starting from the index date until the latest prescription date in the follow-up period for any of the maintenance medications they were using was calculated (Figure 5.)[137]. New variables accounting for the number of follow-up days in the post-index period were created to represent each day in the follow-up period. Each variable records whether the person did or did not have a fill for a COPD maintenance medication. If an included person has a COPD maintenance medication from a particular class on a particular day, he/she is given a value of 1. Whereas, a value of 0 represents no fill. The numerator then is the sum of all the days in the post-index period during which the person had a COPD maintenance medication. For example, for a patient being treated with an inhaled corticosteroid and long-acting beta agonist, the numerator of the adherence measure is the number of days during which he/she had either an inhaled corticosteroid or long-acting beta agonist (Figure 6.)[137]. Similarly, for the calculation of PDC in the pre-index period the numerator was considered to be the number of the days the person had a COPD maintenance medication from the first fill of a maintenance medication in the pre-index period, until the index-date.

Accounting for oversupply when a patient refills a maintenance medication prescription early: When a patient refills a COPD maintenance medication before the last day of the previous dispensing of the same maintenance medication, the new

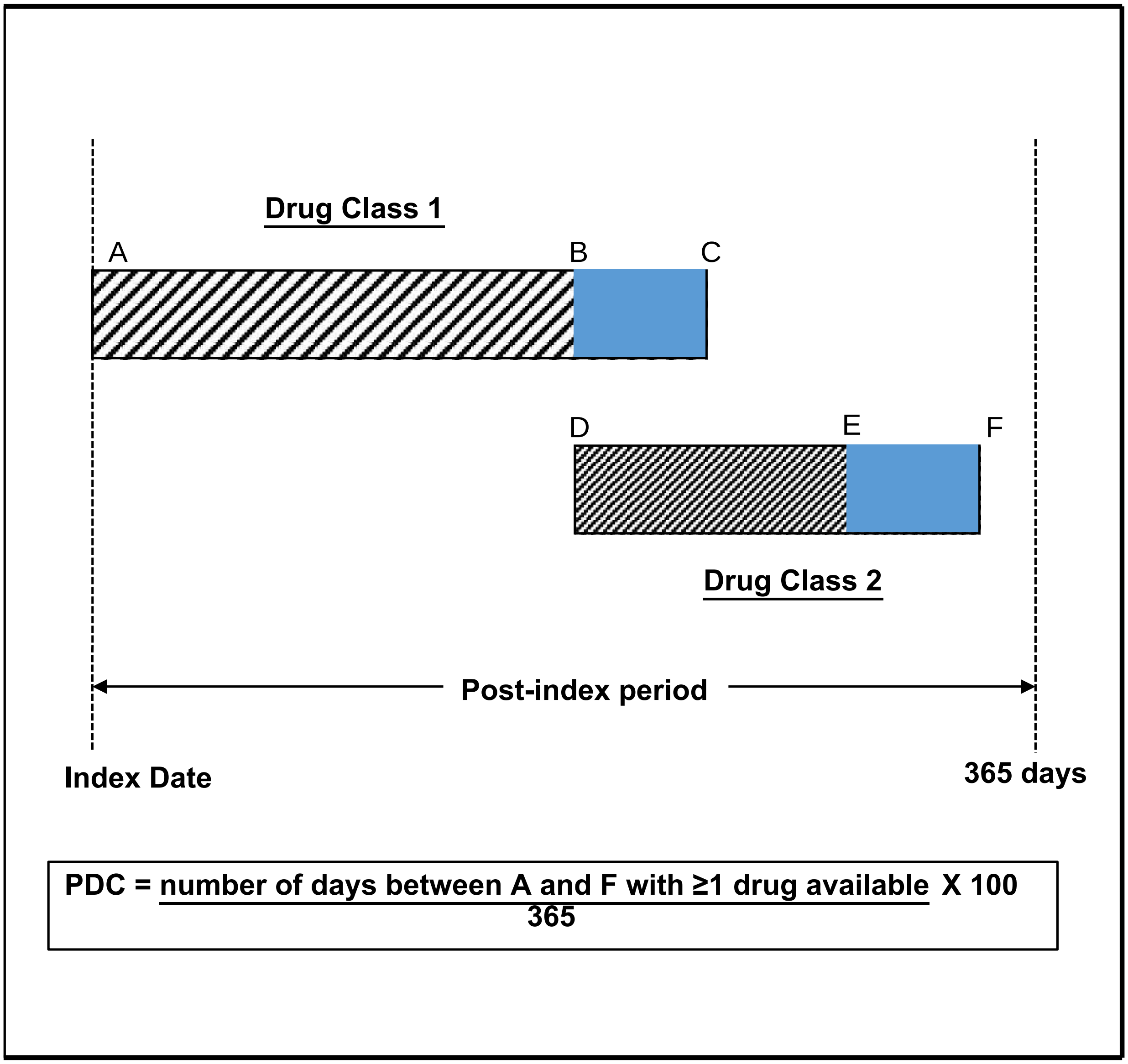
**Figure 5. Measuring medication adherence to individual medication classes using the interval-based approach for PDC**




*Adapted from Choudhry NK et al, 2009[137]

The numerator in the PDC calculation is the total number of days of medication supplied from all prescriptions in a particular medication class (i.e. x+y days). The denominator in the PDC calculation is the total number of days in the specified time interval (i.e. t=365 days).

**Figure 6. Using PDC to measure concurrent medication adherence to multiple classes of COPD maintenance medications**




A, represents the index date or the day the prescription for the first COPD maintenance medication belonging to class 1 was filled
B, represents the last refill date of the first COPD maintenance medication belonging to class 1
C, represents the last day of supply of the first COPD maintenance medication belonging to class 1
D, represents the day the first prescription of a COPD maintenance medication belonging to class 2 was filled

E, represents the last refill date of the second COPD maintenance medication belonging to class 2
F, represents the last day of supply of the second COPD maintenance medication belonging to class 2
B to C, represents the time when the patients has prescriptions for both the first and second COPD maintenance medication belonging to the 2 classes
*Adapted from Choudhry NK et al, 2009[137]

prescription refill is adjusted to begin the day after the last day of the previous prescription refill.

Accounting for oversupply when a patient switches to a different maintenance medication: Unlike oversupply due to early refills, when a patient switches to another COPD maintenance medication the switch is automatically accounted for in the calculation of the PDC. As per PDC, medication adherence for each class of COPD maintenance medication is not calculated rather each day a patient has a controller medication irrespective of the class of the controller medication is calculated. So, oversupply when switching to a different class of COPD controller medications is accounted for in the numerator of the PDC ratio. The length of stay in a hospital, in an event of a hospitalization, is added to the numerator of the PDC calculation. The denominator in the calculation of PDC is capped to the number of days in the follow-up period. For specific aims 1A, 1B, 1C, 1D and 2 the denominators in the PDC calculation are 90 days, 180 days, 270 days, 365 days, and 365 days, respectfully. The denominator in the calculation of PDC in the pre-index period is the total number of days from the first fill of a maintenance medication in the pre-index period until the index date. A patient was considered adherent if his/her PDC value is 0.8 or higher.

**Operational definition of study outcome for Specific Aim 3**

Specific Aim 3 examines the impact of long-term prescription opioid use (≥90-day supply in a one-year period) compared to no prescription opioid use on COPD exacerbations among a real-world, large sample of COPD patients after adjusting for other confounders. The outcomes measured in specific aim 3A and 3B were COPD-related severe exacerbations, and a sum of COPD-related moderate and severe exacerbations, respectively.

COPD-related moderate exacerbations were defined as having an outpatient or emergency room visit with an ICD-9CM diagnosis for COPD, followed by a prescription claim for either a systemic corticosteroid or antibiotic within 7 days of this COPD-related outpatient or emergency room visit[139,140]. COPD-related severe exacerbations were defined by either having an inpatient hospital stay with a primary diagnosis of COPD or having an inpatient hospital stay with a secondary diagnosis of COPD but with the primary diagnosis being respiratory failure (ICD-9CM codes: 518.81, 518.82, 518.84) [139,140]. Furthermore, if a moderate exacerbation occurred within 10 days of a severe exacerbation it was not categorized as a new exacerbation but was considered as a continuation of the original severe exacerbation[141]. If the same type of exacerbation occurred within 10 days of the original exacerbation, it was not counted as a new exacerbation but rather continuation of the original exacerbation[141].

**Operational definition of study outcome for Specific Aim 4**

Specific aim 4 examines the impact of long-term prescription opioid use compared to no prescription opioid use on total all-cause healthcare costs among a real-world, large sample of COPD patients after adjusting for other confounders. The outcome measured in specific aim 4 was total all-cause healthcare costs.

The total, all-cause healthcare costs included costs associated with claims for patients' inpatient visits, emergency room visits, outpatient visits, and all prescription expenditures during the study period. This study was conducted from the payer's perspective i.e. private insurance plans. All costs were adjusted to 2010 USD using the Medical Care component of the Consumer Price Index (CPI).

**Data Analysis**

Descriptive statistics were calculated and presented for sociodemographic characteristics, indicators of COPD severity, physician characteristics, clinical and prior-utilization characteristics for COPD patients with and without the evidence of prescription opioid use. Separate descriptive characteristics were calculated for each specific aim and sub-group analysis. Frequencies and percentages were calculated for categorical variables and mean and standard deviation were reported for continuous variables.

**Matching the exposed and the unexposed groups**

A sample of prescription opioid users with COPD were matched to a sample of COPD patients not using prescription opioids, on a 1:1 ratio. Matching was performed on the variables listed in Table 10. An optimal matching technique, developed by Rosenbaum 1989, was utilized for matching the exposed group (prescription opioid users) to the control groups (non-users of prescription opioids)[142].

**Statistical analyses for Specific Aim 1**

Specific aim 1 examines the impact of prescription opioid use compared to no opioid use on adherence to maintenance mediations for COPD, over four different time periods, among a real-world, large sample of COPD patients after adjusting for other confounders.

**Table 10. Variables for matching the exposed and unexposed groups**

| Variable | Matching criteria |
|---|---|
| Sex | Exact matching:<br>Male<br>Female |
| Age | Matching +/- 3 years |
| Adherent to maintenance medications in the pre-index period | Exact matching:<br><br>Yes (PDC≥80%)<br>No (PDC<80%) |
| Supplemental oxygen use in the pre-index period | Exact matching:<br><br>Yes<br>No |
| Short-acting beta agonist use in the pre-index period | Exact matching:<br><br>Yes<br>No |
| Moderate COPD exacerbations in the pre-index | Exact matching:<br><br>0<br>≥1 |
| Severe COPD exacerbations in the pre-index | Exact matching:<br><br>0<br>≥1 |
| Presence of asthma | Exact matching:<br>Yes<br>No |

To describe differences between patients who are adherent and non-adherent to COPD maintenance medications, descriptive statistics were provided for variables for sociodemographic characteristics, indicators of COPD severity, physician characteristics, and clinical and prior-utilization characteristics. For categorical variables, frequencies and percentages were calculated, and for continuous variables mean and standard deviation was reported. To describe differences in background characteristics between adherent and non-adherent patients to COPD maintenance medications, chi-squared test for categorical variables, t-test for continuous variables and Mann Whitney U tests for total healthcare cost variables were conducted.

Conditional logistic regression was utilized to identify the impact of prescription opioid use on adherence to maintenance medications for COPD (Table 11). Independent variables found significant at alpha<0.20 in univariate regression analysis were considered for inclusion in the multiple regression models. Multiple logistic regression analysis was conducted using step-wise backwards elimination procedure at alpha=0.20. Primary independent variable, for Specific Aims 1 was prescription opioid use and was categorized as no prescription opioid use and any prescription opioid use in the follow-up period. Primary independent variable, for Specific Aims 1 sub-group analyses was prescription opioid use and was categorized as no prescription opioid use, ≥30-day supply of prescription opioid in the follow-up, and <30-day supply of prescription opioid in the follow-up period. Other independent variables included in the analysis are listed in Table 7. The dependent variable was medication adherence to

**Table 11. Specific Aims and corresponding statistical tests**

| Objective | Dependent variable | Measurement level | Statistical procedure |
|---|---|---|---|
| | **Specific aim 1** | | |
| To compare medication adherence to maintenance medications for COPD between prescription opioid users and non-users | Medication adherence (PDC) | Categorical | Conditional logistic regression |
| | **Specific aim 2** | | |
| To compare medication adherence to maintenance medications for COPD between long-term prescription opioid users (≥90 days) and non-users | Medication adherence (PDC) | Categorical | Conditional logistic regression |
| | **Specific aim 3** | | |
| (Specific Aim 3A) To compare the number of severe COPD exacerbations between long-term prescription opioid users (≥90 days) and non-users among COPD patients | Number of severe COPD exacerbations | Count | Negative binomial regression |
| (Specific Aim 3B) To compare the total number of moderate and severe COPD exacerbations between long-term prescription opioid users (≥90 days) and non-users among COPD patients | Total number of moderate and severe COPD exacerbations | Count | Negative binomial regression |
| | **Specific aim 4** | | |
| To compare total COPD-related healthcare costs between long-term | Total medical costs | Continuous | Generalized linear model with gamma |

| Objective | Dependent variable | Measurement level | Statistical procedure |
| --- | --- | --- | --- |
| prescription opioid users (≥90 days) and non-users among COPD patients | | | distribution and log-link function |

*PDC, proportion of days covered

COPD maintenance medications and was categorized as adherent if PDC ≥ 80% and non-adherent if PDC < 80%.

**Statistical analyses for Specific Aim 2**

Specific Aim 2 examines the impact of long-term prescription opioid use (≥90-day supply of prescription opioids in a one-year period) compared to no prescription opioid use on adherence to maintenance mediations for COPD, among a real-world, large sample of COPD patients after adjusting for other confounders.

Similar statistical analysis for Specific Aim 1 was conducted for Specific Aim 2. Conditional logistic regression was used to identify the impact of long-term (≥90-day supply of prescription opioids in a one-year period) compared to no prescription opioid use on adherence to COPD-related maintenance medications (Table 11). Independent variables found significant at alpha=0.20 in univariate regression analysis were considered for inclusion in the multiple regression models. Multiple logistic regression analysis was conducted using step-wise backwards elimination procedure at alpha=0.20. The dependent variable, medication adherence to COPD-related maintenance medications, was categorized as adherent if PDC ≥ 80% and non-adherent if PDC < 80%. Primary independent variable was dichotomized as long-term (≥90-day supply of prescription opioids in a one-year period) no use of prescription opioids. Other independent variables included in the analysis are listed in Table 7.

**Statistical analyses for specific aim 3**

Specific aim 3 examines the impact of long-term prescription opioid use (≥90-day supply of prescription opioids in a one-year period) compared to no prescription opioid use on COPD exacerbations among a real-world, large sample of COPD patients after adjusting for other confounders. The dependent variables measured in Specific Aim 3A and 3B were the number of COPD severe and sum of severe and moderate exacerbations, respectively.

Multivariable analysis was performed to examine the impact of long-term prescription opioid use (≥90-day supply of prescription opioids in a one-year period) versus no prescription opioid use on COPD exacerbations. The independent variables included in the analysis are listed in Table 7.

Incidence rate ratio were calculated using negative binomial regression analyses adjusting for independent variables. Independent variables found significant at alpha=0.20 in univariate regression analysis were considered for inclusion in the multiple regression models.

**Statistical analyses for specific aim 4**

Specific aim 4 examines the impact of long-term prescription opioid use (≥90-day supply of prescription opioids in a one-year period) compared to no prescription opioid use on total, all-cause healthcare costs among a real-world, large sample of COPD patients after adjusting for other confounders. The total, all-cause healthcare costs included all costs associated with claims for patients' inpatient visits, ER visits, outpatient visits, and prescription fills, during the follow-up period.

The unadjusted mean costs for prescription opioid users and non-users with COPD were reported. Independent variables found significant at alpha=0.20 in univariate regression analysis were considered for inclusion in the multiple regression models. Generalized linear regression model with a gamma distribution and log link function was utilized to compare to the adjusted healthcare costs between long-term prescription opioid users (≥90-day supply of prescription opioids in a one-year period) and non-users with COPD (Table 11).

All statistical analysis and data management were conducted using SAS 9.4 (SAS Institute, Cary, NC). An a priori significance level of alpha = 0.05 was used for all statistical procedures.

**Sample size estimation**

For calculation of the required sample size we used Specific Aim 2, to examine the impact of long-term prescription opioid use (>90-day supply of prescription opioids in a one-year period) compared to no prescription opioid use on adherence to maintenance mediations for COPD among a real-world, large sample of COPD patients after adjusting for other confounders as a reference. The independent variable considered for the analysis was long-term use of prescription opioids and the dependent variable was adherence to COPD maintenance medications. The sample size calculations were performed using G*Power 3.1.9.2.

For estimating the required sample size, the two-tailed alpha value (the probability of rejecting the null hypothesis) was set as 0.05 and the required power was set to 0.80. As this is the first study to assess the impact of prescription opioid use on adherence to COPD maintenance medication, estimates of the required total sample size were adopted from a previous study among type 2 diabetes patients which reported rates of adherence to oral antihyperglycemic agents among type 2 diabetes patients with and without evidence of long-term prescription opioid use[65]. As the previous study was not conducted among COPD patients, the odds ratios were varied over a wide range of values to calculate the required sample size. Medication adherence rates among COPD patients is reported to be around 40%[46–48]. Sample sizes were calculated assuming medication adherence rates of 40% and a worst-case scenario of 20%. The calculated sample sizes are reported in Table 12.

Based on the estimates obtained from the sample size calculation, a minimum sample size of 308 to a maximum of 4,683 was required to achieve a power of 80%.

**IRB approval**

Approval from the Institutional Review Board (IRB) at the University of New Mexico was sought prior to the analyses of the study objectives. The final approval letter from the Human Research Review Committee in presented in Appendix A.

**Table 12. Sample size calculation for logistic regression**

| Odds Ratio | COPD maintenance medication adherence rate | Percentage of COPD patients using prescription opioids | Two-tailed alpha | Power | Required sample size |
|---|---|---|---|---|---|
| 0.50 | 40% | 25% | 0.05 | 0.8 | 424 |
| 0.60 | 40% | 25% | 0.05 | 0.8 | 739 |
| 0.70 | 40% | 25% | 0.05 | 0.8 | 1,459 |
| 0.78[a] | 40% | 25% | 0.05 | 0.8 | 2,940 |
| 0.50 | 40% | 33% | 0.05 | 0.8 | 355 |
| 0.60 | 40% | 33% | 0.05 | 0.8 | 623 |
| 0.70 | 40% | 33% | 0.05 | 0.8 | 1,233 |
| 0.78[a] | 40% | 33% | 0.05 | 0.8 | 2,487 |
| 0.50 | 40% | 50% | 0.05 | 0.8 | 308 |
| 0.60 | 40% | 50% | 0.05 | 0.8 | 543 |
| 0.70 | 40% | 50% | 0.05 | 0.8 | 1,081 |
| 0.78[a] | 40% | 50% | 0.05 | 0.8 | 2,187 |
| 0.50 | 20% | 25% | 0.05 | 0.8 | 745 |
| 0.60 | 20% | 25% | 0.05 | 0.8 | 1,250 |
| 0.70 | 20% | 25% | 0.05 | 0.8 | 2,384 |
| 0.78[a] | 20% | 25% | 0.05 | 0.8 | 4,683 |
| 0.50 | 20% | 33% | 0.05 | 0.8 | 619 |
| 0.60 | 20% | 33% | 0.05 | 0.8 | 1,045 |
| 0.70 | 20% | 33% | 0.05 | 0.8 | 2,003 |
| 0.78[a] | 20% | 33% | 0.05 | 0.8 | 3,947 |
| 0.50 | 20% | 50% | 0.05 | 0.8 | 526 |
| 0.60 | 20% | 50% | 0.05 | 0.8 | 898 |
| 0.70 | 20% | 50% | 0.05 | 0.8 | 1,737 |
| 0.78[a] | 20% | 50% | 0.05 | 0.8 | 3,444 |

[a] Effect size obtained from Atreja N, 2016[65]

# CHAPTER 4 RESULTS

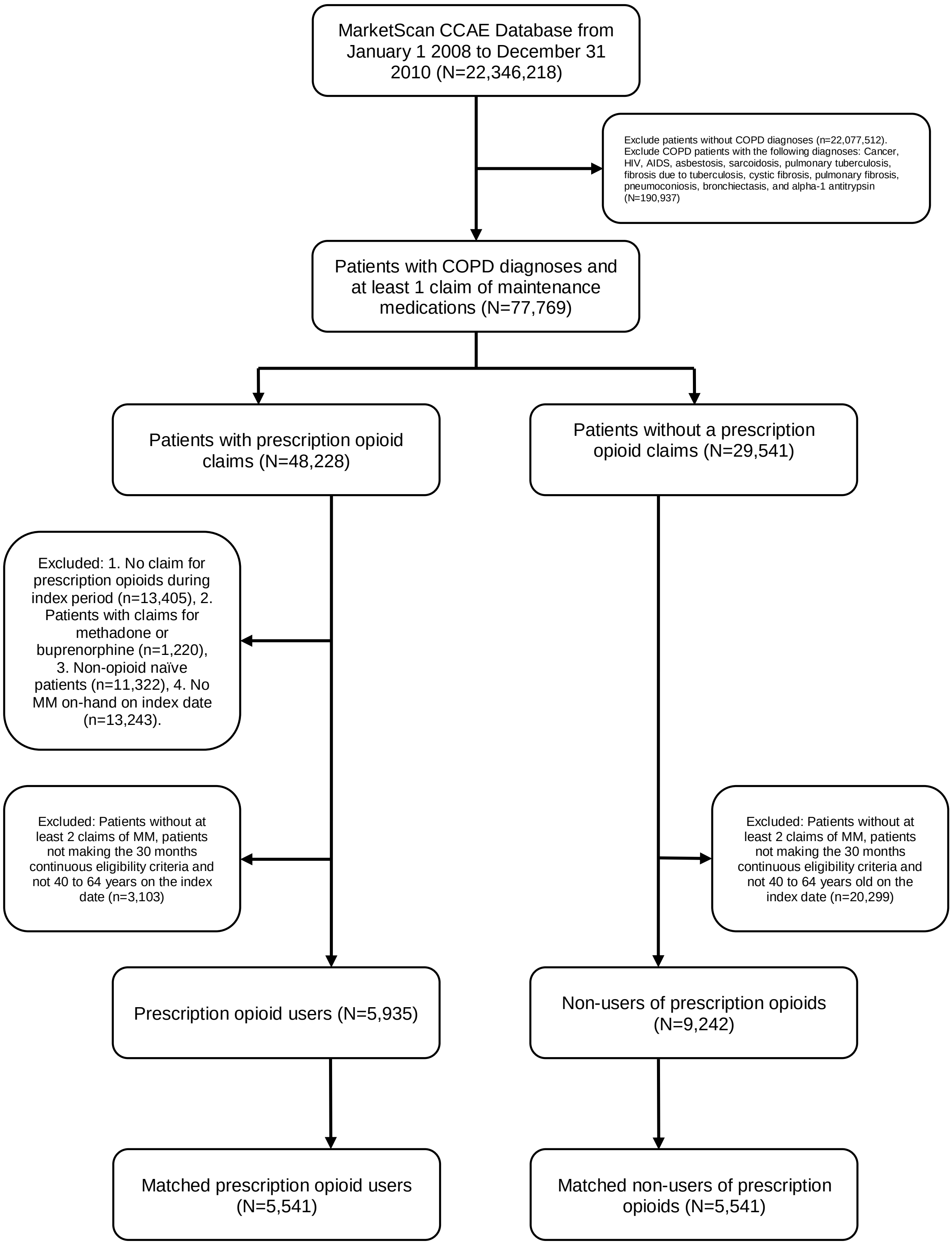
This chapter provides the results of the study. The chapter begins with the description of the study sample including the baseline characteristics of the unmatched and matched sample of exposed (prescription opioid users) and unexposed (non-opioid users) groups of COPD patients. This is followed by a detailed description of the baseline characteristics of the unexposed and exposed groups corresponding to each specific aim of the study. Results of univariate analysis are presented according to each specific aim, followed by the results of the adjusted multiple regression analysis by specific aim.

**Sample Selection**

A total of 22,346,218 unique patients were identified from the Truven Health MarketScan Commercial Claims and Encounters Database from 2008 to 2010. After excluding patients without COPD diagnosis and patients with a diagnosis of selected conditions referred in Table 6, a total of 77,769 patients were left with a diagnosis of COPD and having at least 1 claim for a long-acting COPD maintenance medication. Of these patients 48,228 patients had a claim for a prescription opioid and the remaining 29,541 patients did not have a claim for a prescription opioid. Further applying the study inclusion and exclusion criteria, 5,935 (39.1%) COPD patients were classified as prescription opioid users and 9,242 (60.9%) COPD patients were classified as non-opioid users. A total of 5,541 exact matches of non-opioid users were identified for the prescription opioid group.

Figure 7: Study sample selection flowchart provides a flowchart of the final study sample after applying the study inclusion and exclusion criteria.

## Figure 7: Study sample selection flowchart



**Baseline characteristics of prescription opioid users and non-users pre-matching:**

**Table** 13 presents baseline characteristics of COPD patients with and without prescription opioid use. The mean age of prescription opioid users was significantly lower than non-opioid users [57.0 ± 5.5 years (users) vs 57.4 ± 5.4 years (non-users), p<0.0001], and a greater percentage of prescription opioid users were females (56.1%). Overall, prescription opioid users had higher number of comorbid conditions than non-opioid users. The mean Deyo-Charlson Comorbidity Index (D-CCI) score among prescription opioid users was significantly higher compared to non-opioid users (2.0 ± 1.5 vs 1.7 ± 1.1). Similarly, a higher percentage of prescription opioid users had more than 1 comorbid chronic condition (49.9% vs 33.6%) and comorbid pain conditions (52.5% vs 24.6%) compared to non-opioid users.

**Baseline characteristics of prescription opioid user and non-users post matching:**

Prescription opioid users were matched to non-opioid users on sex, age (±3 years), adherence to COPD maintenance medication in the pre-index period, supplemental oxygen use, SABA use, COPD-related severe and moderate exacerbations, and comorbid asthma. A total of 5,541 pairs of prescription opioid users and non-users were included after matching on the chosen variables and presented in Table 14. No significant differences were found between prescription opioid users and non-opioid users on the matching variables. MSA and mail-order index medication variables found significantly different before matching were not significant post-matching. However, the significant difference between prescription opioid users and

**Table 13: Baseline characteristics of the unmatched study sample**

| Variable | | Prescription Opioid Non-Users (n=9,242) | | Prescription Opioid Users (n=5,935) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col % Row % | N | Col % Row % | |
| **Sociodemographic characteristics** | | | | | | |
| Sex | Male | 4,496 | 48.6 | 2,606 | 43.9 | <0.0001 |
| | | | 63.3 | | 36.7 | |
| | Female | 4,746 | 51.4 | 3,329 | 56.1 | |
| | | | 58.8 | | 41.2 | |
| | | | | | | |
| Age | *mean (±sd)* | 57.4 years (±5.4) | | 57.0 years (±5.5) | | <0.0001 |
| | 40 – 49 years | 962 | 10.4 | 678 | 11.4 | 0.0002 |
| | | | 58.7 | | 41.3 | |
| | 50 – 59 years | 4,068 | 44.0 | 2,753 | 46.4 | |
| | | | 59.6 | | 40.4 | |
| | ≥60 years | 4,212 | 45.6 | 2,504 | 42.2 | |
| | | | 62.7 | | 37.3 | |
| Metropolitan Statistical Area | Urban | 7,465 | 80.8 | 4,714 | 79.4 | 0.03 |
| | | | 61.3 | | 38.7 | |
| | Rural | 1,732 | 18.7 | 1,201 | 20.2 | |
| | | | 59.1 | | 40.9 | |
| | | | | | | |
| Region | Northeast | 1591 | 17.2 | 681 | 11.5 | 0.0001 |
| | | | 70.0 | | 30.0 | |
| | North Central | 3,279 | 35.5 | 2,079 | 35.0 | |
| | | | 61.2 | | 38.8 | |
| | South | 3,120 | 33.8 | 2,356 | 39.7 | |
| | | | 57.0 | | 43.0 | |
| | West | 1,201 | 13.0 | 799 | 13.5 | |
| | | | 60.1 | | 40.0 | |
| | | | | | | |
| Insurance Plan Type | HMO | 1,535 | 16.6 | 997 | 16.8 | 0.9243 |
| | | | 60.6 | | 39.4 | |
| | PPO | 2,451 | 26.5 | 1,586 | 26.7 | |
| | | | 60.7 | | 39.3 | |
| | Other | 5,191 | 56.2 | 3,320 | 55.9 | |
| | | | 61.0 | | 39.0 | |
| **Clinical characteristics** | | | | | | |
| Deyo-Charlson Comorbidity Index | *mean (±sd)* | 1.7 (±1.1) | | 2.0 (±1.5) | | <0.0001 |
| | | | | | | |
| Number of pain conditions | 0 | 2,756 | 29.8 | 809 | 13.6 | <0.0001 |
| | | | 77.3 | | 22.7 | |
| | 1 | 4,214 | 45.6 | 2,009 | 33.9 | |
| | | | 67.7 | | 32.3 | |

| Variable | | Prescription Opioid Non-Users (n=9,242) | | Prescription Opioid Users (n=5,935) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | ≥2 | 2,272 | 24.6 | 3,117 | 52.5 | |
| | | | 42.2 | | 57.8 | |
| | | | | | | |
| Number of comorbid conditions | 0 | 2,531 | 27.4 | 1,003 | 16.9 | <0.0001 |
| | | | 71.6 | | 28.4 | |
| | 1 | 3,603 | 39.0 | 1,973 | 33.2 | |
| | | | 64.6 | | 35.4 | |
| | ≥2 | 3,108 | 33.6 | 2,959 | 49.9 | |
| | | | 51.2 | | 48.8 | |
| | | | | | | |
| Type of index maintenance medication | ICS+LABA | 4,908 | 53.1 | 3,225 | 54.3 | 0.152 |
| | | | 60.3 | | 39.7 | |
| | LAMA+LABA or LAMA+ICS | 85 | 0.9 | 63 | 1.1 | |
| | | | 57.4 | | 42.6 | |
| | ICS+LABA+LAMA | 845 | 9.1 | 564 | 9.5 | |
| | | | 60.0 | | 40.0 | |
| | ICS or LABA or LAMA | 3,404 | 36.8 | 2,083 | 35.1 | |
| | | | 62.0 | | 38.0 | |
| | | | | | | |
| Mail-order index maintenance medication prescription | Yes | 3,391 | 36.7 | 2,448 | 41.2 | <0.0001 |
| | | | 58.1 | | 41.9 | |
| | No | 5,851 | 63.3 | 3,487 | 58.8 | |
| | | | 62.7 | | 37.3 | |
| | | | | | | |
| Adherence to COPD-maintenance medications in the pre-index period | Non-adherent if PDC < 80% | 4,377 | 47.4 | 1,761 | 29.7 | <0.0001 |
| | | | 71.3 | | 28.7 | |
| | Adherent if PDC ≥ 80% | 4,865 | 52.6 | 4,174 | 70.3 | |
| | | | 53.8 | | 46.2 | |
| | | | | | | |
| **COPD severity indicators** | | | | | | |
| Supplemental oxygen use in the pre-index period | No | 7,483 | 81.0 | 4,675 | 78.8 | 0.0009 |

| Variable | | Prescription Opioid Non-Users (n=9,242) | | Prescription Opioid Users (n=5,935) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | | | 61.5 | | 38.5 | |
| | Yes | 1,759 | 19.0 | 1,260 | 21.2 | |
| | | | 58.3 | | 41.7 | |
| | | | | | | |
| SABA use in the pre-index period | No | 4,460 | 48.3 | 2,773 | 46.7 | 0.06 |
| | | | 61.7 | | 38.3 | |
| | Yes | 4,782 | 51.7 | 3,162 | 53.3 | |
| | | | 60.2 | | 39.8 | |
| | | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | 8,896 | 96.3 | 5,715 | 96.3 | 0.91 |
| | | | 60.9 | | 39.1 | |
| | ≥1 | 346 | 3.7 | 220 | 3.7 | |
| | | | 61.1 | | 38.9 | |
| | | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | 8,050 | 87.1 | 5,051 | 85.1 | 0.0005 |
| | | | 61.4 | | 38.6 | |
| | ≥1 | 1,192 | 12.9 | 884 | 14.9 | |
| | | | 57.4 | | 42.6 | |
| | | | | | | |
| **Physician characteristics** | | | | | | |
| Pulmonologist visit in the pre-index period | No | 6,845 | 74.1 | 4,234 | 71.3 | 0.0002 |
| | | | 61.8 | | 38.2 | |
| | Yes | 2,397 | 25.9 | 1,701 | 28.7 | |
| | | | 58.5 | | 41.5 | |
| | | | | | | |
| **Prior utilization characteristics** | | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | *mean (±sd)* | 7,896.1 (±95,445.5) | | 15,684.25 (±122,558.1) | | <0.0001 |
| | <$2,844 | 3472 | 37.6 | 940 | 15.8 | <0.0001 |
| | | | 78.7 | | 21.3 | |
| | $2,844 - $9,838 | 4286 | 46.4 | 2956 | 49.8 | |
| | | | 59.2 | | 40.8 | |
| | >$9,838 | 1484 | 16.1 | 2039 | 34.4 | |

| Variable | | Prescription Opioid Non-Users (n=9,242) | | Prescription Opioid Users (n=5,935) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | | | 42.1 | | 57.9 | |

*sd denotes standard deviation; Col, column; HMO, health maintenance organization; PPO, preferred provider organization; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.

[a] adjusted to 2010 US $

**Table 14: Baseline characteristics of the matched study sample**

| Variable | | Prescription Opioid Non-Users (n=5,541) | | Prescription Opioid Users (n=5,541) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| **Sociodemographic characteristics** | | | | | | |
| Sex | Male | 2,537 | 45.8 | 2,537 | 45.8 | 1 |
| | | | 50.0 | | 50.0 | |
| | Female | 3,004 | 54.2 | 3,004 | 54.2 | |
| | | | 50.0 | | 50.0 | |
| | | | | | | |
| Age | *mean (±sd)* | 57.2 years (±5.4) | | 57.2 years (±5.4) | | 0.83 |
| | 40 – 49 years | 604 | 10.9 | 609 | 11.0 | 0.974 |
| | | | 49.8 | | 50.2 | |
| | 50 – 59 years | 2,555 | 46.1 | 2,544 | 45.9 | |
| | | | 50.1 | | 49.9 | |
| | ≥60 years | 2,382 | 43.0 | 2,388 | 43.1 | |
| | | | 49.9 | | 50.1 | |
| Metropolitan Statistical Area | Urban | 4,408 | 79.6 | 4,405 | 79.5 | 0.84 |
| | | | 50.0 | | 50.0 | |
| | Rural | 1,106 | 20.0 | 1,116 | 20.1 | |
| | | | 49.8 | | 50.2 | |
| | | | | | | |
| Region | Northeast | 910 | 16.4 | 614 | 11.1 | <0.0001 |
| | | | 59.7 | | 40.3 | |
| | North Central | 2,084 | 37.6 | 1,966 | 35.5 | |
| | | | 51.5 | | 48.5 | |
| | South | 1,808 | 32.6 | 2,202 | 39.7 | |
| | | | 45.1 | | 54.9 | |
| | West | 708 | 12.8 | 739 | 13.3 | |
| | | | 48.9 | | 51.1 | |
| | | | | | | |
| Insurance Plan Type | HMO | 879 | 15.9 | 918 | 16.6 | 0.495 |
| | | | 48.9 | | 51.1 | |
| | PPO | 3,118 | 56.3 | 3,115 | 56.2 | |
| | | | 50.0 | | 50.0 | |
| | Other | 1,518 | 27.4 | 1,477 | 26.7 | |
| | | | 50.7 | | 49.3 | |
| **Clinical characteristics** | | | | | | |
| Deyo-Charlson Comorbidity Index | *mean (±sd)* | 1.7 (±1.2) | | 2.0 (±1.5) | | <0.0001 |
| | | | | | | |
| | | | | | | |
| Number of pain conditions | 0 | 1,624 | 29.3 | 776 | 14.0 | <0.0001 |
| | | | 67.7 | | 32.3 | |

| Variable | | Prescription Opioid Non-Users (n=5,541) | | Prescription Opioid Users (n=5,541) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | 1 | 2,515 | 45.4 | 1,879 | 33.9 | |
| | | | 57.2 | | 42.8 | |
| | 2 | 1,402 | 25.3 | 2,886 | 52.1 | |
| | | | 32.7 | | 67.3 | |
| | | | | | | |
| Number of comorbid conditions | 0 | 1,312 | 23.7 | 996 | 18.0 | <0.0001 |
| | | | 56.8 | | 43.2 | |
| | 1 | 2,168 | 39.1 | 1,862 | 33.6 | |
| | | | 53.8 | | 46.2 | |
| | 2 | 2,061 | 37.2 | 2,683 | 48.4 | |
| | | | 43.4 | | 56.6 | |
| | | | | | | |
| Type of index maintenance medication | ICS+LABA | 2,904 | 52.4 | 2,999 | 54.1 | 0.3034 |
| | | | 49.2 | | 50.8 | |
| | LAMA+LABA or LAMA+ICS | 56 | 1.0 | 58 | 1.0 | |
| | | | 49.1 | | 50.9 | |
| | ICS+LABA+LAMA | 538 | 9.7 | 531 | 9.6 | |
| | | | 50.3 | | 49.7 | |
| | ICS or LABA or LAMA | 2,043 | 36.9 | 1,953 | 35.2 | |
| | | | 51.1 | | 48.9 | |
| | | | | | | |
| Mail-order index maintenance medication prescription | Yes | 3,353 | 60.5 | 3,261 | 58.9 | 0.075 |
| | | | 50.7 | | 49.3 | |
| | No | 2,188 | 39.5 | 2,280 | 41.1 | |
| | | | 49.0 | | 51.0 | |
| | | | | | | |
| Adherence to COPD-maintenance medications in the pre-index period | Non-adherent if PDC < 80% | 1,734 | 31.3 | 1,734 | 31.3 | 1 |
| | | | 50.0 | | 50.0 | |
| | Adherent if PDC ≥ 80% | 3,807 | 68.7 | 3,807 | 68.7 | |
| | | | 50.0 | | 50.0 | |
| | | | | | | |
| **COPD severity indicators** | | | | | | |
| Supplemental oxygen use in | No | 4,425 | 79.9 | 4,425 | 79.9 | 1 |

| Variable | | Prescription Opioid Non-Users (n=5,541) | | Prescription Opioid Users (n=5,541) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| the pre-index period | | | | | | |
| | | | 50.0 | | 50.0 | |
| | Yes | 1,116 | 20.1 | 1,116 | 20.1 | |
| | | | 50.0 | | 50.0 | |
| | | | | | | |
| SABA use in the pre-index period | No | 2,590 | 46.7 | 2,590 | 46.7 | 1 |
| | | | 50.0 | | 50.0 | |
| | Yes | 2,951 | 53.3 | 2,951 | 53.3 | |
| | | | 50.0 | | 50.0 | |
| | | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | 5,380 | 97.1 | 5,380 | 97.1 | 1 |
| | | | 50.0 | | 50.0 | |
| | ≥1 | 161 | 2.9 | 161 | 2.9 | |
| | | | 50.0 | | 50.0 | |
| | | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | 4,777 | 86.2 | 4,777 | 86.2 | 1 |
| | | | 50.0 | | 50.0 | |
| | ≥1 | 764 | 13.8 | 764 | 13.8 | |
| | | | 50.0 | | 50.0 | |
| | | | | | | |
| **Physician characteristics** | | | | | | |
| Pulmonologist visit in the pre-index period | No | 4,072 | 73.5 | 3,967 | 71.6 | 0.03 |
| | | | 50.7 | | 49.3 | |
| | Yes | 1,469 | 26.5 | 1,574 | 28.4 | |
| | | | 48.3 | | 51.7 | |
| | | | | | | |
| **Prior utilization characteristics** | | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | *mean (±sd)* | 6,988.4 (±11,358.8) | | 12,498.8 (±19,856) | | <0.0001 |
| | <$2,844 | 1874 | 33.8 | 895 | 16.2 | <0.0001 |
| | | | 67.7 | | 32.3 | |
| | $2,844 - $9,838 | 2752 | 49.7 | 2790 | 50.4 | |

| Variable | | Prescription Opioid Non-Users (n=5,541) | | Prescription Opioid Users (n=5,541) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | | | 49.7 | | 50.3 | |
| | >$9,838 | 915 | 16.5 | 1856 | 33.5 | |
| | | | 33.0 | | 67.0 | |

*sd denotes standard deviation; Col, column; HMO, health maintenance organization; PPO, preferred provider organization; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.

[a] adjusted to 2010 US $

non-users in terms of the number of comorbid conditions persisted after matching. The mean D-CCI score among prescription opioid users was significantly higher compared to non-opioid users ($2.0 \pm 1.5$ vs $1.7 \pm 1.2$, $p<0.0001$) after matching. Similarly, a significantly higher percentage of prescription opioid users had ≥1 comorbid chronic condition (82% vs 76.3%, $p<0.0001$) and ≥1 comorbid pain conditions (86% vs 70.7%, $p<0.0001$) compared to non-opioid users.

**Results for Specific Aim 1**

Specific Aim 1 was to examine the impact of prescription opioid use compared to no prescription opioid use on adherence to COPD maintenance medications, over four different time periods, among a real-world, large sample of COPD patients after adjusting for other confounders.

**Results for Specific Aim 1A**

**Baseline characteristics as per specific aim 1A:**

Specific aim 1A was to examine the impact of prescription opioid use compared to no prescription opioid use on adherence to COPD maintenance medications, within the first 90 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders. Table 15 provides baseline characteristics of the included sample of COPD patients and adherence to COPD maintenance medications in the 90-day follow-up period. Overall, 59.4% of the included matched sample of COPD patients were adherent (defined as PDC ≥0.8) to their COPD maintenance medications in the 90-day follow-up period after the index date. A smaller percentage of prescription opioid users were adherent to their COPD maintenance medications in the 90-day follow-up period compared to non-opioid users (49.2% vs

**Table 15: Baseline characteristics for Specific Aim 1A**

| Variable | | Non-Adherent in 90 days (n=4,502) | | Adherent in 90 days (n=6,580) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| **Sociodemographic characteristics** | | | | | | |
| Sex | Male | 1,977 | 43.9 | 3,097 | 47.1 | 0.001 |
| | | | 39.0 | | 61.0 | |
| | Female | 2,525 | 56.1 | 3,483 | 52.9 | |
| | | | 42.0 | | 58.0 | |
| | | | | | | |
| Age | *mean (±sd)* | 56.1 years (±5.8) | | 57.9 years (±4.9) | | <0.0001 |
| | 40 – 49 years | 699 | 15.5 | 514 | 7.8 | <0.0001 |
| | | | 57.6 | | 42.4 | |
| | 50 – 59 years | 2,157 | 47.9 | 2,942 | 44.7 | |
| | | | 42.3 | | 57.7 | |
| | ≥60 years | 1,646 | 36.6 | 3,124 | 47.5 | |
| | | | 34.5 | | 65.5 | |
| | | | | | | |
| Metropolitan Statistical Area | Urban | 3,566 | 79.2 | 5,247 | 79.7 | 0.34 |
| | | | 40.5 | | 59.5 | |
| | Rural | 924 | 20.5 | 1,298 | 19.7 | |
| | | | 41.6 | | 58.4 | |
| | | | | | | |
| Region | Northeast | 568 | 12.6 | 956 | 14.5 | <0.0001 |
| | | | 37.3 | | 62.7 | |
| | North Central | 1,466 | 32.6 | 2,584 | 39.3 | |
| | | | 36.2 | | 63.8 | |
| | South | 1,835 | 40.8 | 2,175 | 33.1 | |
| | | | 45.8 | | 54.2 | |
| | West | 617 | 13.7 | 830 | 12.6 | |
| | | | 42.6 | | 57.4 | |
| | | | | | | |
| Insurance Plan Type | HMO | 874 | 19.4 | 923 | 14.0 | <0.0001 |
| | | | 48.6 | | 51.4 | |
| | PPO | 2,444 | 54.3 | 3,789 | 57.6 | |
| | | | 39.2 | | 60.8 | |
| | Other | 1,164 | 25.9 | 1,831 | 27.8 | |
| | | | 38.9 | | 61.1 | |
| **Clinical characteristics** | | | | | | |
| Prescription opioid use | No use | 1,688 | 37.5 | 3,853 | 58.6 | <0.0001 |
| | | | 30.5 | | 69.5 | |
| | Use | 2,814 | 62.5 | 2,727 | 41.4 | |
| | | | 50.8 | | 49.2 | |
| Prescription opioid use | No use | 1,688 | 37.5 | 3,853 | 58.6 | <0.0001 |
| | | | 30.5 | | 69.5 | |

| Variable | | Non-Adherent in 90 days (n=4,502) | | Adherent in 90 days (n=6,580) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | ≤30 days supply of prescription opioids | 2,492 | 55.4 | 2,402 | 36.5 | |
| | | | 50.9 | | 49.1 | |
| | >30 days supply of prescription opioids | 322 | 7.2 | 325 | 4.9 | |
| | | | 49.8 | | 50.2 | |
| Deyo-Charlson Comorbidity Index | *mean (±sd)* | 1.9 (±1.4) | | 1.8 (±1.3) | | 0.006 |
| | | | | | | |
| Number of pain conditions | 0 | 851 | 18.9 | 1,549 | 23.5 | <0.0001 |
| | | | 35.5 | | 64.5 | |
| | 1 | 1696 | 37.7 | 2,698 | 41.0 | |
| | | | 38.6 | | 61.4 | |
| | 2 | 1955 | 43.4 | 2,333 | 35.5 | |
| | | | 45.6 | | 54.4 | |
| | | | | | | |
| Number of comorbid conditions | 0 | 878 | 19.5 | 1,430 | 21.7 | 0.0008 |
| | | | 38.0 | | 62.0 | |
| | 1 | 1608 | 35.7 | 2,422 | 36.8 | |
| | | | 39.9 | | 60.1 | |
| | 2 | 2016 | 44.8 | 2,728 | 41.5 | |
| | | | 42.5 | | 57.5 | |
| | | | | | | |
| Type of index maintenance medication | ICS+LABA | 2806 | 62.3 | 3,097 | 47.1 | <0.0001 |
| | | | 47.5 | | 52.5 | |
| | LAMA+LABA or LAMA+ICS | 31 | 0.7 | 83 | 1.3 | |
| | | | 27.2 | | 72.8 | |
| | ICS+LABA+LAMA | 295 | 6.6 | 774 | 11.8 | |
| | | | 27.6 | | 72.4 | |
| | ICS or LABA or LAMA | 1370 | 30.4 | 2,626 | 39.9 | |
| | | | 34.3 | | 65.7 | |
| | | | | | | |
| Mail-order index maintenance medication prescription | No | 3599 | 79.9 | 3,015 | 45.8 | <0.0001 |
| | | | 54.4 | | 45.6 | |

| Variable | | Non-Adherent in 90 days (n=4,502) | | Adherent in 90 days (n=6,580) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | Yes | 903 | 20.1 | 3,565 | 54.2 | |
| | | | 20.2 | | 79.8 | |
| | | | | | | |
| Adherence to COPD-maintenance medications in the pre-index period | Non-adherent if PDC < 80% | 2344 | 52.1 | 1,124 | 17.1 | <0.0001 |
| | | | 67.6 | | 32.4 | |
| | Adherent if PDC ≥ 80% | 2158 | 47.9 | 5,456 | 82.9 | |
| | | | 28.3 | | 71.7 | |
| | | | | | | |
| **COPD severity indicators** | | | | | | |
| Supplemental oxygen use in the pre-index period | No | 3744 | 83.2 | 5,106 | 77.6 | <0.0001 |
| | | | 42.3 | | 57.7 | |
| | Yes | 758 | 16.8 | 1,474 | 22.4 | |
| | | | 34.0 | | 66.0 | |
| | | | | | | |
| SABA use in the pre-index period | No | 2088 | 46.4 | 3,092 | 47.0 | 0.53 |
| | | | 40.3 | | 59.7 | |
| | Yes | 2414 | 53.6 | 3,488 | 53.0 | |
| | | | 40.9 | | 59.1 | |
| | | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | 4382 | 97.3 | 6,378 | 96.9 | 0.213 |
| | | | 40.7 | | 59.3 | |
| | ≥1 | 120 | 2.7 | 202 | 3.1 | |
| | | | 37.3 | | 62.7 | |
| | | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | 3894 | 86.5 | 5,660 | 86.0 | 0.475 |
| | | | 40.8 | | 59.2 | |
| | ≥1 | 608 | 13.5 | 920 | 14.0 | |
| | | | 39.8 | | 60.2 | |
| | | | | | | |
| **Physician characteristics** | | | | | | |

| Variable | | Non-Adherent in 90 days (n=4,502) | | Adherent in 90 days (n=6,580) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| Pulmonologist visited in the pre-index period | No | 3370 | 74.9 | 4,669 | 71.0 | <0.0001 |
| | | | 41.9 | | 58.1 | |
| | Yes | 1132 | 25.1 | 1,911 | 29.0 | |
| | | | 37.2 | | 62.8 | |
| | | | | | | |
| **Prior utilization characteristics** | | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | *mean (±sd)* | 10,241.1 (±17,573.4) | | 9,403.2 (±15,552) | | <0.0001 |
| | <$2,844 | 1355 | 30.1 | 1414 | 21.5 | <0.0001 |
| | | | 48.9 | | 51.1 | |
| | $2,844 - $9,838 | 1976 | 43.9 | 3566 | 54.2 | |
| | | | 35.7 | | 64.3 | |
| | >$9,838 | 1171 | 26.0 | 1600 | 24.3 | |
| | | | 42.3 | | 57.7 | |

*sd denotes standard deviation; Col, column; HMO, health maintenance organization; PPO, preferred provider organization; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

69.5%, p<0.0001). Patients who were non-adherent to their COPD maintenance medications in the 90-day follow-up period were more likely to be prescription opioid users than non-opioid users (62.5% vs 37.5%, p<0.0001). A greater percentage of patients non-adherent to their COPD maintenance medications in the 90-day follow-up period had comorbid conditions than patients adherent to their COPD maintenance medications. Non-adherent patients had a significantly higher mean D-CCI score (1.9 ± 1.4 vs 1.8 ± 1.3, p=0.006). Non-adherent patients also had a higher percentage of patients with ≥1 comorbid chronic conditions (80.5% vs 78.3%, p<0.001) and ≥1 comorbid pain conditions (81.1% vs 76.5%, p<0.0001).

Specific Aim 1A sub-analysis was to examine the impact of prescription opioid use (classified as having > 30-day supply of prescription opioids and ≤ 30-day supply of prescription opioids) compared to no prescription opioid use, within the first 90 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders. A significantly lower percentage of prescription opioid users, either ≤30-day supply of prescription (49.1% vs 69.5%, p<0.0001) or >30-day supply of prescription opioids (50.2% vs 69.5%, p<0.0001), were adherent to their COPD maintenance medications in the 90-day follow-up period compared to non-opioid users (69.5%) (Table 15).

**Unadjusted logistic regression analyses:**

Table 16 provides the results of the unadjusted logistic regression analysis of the odds of being adherent to COPD maintenance medications in the 90-day follow-up period for Specific Aim 1A. Prescription opioid users were found to have 0.36 times (95% CI 0.33-0.40, p<0.0001) significantly lower odds of being adherent to their COPD

**Table 16: Unadjusted logistic regression predicting the odds of being adherent to COPD maintenance medications in 90 days follow-up**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Metropolitan Statistical Area | Rural | Reference | | | |
| | Urban | 1.15 | 0.99 | 1.32 | 0.06 |
| | | | | | |
| Region | Northeast | Reference | | | |
| | North Central | 0.86 | 0.73 | 1.05 | 0.15 |
| | South | 0.64 | 0.53 | 0.77 | <0.0001 |
| | West | 0.74 | 0.60 | 0.93 | 0.008 |
| | | | | | |
| Insurance Plan Type | Health maintenance organization | Reference | | | |
| | Preferred provider organization | 1.28 | 1.09 | 1.71 | 0.003 |
| | Other | 1.42 | 1.18 | 1.71 | <0.001 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Use | 0.36 | 0.33 | 0.40 | <0.0001 |
| | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | ≤30-day supply of prescription opioids | 0.37 | 0.33 | 0.40 | <0.0001 |
| | >30-day supply of prescription opioids | 0.33 | 0.25 | 0.44 | <0.0001 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.85 | 0.82 | 0.89 | <0.0001 |
| | | | | | |
| Number of pain conditions | 0 | Reference | | | |
| | 1 | 0.79 | 0.68 | 0.93 | 0.003 |
| | 2 | 0.48 | 0.42 | 0.57 | <0.0001 |
| | | | | | |
| Number of comorbid conditions | 0 | Reference | | | |
| | 1 | 0.93 | 0.78 | 1.12 | 0.46 |
| | 2 | 0.68 | 0.56 | 0.56 | <0.0001 |

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 1.70 | 0.99 | 2.94 | 0.05 |
| | ICS+LABA+LAMA | 1.78 | 1.45 | 2.19 | <0.0001 |
| | ICS or LABA or LAMA | 1.51 | 1.33 | 1.72 | <0.0001 |
| | | | | | |
| Mail-order index maintenance medication prescription | No | Reference | | | |
| | Yes | 3.28 | 2.87 | 3.75 | <0.0001 |
| | | | | | |
| **Physician characteristics** | | | | | |
| Pulmonologist visit in the pre-index period | No | Reference | | | |
| | Yes | 1.05 | 0.92 | 1.20 | 0.48 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period [a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 1.27 | 1.10 | 1.46 | 0.0009 |
| | >$9,838 | 0.73 | 0.62 | 0.86 | 0.0002 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.

[a] adjusted to 2010 US $

maintenance medications in the 90-day follow-up period compared to non-opioid users. In the sub-group analysis patients with ≤30-day supply of prescription opioids had 0.37 times (95% CI 0.33-0.40, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 90-day follow-up period as compared to non-opioid users. Similarly, patients with >30-day supply of prescription opioids had 0.33 times (95% CI 0.25-0.44, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 90-day follow-up period as compared to non-opioid users. MSA, region, insurance plan type, D-CCI, number of comorbid pain conditions, number of comorbid chronic conditions, type of index maintenance medication, mail-order index maintenance medication, and total all-cause healthcare expenditures were found significant at $p<0.2$ and were considered in the adjusted logistic regression analysis.

**Multiple logistic regression analyses:**

Table 17 provides the results of the adjusted multiple logistic regression analysis of the odds of being adherent to COPD maintenance medications in the 90-day follow-up period, for Specific Aim 1A. The overall model was statistically significant (Wald's $x^2$=593.75, df=13, $p<0.0001$). The significant impact of prescription opioid use in the unadjusted logistic regression analysis persisted in the multiple logistic regression analysis, after adjusting for other factors. Prescription opioid users were found to have 0.29 times (95% CI 0.26-0.37, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 90-day follow-up period compared to non-opioid users, independent of other factors. Region, D-CCI, number of pain conditions, type of index maintenance medication, mail-order index maintenance medication and

**Table 17: Multiple logistic regression predicting the odds of being adherent to COPD maintenance medications in 90 days follow-up**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Region | Northeast | Reference | | | |
| | North Central | 1.03 | 0.82 | 1.29 | 0.82 |
| | South | 0.94 | 0.75 | 1.19 | 0.61 |
| | West | 1.31 | 0.98 | 1.73 | 0.06 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Use | 0.29 | 0.26 | 0.37 | <0.0001 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.91 | 0.85 | 0.96 | 0.001 |
| | | | | | |
| Number of pain conditions | 0 | Reference | | | |
| | 1 | 0.90 | 0.74 | 1.09 | 0.26 |
| | 2 | 0.82 | 0.67 | 1.01 | 0.06 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 1.87 | 0.93 | 3.73 | 0.07 |
| | ICS+LABA+LAMA | 1.76 | 1.35 | 2.30 | <0.0001 |
| | ICS or LABA or LAMA | 1.60 | 1.36 | 1.88 | <0.0001 |
| | | | | | |
| Mail-order index maintenance medication prescription | No | Reference | | | |
| | Yes | 4.56 | 3.84 | 5.42 | <0.0001 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 1.81 | 1.5 | 2.18 | <0.0001 |
| | >$9,838 | 1.53 | 1.21 | 1.92 | 0.0003 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

total all-cause healthcare expenditures were retained in the backwards elimination model at $p<0.20$.

**Multiple logistic regression analyses, sub-group analysis:**

Table 18 provides the results of the adjusted multiple logistic regression analysis of the odds of being adherent to COPD maintenance medications in the 90-day follow-up period, for Specific Aim 1A sub-group analysis. The overall model was statistically significant (Wald's $x^2$=593.56, df=14, $p<0.0001$). The significant impact of prescription opioid use (≤30-day and >30-day supply of prescription opioids) in the unadjusted logistic regression analysis persisted in the multiple logistic regression analysis after adjusting for other factors. In the sub-group analysis patients with ≤30-day supply of prescription opioids had 0.30 times (95% CI 0.26-0.34, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 90-day follow-up period as compared to non-opioid users independent of other factors. Similarly, patients with >30-day supply of prescription opioids had 0.32 times (95% CI 0.23-0.44, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 90-day follow-up period as compared to non-opioid users independent of other factors. Region, D-CCI, number of pain conditions, type of index maintenance medication, mail-order index maintenance medication and total all-cause healthcare expenditures were retained in the backwards elimination model at $p<0.20$.

**Table 18: Multiple logistic regression predicting the odds of being adherent to COPD maintenance medications in 90 days follow-up (sub-group analysis)**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Region | Northeast | Reference | | | |
| | North Central | 1.03 | 0.82 | 1.29 | 0.83 |
| | South | 0.94 | 0.75 | 1.19 | 0.61 |
| | West | 1.30 | 0.98 | 1.73 | 0.07 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | ≤30-day supply of prescription opioids | 0.30 | 0.26 | 0.34 | <0.0001 |
| | >30-day supply of prescription opioids | 0.32 | 0.23 | 0.44 | <0.0001 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.90 | 0.85 | 0.96 | 0.001 |
| | | | | | |
| Number of pain conditions | 0 | Reference | | | |
| | 1 | 0.90 | 0.74 | 1.09 | 0.27 |
| | 2 | 0.82 | 0.67 | 1.01 | 0.06 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 1.87 | 0.93 | 3.74 | 0.08 |
| | ICS+LABA+LAMA | 1.76 | 1.35 | 2.30 | <0.0001 |
| | ICS or LABA or LAMA | 1.60 | 1.36 | 1.89 | <0.0001 |
| | | | | | |
| Mail-order index maintenance medication prescription | No | Reference | | | |
| | Yes | 4.57 | 3.85 | 5.42 | <0.0001 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare | <$2,844 | Reference | | | |

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| expenditures in the pre-index period[a] | | | | | |
| | $2,844 - $9,838 | 1.81 | 1.5 | 2.18 | <0.0001 |
| | >$9,838 | 1.52 | 1.21 | 1.92 | 0.0004 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

**Results for Specific Aim 1B**

**Baseline characteristics as per specific aim 1B:**

Specific Aim 1B was to examine the impact of prescription opioid use compared to no prescription opioid use on adherence to COPD maintenance medications, within the first 180 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders. Table 19 provides baseline characteristics of the included sample of COPD patients and adherence to COPD maintenance medications in the 180-day follow-up period. Nearly half (50.9%) of the included matched sample of COPD patients were adherent (defined as PDC ≥0.8 PDC) to their COPD maintenance medications in the 180-day follow-up period after the index date. A smaller percentage of prescription opioid users were adherent to their COPD maintenance medications in the 180-day follow-up period as compared to non-opioid users (45.3% vs 56.6%, $p<0.0001$). Patients who were non-adherent to their COPD maintenance medications in the 180-day follow-up period were more likely to be prescription opioid users than non-opioid users (55.8% vs 44.2%, $p<0.0001$). A greater percentage of patients non-adherent to their COPD maintenance medications in the 180-day follow-up period had comorbid conditions than patients adherent to their COPD maintenance medications. Non-adherent patients had a significantly higher mean D-CCI score ($1.9 \pm 1.4$ vs $1.8 \pm 1.3$, $p=0.0018$). Non-adherent patients also had a higher percentage of patients with ≥1 comorbid chronic conditions (80.5% vs 77.9%, $p=0.0004$) and ≥1 comorbid pain conditions (79.6% vs 77.1%, $p<0.0001$).

**Table 19: Baseline characteristics for Specific Aim 1B**

| Variable | | Non-Adherent in 180 days (n=5,436) | | Adherent in 180 days (n=5,646) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| **Sociodemographic characteristics** | | | | | | |
| Sex | Male | 2,395 | 44.1 | 2,679 | 47.4 | 0.0003 |
| | | | 47.2 | | 52.8 | |
| | Female | 3,041 | 55.9 | 2,967 | 52.6 | |
| | | | 50.6 | | 49.4 | |
| | | | | | | |
| Age | *mean (±sd)* | 56.3 years (±5.8) | | 58 years (±4.9) | | <0.0001 |
| | 40 – 49 years | 797 | 14.7 | 416 | 7.4 | <0.0001 |
| | | | 65.7 | | 34.3 | |
| | 50 – 59 years | 2,619 | 48.2 | 2,480 | 43.9 | |
| | | | 51.4 | | 48.6 | |
| | ≥60 years | 2,020 | 37.2 | 2,750 | 48.7 | |
| | | | 42.3 | | 57.7 | |
| Metropolitan Statistical Area | Urban | 4,323 | 79.5 | 4,490 | 79.5 | 0.85 |
| | | | 49.1 | | 50.9 | |
| | Rural | 1,095 | 20.1 | 1,127 | 20.0 | |
| | | | 49.3 | | 50.7 | |
| | | | | | | |
| Region | Northeast | 693 | 12.7 | 831 | 14.7 | <0.0001 |
| | | | 45.5 | | 54.5 | |
| | North Central | 1,850 | 34.0 | 2,200 | 39.0 | |
| | | | 45.7 | | 54.3 | |
| | South | 2,130 | 39.2 | 1,880 | 33.3 | |
| | | | 53.1 | | 46.9 | |
| | West | 741 | 13.6 | 706 | 12.5 | |
| | | | 51.2 | | 48.8 | |
| | | | | | | |
| Insurance Plan Type | HMO | 989 | 18.2 | 808 | 14.3 | <0.0001 |
| | | | 55.0 | | 45.0 | |
| | PPO | 3,024 | 55.6 | 3,209 | 56.8 | |
| | | | 48.5 | | 51.5 | |
| | Other | 1,392 | 25.6 | 1,603 | 28.4 | |
| | | | 46.5 | | 53.5 | |
| **Clinical characteristics** | | | | | | |
| Prescription opioid use | No use | 2,404 | 44.2 | 3,137 | 55.6 | <0.0001 |
| | | | 43.4 | | 56.6 | |
| | Use | 3,032 | 55.8 | 2,509 | 44.4 | |
| | | | 54.7 | | 45.3 | |
| Prescription opioid use | No use | 2,404 | 44.2 | 3,137 | 55.6 | <0.0001 |
| | | | 43.4 | | 56.6 | |

| Variable | | Non-Adherent in 180 days (n=5,436) | | Adherent in 180 days (n=5,646) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | ≤30-day supply of prescription opioids | 2,513 | 46.2 | 2,072 | 36.7 | |
| | | | 54.8 | | 45.2 | |
| | >30-day supply of prescription opioids | 519 | 9.5 | 437 | 7.7 | |
| | | | 54.3 | | 45.7 | |
| | | | | | | |
| Deyo-Charlson Comorbidity Index | *mean (±sd)* | 1.9 (±1.4) | | 1.8 (±1.3) | | 0.0018 |
| | | | | | | |
| Number of pain conditions | 0 | 1,107 | 20.4 | 1,293 | 22.9 | <0.0001 |
| | | | 46.1 | | 53.9 | |
| | 1 | 2,063 | 38.0 | 2,331 | 41.3 | |
| | | | 47.0 | | 53.0 | |
| | 2 | 2,266 | 41.7 | 2,022 | 35.8 | |
| | | | 52.8 | | 47.2 | |
| | | | | | | |
| | | | | | | |
| Number of comorbid conditions | 0 | 1,059 | 19.5 | 1,249 | 22.1 | 0.0004 |
| | | | 45.9 | | 54.1 | |
| | 1 | 1,963 | 36.1 | 2,067 | 36.6 | |
| | | | 48.7 | | 51.3 | |
| | 2 | 2,414 | 44.4 | 2,330 | 41.3 | |
| | | | 50.9 | | 49.1 | |
| | | | | | | |
| Type of index maintenance medication | ICS+LABA | 3,378 | 62.1 | 2,525 | 44.7 | <0.0001 |
| | | | 57.2 | | 42.8 | |
| | LAMA+LABA or LAMA+ICS | 36 | 0.7 | 78 | 1.4 | |
| | | | 31.6 | | 68.4 | |
| | ICS+LABA+LAMA | 356 | 6.5 | 713 | 12.6 | |
| | | | 33.3 | | 66.7 | |
| | ICS or LABA or LAMA | 1,666 | 30.6 | 2,330 | 41.3 | |
| | | | 41.7 | | 58.3 | |
| | | | | | | |
| Mail-order index maintenance | No | 3,812 | 70.1 | 2,802 | 49.6 | <0.0001 |

| Variable | | Non-Adherent in 180 days (n=5,436) | | Adherent in 180 days (n=5,646) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| medication prescription | | | | | | |
| | | | 57.6 | | 42.4 | |
| | Yes | 1,624 | 29.9 | 2,844 | 50.4 | |
| | | | 36.3 | | 63.7 | |
| | | | | | | |
| Adherence to COPD-maintenance medications in the pre-index period | Non-adherent if PDC < 80% | 2,629 | 48.4 | 839 | 14.9 | <0.0001 |
| | | | 75.8 | | 24.2 | |
| | Adherent if PDC ≥ 80% | 2,807 | 51.6 | 4,807 | 85.1 | |
| | | | 36.9 | | 63.1 | |
| | | | | | | |
| **COPD severity indicators** | | | | | | |
| Supplemental oxygen use in the pre-index period | No | 4,563 | 83.9 | 4,287 | 75.9 | <0.0001 |
| | | | 51.6 | | 48.4 | |
| | Yes | 873 | 16.1 | 1,359 | 24.1 | |
| | | | 39.1 | | 60.9 | |
| | | | | | | |
| SABA use in the pre-index period | No | 2,567 | 47.2 | 2,613 | 46.3 | 0.32 |
| | | | 49.6 | | 50.4 | |
| | Yes | 2,869 | 52.8 | 3,033 | 53.7 | |
| | | | 48.6 | | 51.4 | |
| | | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | 5,306 | 97.6 | 5,454 | 96.6 | 0.002 |
| | | | 49.3 | | 50.7 | |
| | ≥1 | 130 | 2.4 | 192 | 3.4 | |
| | | | 40.4 | | 59.6 | |
| | | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | 4,741 | 87.2 | 4,813 | 85.2 | 0.003 |
| | | | 49.6 | | 50.4 | |
| | ≥1 | 695 | 12.8 | 833 | 14.8 | |
| | | | 45.5 | | 54.5 | |

| Variable | | Non-Adherent in 180 days (n=5,436) | | Adherent in 180 days (n=5,646) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | | | | | | |
| **Physician characteristics** | | | | | | |
| Pulmonologist visit in the pre-index period | No | 4,072 | 74.9 | 3,967 | 70.3 | <0.0001 |
| | | | 50.7 | | 49.3 | |
| | Yes | 1,364 | 25.1 | 1,679 | 29.7 | |
| | | | 44.8 | | 55.2 | |
| | | | | | | |
| **Prior utilization characteristics** | | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | *mean (±sd)* | 9,827.7 (±17,555.5) | | 9,662.6 (±15,222) | | <0.0001 |
| | <$2,844 | 1645 | 30.3 | 1124 | 19.9 | <0.0001 |
| | | | 59.4 | | 40.6 | |
| | $2,844 - $9,838 | 2440 | 44.9 | 3102 | 54.9 | |
| | | | 44.0 | | 56.0 | |
| | >$9,838 | 1351 | 24.9 | 1420 | 25.2 | |
| | | | 48.8 | | 51.2 | |

*sd denotes standard deviation; Col, column; HMO, health maintenance organization; PPO, preferred provider organization; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

Specific Aim 1B sub-analysis was to examine the impact of prescription opioid use (classified as having > 30-day supply of prescription opioids and ≤ 30-day supply of prescription opioids) compared to no prescription opioid use, within the first 180 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders. A significantly lower percentage ($p<0.0001$) of prescription opioid users, either ≤30-day supply of prescription (45.2%) or >30-day supply of prescription opioids (45.7%), were adherent to their COPD maintenance medications in the 180-day follow-up period as compared to nonopioid users (56.6%) (Table 19).

**Unadjusted logistic regression analyses:**

Table 20 provides the results of the unadjusted logistic regression analysis of the odds of being adherent to COPD maintenance medications in the 180-day follow-up period, for specific aim 1B. Prescription opioid users were found to have 0.59 times (95% CI 0.54-0.64, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 180-day follow-up period compared to non-opioid users. In the sub-group analysis patients with ≤30-day supply of prescription opioids had 0.59 times (95% CI 0.54-0.64, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 180-day follow-up period as compared to non-opioid users. Similarly, patients with >30-day supply of prescription opioids had 0.61 times (95% CI 0.40-0.75, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 180-day follow-up period as compared to non-opioid users. Region, insurance plan type, D-CCI, number of comorbid pain conditions, number of comorbid chronic conditions, type of index maintenance

**Table 20: Unadjusted logistic regression predicting the odds of being adherent to COPD maintenance medications in 180 days follow-up**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Metropolitan Statistical Area | Rural | Reference | | | |
| | Urban | 0.96 | 0.83 | 1.10 | 0.57 |
| | | | | | |
| Region | Northeast | Reference | | | |
| | North Central | 0.83 | 0.69 | 0.99 | 0.04 |
| | South | 0.68 | 0.57 | 0.82 | <0.0001 |
| | West | 0.70 | 0.57 | 0.89 | 0.002 |
| | | | | | |
| Insurance Plan Type | Health maintenance organization | Reference | | | |
| | Preferred provider organization | 1.13 | 0.96 | 1.33 | 0.142 |
| | Other | 1.37 | 1.14 | 1.64 | 0.0008 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Use | 0.59 | 0.54 | 0.64 | <0.0001 |
| | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | ≤30-day supply of prescription opioids | 0.59 | 0.54 | 0.64 | <0.0001 |
| | >30-day supply of prescription opioids | 0.61 | 0.40 | 0.75 | <0.0001 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.86 | 0.83 | 0.90 | <0.0001 |
| | | | | | |
| Number of pain conditions | 0 | Reference | | | |
| | 1 | 0.89 | 0.77 | 1.04 | 0.14 |
| | 2 | 0.68 | 0.59 | 0.79 | <0.0001 |
| | | | | | |
| Number of comorbid conditions | 0 | Reference | | | |
| | 1 | 0.91 | 0.76 | 1.08 | 0.28 |
| | 2 | 0.69 | 0.57 | 0.84 | <0.001 |

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 1.90 | 1.10 | 3.28 | 0.02 |
| | ICS+LABA+LAMA | 1.91 | 1.56 | 2.33 | <0.0001 |
| | ICS or LABA or LAMA | 1.67 | 1.47 | 1.89 | <0.0001 |
| | | | | | |
| Mail-order index maintenance medication prescription | No | Reference | | | |
| | Yes | 1.66 | 1.47 | 1.87 | <0.0001 |
| | | | | | |
| **Physician characteristics** | | | | | |
| Pulmonologist visit in the pre-index period | No | Reference | | | |
| | Yes | 1.09 | 0.95 | 1.24 | 0.22 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period [a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 1.39 | 1.21 | 1.61 | <0.0001 |
| | >$9,838 | 0.95 | 0.81 | 1.12 | 0.52 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.

[a] adjusted to 2010 US $

medication, mail-order index maintenance medication, and total all-cause healthcare expenditures were found significant at $p<0.2$ and were considered in the adjusted logistic regression analysis.

**Multiple logistic regression analyses:**

Table 21 provides the results of the adjusted multiple logistic regression analysis of the odds of being adherent to COPD maintenance medications in the 180-day follow-up period, for Specific Aim 1B. The overall model was statistically significant (Wald's $x^2$=317.98, df=10, $p<0.0001$). The significant impact of prescription opioid use in the unadjusted logistic regression analysis persisted in the multiple logistic regression analysis after adjusting for other factors. Prescription opioid users were found to have 0.55 times (95% CI 0.50-0.61, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 180-day follow-up period as compared to non-opioid users, independent of other predictors. Insurance plan type, D-CCI, type of index maintenance medication, mail-order index maintenance medication and total all-cause healthcare expenditures were retained in the backwards elimination model at $p<0.20$.

**Multiple logistic regression analyses, sub-group analysis:**

Table 22 provides the results of the adjusted multiple logistic regression analysis of the odds of being adherent to COPD maintenance medications in the 180-day follow-up period, for Specific Aim 1B sub-group analysis. The overall model was statistically significant (Wald's $x^2$=318.03, df=11, $p<0.0001$). The significant impact of prescription opioid use (≤30-day and >30-day supply of prescription opioids) in the unadjusted logistic regression analysis persisted in the multiple logistic regression analysis after

**Table 21: Multiple logistic regression predicting the odds of being adherent to COPD maintenance medications in 180 days follow-up**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Insurance Plan Type | Health maintenance organization | Reference | | | |
| | Preferred provider organization | 1.00 | 0.84 | 1.20 | 0.99 |
| | Other | 1.21 | 0.99 | 1.48 | 0.06 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Use | 0.55 | 0.50 | 0.61 | <0.0001 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.88 | 0.83 | 0.92 | <0.0001 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 2.31 | 1.27 | 4.18 | 0.006 |
| | ICS+LABA+LAMA | 1.87 | 1.50 | 2.33 | <0.0001 |
| | ICS or LABA or LAMA | 1.76 | 1.53 | 2.02 | <0.0001 |
| | | | | | |
| Mail-order index maintenance medication prescription | No | Reference | | | |
| | Yes | 1.63 | 1.43 | 1.86 | <0.0001 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 1.78 | 1.51 | 2.09 | <0.0001 |
| | >$9,838 | 1.54 | 1.26 | 1.88 | <0.0001 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.

[a] adjusted to 2010 US $

**Table 22: Multiple logistic regression predicting the odds of being adherent to COPD maintenance medications in 180 days follow-up (sub-group analysis)**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Insurance Plan Type | Health maintenance organization | Reference | | | |
| | Preferred provider organization | 1.00 | 0.84 | 1.20 | 0.99 |
| | Other | 1.21 | 0.99 | 1.48 | 0.06 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | ≤30-day supply of prescription opioids | 0.55 | 0.50 | 0.61 | <0.0001 |
| | >30-day supply of prescription opioids | 0.58 | 0.46 | 0.72 | <0.0001 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.88 | 0.83 | 0.92 | <0.0001 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 2.30 | 1.27 | 4.17 | 0.006 |
| | ICS+LABA+LAMA | 1.87 | 1.50 | 2.33 | <0.0001 |
| | ICS or LABA or LAMA | 1.76 | 1.53 | 2.02 | <0.0001 |
| | | | | | |
| Mail-order index maintenance medication prescription | No | Reference | | | |
| | Yes | 1.63 | 1.43 | 1.87 | <0.0001 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 1.78 | 1.51 | 2.09 | <0.0001 |
| | >$9,838 | 1.54 | 1.26 | 1.87 | <0.0001 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

adjusting for other factors. In the sub-group analysis patients with ≤30-day supply of prescription opioids had 0.55 times (95% CI 0.50-0.61, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 180-day follow-up period as compared to non-opioid users independent of other factors. Similarly, patients with >30-day supply of prescription opioids had 0.58 times (95% CI 0.46-0.72, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 180-day follow-up period compared to non-opioid users independent of other factors. Insurance plan type, D-CCI, type of index maintenance medication, mail-order index maintenance medication and total all-cause healthcare expenditures were retained in the backwards elimination model at $p<0.20$.

**Results for Specific Aim 1C**

**Baseline characteristics as per Specific Aim 1C:**

Specific aim 1C was to examine the impact of prescription opioid use compared to no prescription opioid use on adherence to COPD maintenance medications, within the first 270 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders. Table 23 provides baseline characteristics of the included sample of COPD patients and adherence to COPD maintenance medications in the 270 days follow-up period. Less than half (47.3%) of the included matched sample of COPD patients were adherent (defined as PDC ≥0.8) to their COPD maintenance medications in the 270-day follow-up period after the index date. A smaller proportion of prescription opioid users were adherent to their COPD maintenance medications in the 270-day follow-up period as compared to non-opioid users (43.3% vs 51.2%, $p<0.0001$). Patients who were non-adherent to their COPD

## Table 23: Baseline characteristics for Specific Aim 1C

| Variable | | Non-Adherent in 270 days (n=5,845) | | Adherent in 270 days (n=5,237) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col % Row % | N | Col % Row % | |
| **Sociodemographic characteristics** | | | | | | |
| Sex | Male | 2,547 | 43.6 | 2,527 | 48.3 | <0.0001 |
| | | | 50.2 | | 49.8 | |
| | Female | 3,298 | 56.4 | 2,710 | 51.7 | |
| | | | 54.9 | | 45.1 | |
| | | | | | | |
| Age | *mean (±sd)* | 56.3 years (±5.8) | | 58.1 years (±4.8) | | <0.0001 |
| | 40 – 49 years | 849 | 14.5 | 364 | 7.0 | <0.0001 |
| | | | 70.0 | | 30.0 | |
| | 50 – 59 years | 2,799 | 47.9 | 2,300 | 43.9 | |
| | | | 54.9 | | 45.1 | |
| | ≥60 years | 2,197 | 37.6 | 2,573 | 49.1 | |
| | | | 46.1 | | 53.9 | |
| Metropolitan Statistical Area | Urban | 4,665 | 79.8 | 4,148 | 79.2 | 0.54 |
| | | | 52.9 | | 47.1 | |
| | Rural | 1,160 | 19.8 | 1,062 | 20.3 | |
| | | | 52.2 | | 47.8 | |
| | | | | | | |
| Region | Northeast | 776 | 13.3 | 748 | 14.3 | <0.0001 |
| | | | 50.9 | | 49.1 | |
| | North Central | 1,996 | 34.1 | 2,054 | 39.2 | |
| | | | 49.3 | | 50.7 | |
| | South | 2,260 | 38.7 | 1,750 | 33.4 | |
| | | | 56.4 | | 43.6 | |
| | West | 789 | 13.5 | 658 | 12.6 | |
| | | | 54.5 | | 45.5 | |
| | | | | | | |
| Insurance Plan Type | HMO | 1,046 | 17.9 | 751 | 14.3 | <0.0001 |
| | | | 58.2 | | 41.8 | |
| | PPO | 3,266 | 55.9 | 2,967 | 56.7 | |
| | | | 52.4 | | 47.6 | |
| | Other | 1,494 | 25.6 | 1,501 | 28.7 | |
| | | | 49.9 | | 50.1 | |
| **Clinical characteristics** | | | | | | |
| Prescription opioid use | No use | 2,703 | 46.2 | 2,838 | 54.2 | <0.0001 |
| | | | 48.8 | | 51.2 | |
| | Use | 3,142 | 53.8 | 2,399 | 45.8 | |
| | | | 56.7 | | 43.3 | |
| Prescription opioid use | No use | 2,703 | 46.2 | 2,838 | 54.2 | <0.0001 |
| | | | 48.8 | | 51.2 | |

| Variable | | Non-Adherent in 270 days (n=5,845) | | Adherent in 270 days (n=5,237) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | ≤30-day supply of prescription opioids | 2,467 | 42.2 | 1,881 | 35.9 | |
| | | | 56.7 | | 43.3 | |
| | >30-day supply of prescription opioids | 675 | 11.5 | 518 | 9.9 | |
| | | | 56.6 | | 43.4 | |
| | | | | | | |
| Deyo-Charlson Comorbidity Index | *mean (±sd)* | 1.9 (±1.4) | | 1.8 (±1.2) | | 0.0003 |
| | | | | | | |
| Number of pain conditions | 0 | 1,196 | 20.5 | 1,204 | 23.0 | <0.0001 |
| | | | 49.8 | | 50.2 | |
| | 1 | 2,236 | 38.3 | 2,158 | 41.2 | |
| | | | 50.9 | | 49.1 | |
| | 2 | 2,413 | 41.3 | 1,875 | 35.8 | |
| | | | 56.3 | | 43.7 | |
| | | | | | | |
| Number of comorbid conditions | 0 | 1,137 | 19.5 | 1,171 | 22.4 | <0.0001 |
| | | | 49.3 | | 50.7 | |
| | 1 | 2,098 | 35.9 | 1,932 | 36.9 | |
| | | | 52.1 | | 47.9 | |
| | 2 | 2,610 | 44.7 | 2,134 | 40.7 | |
| | | | 55.0 | | 45.0 | |
| | | | | | | |
| Type of index maintenance medication | ICS+LABA | 3,590 | 61.4 | 2,313 | 44.2 | <0.0001 |
| | | | 60.8 | | 39.2 | |
| | LAMA+LABA or LAMA+ICS | 39 | 0.7 | 75 | 1.4 | |
| | | | 34.2 | | 65.8 | |
| | ICS+LABA+LAMA | 384 | 6.6 | 685 | 13.1 | |
| | | | 35.9 | | 64.1 | |
| | ICS or LABA or LAMA | 1,832 | 31.3 | 2,164 | 41.3 | |
| | | | 45.8 | | 54.2 | |
| | | | | | | |
| Mail-order index maintenance medication prescription | No | 4,012 | 68.6 | 2,602 | 49.7 | <0.0001 |

| Variable | | Non-Adherent in 270 days (n=5,845) | | Adherent in 270 days (n=5,237) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | | | 60.7 | | 39.3 | |
| | Yes | 1,833 | 31.4 | 2,635 | 50.3 | |
| | | | 41.0 | | 59.0 | |
| | | | | | | |
| Adherence to COPD-maintenance medications in the pre-index period | Non-adherent if PDC < 80% | 2,754 | 47.1 | 714 | 13.6 | <0.0001 |
| | | | 79.4 | | 20.6 | |
| | Adherent if PDC ≥ 80% | 3,091 | 52.9 | 4,523 | 86.4 | |
| | | | 40.6 | | 59.4 | |
| | | | | | | |
| **COPD severity indicators** | | | | | | |
| Supplemental oxygen use in the pre-index period | No | 4,931 | 84.4 | 3,919 | 74.8 | <0.0001 |
| | | | 55.7 | | 44.3 | |
| | Yes | 914 | 15.6 | 1,318 | 25.2 | |
| | | | 40.9 | | 59.1 | |
| | | | | | | |
| SABA use in the pre-index period | No | 2,764 | 47.3 | 2,416 | 46.1 | 0.224 |
| | | | 53.4 | | 46.6 | |
| | Yes | 3,081 | 52.7 | 2,821 | 53.9 | |
| | | | 52.2 | | 47.8 | |
| | | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | 5,700 | 97.5 | 5,060 | 96.6 | 0.005 |
| | | | 53.0 | | 47.0 | |
| | ≥1 | 145 | 2.5 | 177 | 3.4 | |
| | | | 45.0 | | 55.0 | |
| | | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | 5,095 | 87.2 | 4,459 | 85.1 | 0.002 |
| | | | 53.3 | | 46.7 | |
| | ≥1 | 750 | 12.8 | 778 | 14.9 | |
| | | | 49.1 | | 50.9 | |
| | | | | | | |
| **Physician characteristics** | | | | | | |

| Variable | | Non-Adherent in 270 days (n=5,845) | | Adherent in 270 days (n=5,237) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col % Row % | N | Col % Row % | |
| Pulmonologist visit in the pre-index period | No | 4,389 | 75.1 | 3,650 | 69.7 | <0.0001 |
| | | | 54.6 | | 45.4 | |
| | Yes | 1,456 | 24.9 | 1,587 | 30.3 | |
| | | | 47.8 | | 52.2 | |
| | | | | | | |
| **Prior utilization characteristics** | | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | *mean (±sd)* | 9,724.9 (±17,360.4) | | 9,764.5 (±15,275.8) | | <0.0001 |
| | <$2,844 | 1751 | 30.0 | 1018 | 19.4 | <0.0001 |
| | | | 63.2 | | 36.8 | |
| | $2,844 - $9,838 | 2654 | 45.4 | 2888 | 55.1 | |
| | | | 47.9 | | 52.1 | |
| | >$9,838 | 1440 | 24.6 | 1331 | 25.4 | |
| | | | 52.0 | | 48.0 | |

*sd denotes standard deviation; Col, column; HMO, health maintenance organization; PPO, preferred provider organization; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

maintenance medications in the 270-day follow-up period were more likely to be prescription opioid users than non-opioid users (53.8% vs 46.2%, $p<0.0001$). A greater percentage of patients non-adherent to their COPD maintenance medications in the 270-day follow-up period had comorbid conditions than patients adherent to their COPD maintenance medications. Non-adherent patients had a significantly higher mean D-CCI score ($1.9 \pm 1.4$ vs $1.8 \pm 1.2$, $p=0.0003$). Non-adherent patients also had a percentage of patients with ≥1 comorbid chronic conditions (80.5% vs 77.6%, $p<0.0001$) and ≥1 comorbid pain conditions (79.5% vs 77%, $p<0.0001$).

Specific Aim 1C sub-analysis was to examine the impact of prescription opioid use (classified as having > 30-day supply of prescription opioids and ≤ 30-day supply of prescription opioids) compared to no prescription opioid use, within the first 270 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders. A significantly lower percentage of prescription opioid users ($p<0.0001$), either ≤30-day supply of prescription (43.3%) or >30-day supply of prescription opioids (43.4%), were adherent to their COPD maintenance medications in the 270-day follow-up period as compared to non-users of prescription opioid users (51.2%) (Table 23).

**Unadjusted logistic regression analyses:**

Table 24 provides the results of the unadjusted logistic regression analysis of the odds of being adherent to COPD maintenance medications in the 270-day follow-up period, for Specific Aim 1C. Prescription opioid users were found to have 0.69 times (95% CI 0.63-0.74, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 270-day follow-up period as compared to non-opioid

**Table 24: Unadjusted logistic regression predicting the odds of being adherent to COPD maintenance medications in 270 days follow-up**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Metropolitan Statistical Area | Rural | Reference | | | |
| | Urban | 0.94 | 0.83 | 1.08 | 0.37 |
| | | | | | |
| Region | Northeast | Reference | | | |
| | North Central | 0.93 | 0.78 | 1.18 | 0.45 |
| | South | 0.78 | 0.65 | 0.93 | 0.006 |
| | West | 0.82 | 0.65 | 1.02 | 0.07 |
| | | | | | |
| Insurance Plan Type | Health maintenance organization | Reference | | | |
| | Preferred provider organization | 1.14 | 0.97 | 1.35 | 0.0002 |
| | Other | 1.42 | 1.18 | 1.71 | 0.12 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Use | 0.69 | 0.63 | 0.74 | <0.0001 |
| | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | ≤30-day supply of prescription opioids | 0.68 | 0.62 | 0.75 | <0.0001 |
| | >30-day supply of prescription opioids | 0.70 | 0.59 | 0.84 | <0.0001 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.85 | 0.81 | 0.89 | <0.0001 |
| | | | | | |
| Number of pain conditions | 0 | Reference | | | |
| | 1 | 0.88 | 0.76 | 1.03 | 0.12 |
| | 2 | 0.71 | 0.61 | 0.83 | <0.001 |
| | | | | | |
| Number of comorbid conditions | 0 | Reference | | | |
| | 1 | 0.90 | 0.74 | 1.08 | 0.24 |
| | 2 | 0.66 | 0.55 | 0.80 | <0.0001 |

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 2.02 | 1.14 | 3.58 | 0.02 |
| | ICS+LABA+LAMA | 1.93 | 1.58 | 2.37 | <0.0001 |
| | ICS or LABA or LAMA | 1.62 | 1.42 | 1.84 | <0.0001 |
| | | | | | |
| Mail-order index maintenance medication prescription | No | Reference | | | |
| | Yes | 1.61 | 1.42 | 1.82 | <0.0001 |
| | | | | | |
| **Physician characteristics** | | | | | |
| Pulmonologist visit in the pre-index period | Other | Reference | | | |
| | Pulmonologist | 1.07 | 0.93 | 1.22 | 0.35 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | <$2,844 | Ref | | | |
| | $2,844 - $9,838 | 1.36 | 1.18 | 1.58 | <0.0001 |
| | >$9,838 | 0.96 | 0.81 | 1.14 | 0.66 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.

[a] adjusted to 2010 US $

users. Patients with ≤30-day supply of prescription opioids had 0.68 times (95% CI 0.62-0.75, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 270-day follow-up period as compared to non-opioid users. Similarly, patients with >30-day supply of prescription opioids had 0.70 times (95% CI 0.59-0.84, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 270-day follow-up period as compared to non-opioid users. Region, insurance plan type, D-CCI, number of comorbid pain conditions, number of comorbid chronic conditions, type of index maintenance medication, mail-order index maintenance medication, and total all-cause healthcare expenditures were found significant at $p<0.2$ and were considered in the adjusted logistic regression analysis.

**Multiple logistic regression analyses:**

Table 25 provides the results of the adjusted multiple logistic regression analysis of the odds of being adherent to COPD maintenance medications in the 270-day follow-up period, for specific aim 1C. The overall model was statistically significant (Wald's $x^2$=248.29, df=10, $p<0.0001$). The significant impact of prescription opioid use in the unadjusted logistic regression analysis persisted in the multiple logistic regression analysis after adjusting for other factors. Prescription opioid users were found to have 0.66 times (95% CI 0.60-0.73, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 270-day follow-up period as compared to non-opioid users, independent of other predictors. Insurance plan type, D-CCI, type of index maintenance medication, mail-order index maintenance medication and total all-

**Table 25: Multiple logistic regression predicting the odds of being adherent to COPD maintenance medications in 270 days follow-up**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Insurance Plan Type | Health maintenance organization | Reference | | | |
| | Preferred provider organization | 1.04 | 0.87 | 1.25 | 0.68 |
| | Other | 1.29 | 1.05 | 1.57 | 0.01 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Use | 0.66 | 0.60 | 0.73 | <0.0001 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.85 | 0.81 | 0.90 | <0.0001 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 2.33 | 1.26 | 4.29 | 0.006 |
| | ICS+LABA+LAMA | 1.90 | 1.52 | 2.36 | <0.0001 |
| | ICS or LABA or LAMA | 1.66 | 1.45 | 1.91 | <0.0001 |
| | | | | | |
| Mail-order index maintenance medication prescription | No | Reference | | | |
| | Yes | 1.57 | 1.38 | 1.79 | <0.0001 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 1.64 | 1.4 | 1.93 | <0.0001 |
| | >$9,838 | 1.46 | 1.2 | 1.79 | 0.0002 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.

[a] adjusted to 2010 US $

cause healthcare expenditures were retained in the backwards elimination model at $p<0.20$.

**Multiple logistic regression analyses, sub-group analysis:**

Table 26 provides the results of the adjusted multiple logistic regression analysis of the odds of being adherent to COPD maintenance medications in the 270-day follow-up period, for Specific Aim 1C sub-group analysis. The overall model was statistically significant (Wald's $x^2$=248.34, df=11, $p<0.0001$). The significant impact of prescription opioid use (≤30-day and >30-day supply of prescription opioids) in the unadjusted logistic regression analysis persisted in the multiple logistic regression analysis after adjusting for other factors. In the sub-group analysis patients with ≤30-day supply of prescription opioids had 0.66 times (95% CI 0.59-0.73, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 270-day follow-up period as compared to non-opioid users independent of other factors. Similarly, patients with >30-day supply of prescription opioids had 0.68 times (95% CI 0.56-0.83, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 270-day follow-up period as compared to non-opioid users independent of other factors. Insurance plan type, D-CCI, type of index maintenance medication, mail-order index maintenance medication and total all-cause healthcare expenditures were retained in the backwards elimination model at $p<0.20$.

**Table 26: Multiple logistic regression predicting the odds of being adherent to COPD maintenance medications in 270 days follow-up (sub-group analysis)**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Insurance Plan Type | Health maintenance organization | Reference | | | |
| | Preferred provider organization | 1.04 | 0.87 | 1.25 | 0.68 |
| | Other | 1.29 | 1.05 | 1.57 | 0.01 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | ≤30-day supply of prescription opioids | 0.66 | 0.59 | 0.73 | <0.0001 |
| | >30-day supply of prescription opioids | 0.68 | 0.56 | 0.83 | 0.0001 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.85 | 0.81 | 0.90 | <0.0001 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 2.33 | 1.26 | 4.29 | 0.007 |
| | ICS+LABA+LAMA | 1.90 | 1.52 | 2.36 | <0.0001 |
| | ICS or LABA or LAMA | 1.66 | 1.45 | 1.91 | <0.0001 |
| | | | | | |
| Mail-order index maintenance medication prescription | No | Reference | | | |
| | Yes | 1.57 | 1.38 | 1.80 | <0.0001 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 1.64 | 1.4 | 1.93 | <0.0001 |

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| | >$9,838 | 1.46 | 1.19 | 1.79 | 0.0002 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

## Results for Specific Aim 1D

### Baseline characteristics as per Specific Aim 1D:

Specific Aim 1D was to examine the impact of prescription opioid use compared to no prescription opioid use on adherence to COPD maintenance medications, within the first 365 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders. Table 27 provides baseline characteristics of the included sample of COPD patients and adherence to COPD maintenance medications in the 365 days follow-up period. Less than half (45.9%) of the included matched sample of COPD patients were adherent (defined as PDC ≥0.8) to their COPD maintenance medications in the 365-day follow-up period after the index date. A smaller percentage of prescription opioid users were adherent to their COPD maintenance medications in the 365-day follow-up period as compared to their non-user counterparts (42.1% vs 49.7%, p<0.0001). Patients who were non-adherent to their COPD maintenance medications in the 365-day follow-up period were more likely to be prescription opioid users than non-opioid users (53.6% vs 46.4%, p<0.0001). A greater percentage of patients non-adherent to their COPD maintenance medications in the 365-day follow-up period had comorbid conditions than patients adherent to their COPD maintenance medications. Non-adherent patients had a significantly higher mean D-CCI score (1.9 ± 1.4 vs 1.8 ± 1.2, p=0.0006). Non-adherent patients also had a percentage of patients with ≥1 comorbid chronic conditions (80.8% vs 77.3%, p<0.0001) and ≥1 comorbid pain conditions (79.7% vs 76.8%, p<0.0001).

Specific Aim 1D sub-analysis was to examine the impact of prescription opioid use (classified as having >30-day supply of prescription opioids and ≤30-day supply of

**Table 27: Baseline characteristics for Specific Aim 1D**

| Variable | | Non-Adherent in 365 days (n=5,996) | | Adherent in 365 days (n=5,086) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| **Sociodemographic characteristics** | | | | | | |
| Sex | Male | 2,630 | 43.9 | 2,444 | 48.1 | <0.0001 |
| | | | 51.8 | | 48.2 | |
| | Female | 3,366 | 56.1 | 2,642 | 51.9 | |
| | | | 56.0 | | 44.0 | |
| | | | | | | |
| Age | *mean (±sd)* | 56.4 years (±5.7) | | 59.1 years (±4.8) | | <0.0001 |
| | 40 – 49 years | 861 | 14.4 | 352 | 6.9 | <0.0001 |
| | | | 71.0 | | 29.0 | |
| | 50 – 59 years | 2,880 | 48.0 | 2,219 | 43.6 | |
| | | | 56.5 | | 43.5 | |
| | ≥60 years | 2,255 | 37.6 | 2,515 | 49.4 | |
| | | | 47.3 | | 52.7 | |
| Metropolitan Statistical Area | Urban | 4,769 | 79.5 | 4,044 | 79.5 | 0.95 |
| | | | 54.1 | | 45.9 | |
| | Rural | 1,204 | 20.1 | 1,018 | 20.0 | |
| | | | 54.2 | | 45.8 | |
| | | | | | | |
| Region | Northeast | 807 | 13.5 | 717 | 14.1 | <0.0001 |
| | | | 53.0 | | 47.0 | |
| | North Central | 2,044 | 34.1 | 2,006 | 39.4 | |
| | | | 50.5 | | 49.5 | |
| | South | 2,316 | 38.6 | 1,694 | 33.3 | |
| | | | 57.8 | | 42.2 | |
| | West | 802 | 13.4 | 645 | 12.7 | |
| | | | 55.4 | | 44.6 | |
| | | | | | | |
| Insurance Plan Type | HMO | 1,062 | 17.7 | 735 | 14.5 | <0.0001 |
| | | | 59.1 | | 40.9 | |
| | PPO | 3,340 | 55.7 | 2,893 | 56.9 | |
| | | | 53.6 | | 46.4 | |
| | Other | 1,555 | 25.9 | 1,440 | 28.3 | |
| | | | 51.9 | | 48.1 | |
| **Clinical characteristics** | | | | | | |
| Prescription opioid use | No use | 2,785 | 46.4 | 2,756 | 54.2 | <0.0001 |
| | | | 50.3 | | 49.7 | |
| | Use | 3,211 | 53.6 | 2,330 | 45.8 | |
| | | | 57.9 | | 42.1 | |
| Prescription opioid use | No use | 2,785 | 46.4 | 2,756 | 54.2 | <0.0001 |
| | | | 50.3 | | 49.7 | |

| Variable | | Non-Adherent in 365 days (n=5,996) | | Adherent in 365 days (n=5,086) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | ≤30-day supply of prescription opioids | 2,408 | 40.2 | 1,762 | 34.6 | |
| | | | 57.7 | | 42.3 | |
| | >30-day supply of prescription opioids | 803 | 13.4 | 568 | 11.2 | |
| | | | 58.6 | | 41.4 | |
| | | | | | | |
| Deyo-Charlson Comorbidity Index | *mean (±sd)* | 1.9 (±1.4) | | 1.8 (±1.2) | | 0.0006 |
| | | | | | | |
| Number of pain conditions | 0 | 1,219.00 | 20.3 | 1,181 | 23.2 | <0.0001 |
| | | | 50.8 | | 49.2 | |
| | 1 | 2,296.00 | 38.3 | 2,098 | 41.3 | |
| | | | 52.3 | | 47.7 | |
| | 2 | 2,481.00 | 41.4 | 1,807 | 35.5 | |
| | | | 57.9 | | 42.1 | |
| | | | | | | |
| Number of comorbid conditions | 0 | 1,154 | 19.2 | 1,154 | 22.7 | <0.0001 |
| | | | 50.0 | | 50.0 | |
| | 1 | 2,167 | 36.1 | 1,863 | 36.6 | |
| | | | 53.8 | | 46.2 | |
| | 2 | 2,675 | 44.6 | 2,069 | 40.7 | |
| | | | 56.4 | | 43.6 | |
| | | | | | | |
| Type of index maintenance medication | ICS+LABA | 3,658 | 61.0 | 2,245 | 44.1 | <0.0001 |
| | | | 62.0 | | 38.0 | |
| | LAMA+LABA or LAMA+ICS | 42 | 0.7 | 72 | 1.4 | |
| | | | 36.8 | | 63.2 | |
| | ICS+LABA+LAMA | 406 | 6.8 | 663 | 13.0 | |
| | | | 38.0 | | 62.0 | |
| | ICS or LABA or LAMA | 1,890 | 31.5 | 2,106 | 41.4 | |
| | | | 47.3 | | 52.7 | |
| | | | | | | |
| Mail-order index maintenance medication prescription | No | 4,083 | 68.1 | 2,531 | 49.8 | <0.0001 |

| Variable | | Non-Adherent in 365 days (n=5,996) | | Adherent in 365 days (n=5,086) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| | | | 61.7 | | 38.3 | |
| | Yes | 1,913 | 31.9 | 2,555 | 50.2 | |
| | | | 42.8 | | 57.2 | |
| | | | | | | |
| Adherence to COPD-maintenance medications in the pre-index period | Non-adherent if PDC < 80% | 2,788 | 46.5 | 680 | 13.4 | <0.0001 |
| | | | 80.4 | | 19.6 | |
| | Adherent if PDC ≥ 80% | 3,208 | 53.5 | 4,406 | 86.6 | |
| | | | 42.1 | | 57.9 | |
| | | | | | | |
| **COPD severity indicators** | | | | | | |
| Supplemental oxygen use in the pre-index period | No | 5,054 | 84.3 | 3,796 | 74.6 | <0.0001 |
| | | | 57.1 | | 42.9 | |
| | Yes | 942 | 15.7 | 1,290 | 25.4 | |
| | | | 42.2 | | 57.8 | |
| | | | | | | |
| SABA use in the pre-index period | No | 2,834 | 47.3 | 2,346 | 46.1 | 0.231 |
| | | | 54.7 | | 45.3 | |
| | Yes | 3,162 | 52.7 | 2,740 | 53.9 | |
| | | | 53.6 | | 46.4 | |
| | | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | 5,844 | 97.5 | 4,916 | 96.7 | 0.012 |
| | | | 54.3 | | 45.7 | |
| | ≥1 | 152 | 2.5 | 170 | 3.3 | |
| | | | 47.2 | | 52.8 | |
| | | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | 5,238 | 87.4 | 4,316 | 84.9 | 0.0001 |
| | | | 54.8 | | 45.2 | |
| | ≥1 | 758 | 12.6 | 770 | 15.1 | |
| | | | 49.6 | | 50.4 | |
| | | | | | | |
| **Physician characteristics** | | | | | | |

| Variable | | Non-Adherent in 365 days (n=5,996) | | Adherent in 365 days (n=5,086) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| Pulmonologist visit in the pre-index period | No | 4,465 | 74.5 | 3,574 | 70.3 | <0.0001 |
| | | | 55.5 | | 44.5 | |
| | Yes | 1,531 | 25.5 | 1,512 | 29.7 | |
| | | | 50.3 | | 49.7 | |
| | | | | | | |
| **Prior utilization characteristics** | | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | *mean (±sd)* | 9,739.9 (±17,164.6) | | 9,748 (±15,469.4) | | <0.0001 |
| | <$2,844 | 1765 | 29.4 | 1004 | 19.7 | <0.0001 |
| | | | 63.7 | | 36.3 | |
| | $2,844 - $9,838 | 2736 | 45.6 | 2806 | 55.2 | |
| | | | 49.4 | | 50.6 | |
| | >$9,838 | 1495 | 24.9 | 1276 | 25.1 | |
| | | | 54.0 | | 46.0 | |

*sd denotes standard deviation; Col, column; HMO, health maintenance organization; PPO, preferred provider organization; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

prescription opioids) compared to no prescription opioid use, within the first 365 days of initiating a prescription opioid, among a real-world, large sample of COPD patients after adjusting for other confounders. A significantly lower percentage ($p<0.0001$) of prescription opioid users, either ≤30-day supply of prescription (42.3%) or >30-day supply of prescription opioids (41.4%), were adherent to their COPD maintenance medications in the 365-day follow-up period as compared to non-users of prescription opioid users (49.7%) (Table 27).

**Unadjusted logistic regression analyses:**

Table 28 provides the results of the unadjusted logistic regression analysis of the odds of being adherent to COPD maintenance medications in the 365-day follow-up period for Specific Aim 1D. Prescription opioid users were found to have 0.69 times (95% CI 0.64-0.75, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 365-day follow-up period as compared to non-opioid users. In the sub-group analysis patients with ≤30-day supply of prescription opioids had 0.69 times (95% CI 0.63-0.76, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 365-day follow-up period as compared to non-opioid users. Similarly, patients with >30-day supply of prescription opioids had 0.69 times (95% CI 0.58-0.81, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 365-day follow-up period as compared to non-opioid users. Region, insurance plan type, D-CCI, number of comorbid pain conditions, number of comorbid chronic conditions, type of index maintenance medication, mail-order index maintenance medication, and total all-cause healthcare

**Table 28: Unadjusted logistic regression predicting the odds of being adherent to COPD maintenance medications in 365 days follow-up**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Metropolitan Statistical Area | Rural | Reference | | | |
| | Urban | 0.96 | 0.83 | 1.11 | <0.61 |
| | | | | | |
| Region | Northeast | Reference | | | |
| | North Central | 0.92 | 0.77 | 1.11 | 0.39 |
| | South | 0.76 | 0.63 | 0.91 | 0.003 |
| | West | 0.81 | 0.65 | 1.01 | 0.06 |
| | | | | | |
| Insurance Plan Type | Health maintenance organization | Reference | | | |
| | Preferred provider organization | 1.15 | 0.97 | 1.36 | 0.0006 |
| | Other | 1.38 | 1.15 | 1.67 | 0.11 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Use | 0.69 | 0.64 | 0.75 | <0.0001 |
| | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | ≤30-day supply of rescription opioids | 0.69 | 0.63 | 0.76 | <0.0001 |
| | >30-day supply of prescription opioids | 0.69 | 0.58 | 0.81 | <0.0001 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.86 | 0.82 | 0.90 | <0.0001 |
| | | | | | |
| Number of pain conditions | 0 | Reference | | | |
| | 1 | 0.85 | 0.73 | 1.00 | 0.05 |
| | 2 | 0.66 | 0.57 | 0.77 | <0.0001 |
| | | | | | |
| Number of comorbid conditions | 0 | Reference | | | |
| | 1 | 0.83 | 0.69 | 0.99 | 0.04 |
| | 2 | 0.63 | 0.52 | 0.76 | <0.0001 |
| | | | | | |

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 1.95 | 1.15 | 3.31 | 0.014 |
| | ICS+LABA+LAMA | 1.83 | 1.48 | 2.25 | <0.0001 |
| | ICS or LABA or LAMA | 1.49 | 1.31 | 1.70 | <0.0001 |
| | | | | | |
| Mail-order index maintenance medication prescription | No | Reference | | | |
| | Yes | 1.54 | 1.36 | 1.74 | <0.0001 |
| | | | | | |
| **Physician characteristics** | | | | | |
| Pulmonologist visit in the pre-index period | No | Reference | | | |
| | Yes | 1.05 | 0.92 | 1.19 | 0.52 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 1.28 | 1.11 | 1.48 | 0.0007 |
| | >$9,838 | 0.92 | 0.78 | 1.09 | 0.33 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.

[a] adjusted to 2010 US $

expenditures were found significant at $p<0.2$ and were considered in the adjusted logistic regression analysis.

**Multiple logistic regression analyses:**

Table 29 provides the results of the adjusted multiple logistic regression analysis of the odds of being adherent to COPD maintenance medications in the 365-day follow-up period, for Specific Aim 1D. The overall model was statistically significant (Wald's $x^2$=221.03, df=12, $p<0.0001$). The significant impact of prescription opioid use in the unadjusted logistic regression analysis persisted in the multiple logistic regression analysis after adjusting for other factors. Prescription opioid users were found to have 0.69 times (95% CI 0.63-0.76, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 365-day follow-up period as compared to non-opioid users, independent of other predictors. Insurance plan type, D-CCI, number of pain conditions, type of index maintenance medication, mail-order index maintenance medication and total all-cause healthcare expenditures were retained in the backwards elimination model at $p<0.20$.

**Multiple logistic regression analyses, sub-group analysis:**

Table 30 provides the results of the adjusted multiple logistic regression analysis of the odds of being adherent to COPD maintenance medications in the 365-day follow-up period, for Specific Aim 1D sub-group analysis. The overall model was statistically significant (Wald's $x^2$=221.07, df=13, $p<0.0001$). The significant impact of prescription opioid use (≤30-day and >30-day supply of prescription opioids) in the unadjusted logistic regression analysis persisted in the multiple logistic regression analysis after adjusting for other factors. In the sub-group analysis patients with ≤30-day supply of

**Table 29: Multiple logistic regression predicting the odds of being adherent to COPD maintenance medications in 365 days follow-up**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Insurance Plan Type | Health maintenance organization | Reference | | | |
| | Preferred provider organization | 1.06 | 0.88 | 1.27 | 0.54 |
| | Other | 1.25 | 1.03 | 1.55 | 0.02 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Use | 0.69 | 0.63 | 0.76 | <0.0001 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.87 | 0.83 | 0.92 | <0.0001 |
| | | | | | |
| Number of pain conditions | 0 | Reference | | | |
| | 1 | 0.86 | 0.73 | 1.01 | 0.07 |
| | 2 | 0.80 | 0.67 | 0.95 | 0.01 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 2.19 | 1.24 | 3.86 | 0.006 |
| | ICS+LABA+LAMA | 1.81 | 1.45 | 2.25 | <0.0001 |
| | ICS or LABA or LAMA | 1.52 | 1.33 | 1.75 | <0.0001 |
| | | | | | |
| Mail-order index maintenance medication prescription | No | Reference | | | |
| | Yes | 1.51 | 1.32 | 1.72 | <0.0001 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 1.57 | 1.34 | 1.84 | <0.0001 |
| | >$9,838 | 1.42 | 1.16 | 1.74 | 0.0006 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

**Table 30: Multiple logistic regression predicting the odds of being adherent to COPD maintenance medications in 365 days follow-up (sub-group analysis)**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Insurance Plan Type | Health maintenance organization | Reference | | | |
| | Preferred provider organization | 1.06 | 0.88 | 1.27 | 0.53 |
| | Other | 1.26 | 1.03 | 1.55 | 0.02 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | ≤30-day supply of prescription opioids | 0.69 | 0.62 | 0.77 | <0.0001 |
| | >30-day supply of prescription opioids | 0.71 | 0.59 | 0.85 | 0.0003 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.87 | 0.83 | 0.92 | <0.0001 |
| | | | | | |
| Number of pain conditions | 0 | Reference | | | |
| | 1 | 0.86 | 0.73 | 1.01 | 0.07 |
| | 2 | 0.79 | 0.66 | 0.95 | 0.01 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 2.19 | 1.25 | 3.87 | 0.007 |
| | ICS+LABA+LAMA | 1.81 | 1.45 | 2.25 | <0.0001 |
| | ICS or LABA or LAMA | 1.52 | 1.33 | 1.75 | <0.0001 |
| | | | | | |
| Mail-order index maintenance medication prescription | No | | | | |
| | Yes | 1.51 | 1.32 | 1.72 | <0.0001 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 1.57 | 1.34 | 1.84 | <0.0001 |

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| | >$9,838 | 1.42 | 1.16 | 1.74 | 0.0006 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

prescription opioids had 0.69 times (95% CI 0.62-0.77, $p<0.0001$) significantly lower odds of being adherent to their COPD maintenance medications in the 365-day follow-up period compared to non-opioid users independent of other factors. Similarly, patients with >30-day supply of prescription opioids had 0.71 times (95% CI 0.59-0.85, $p<0.0003$) significantly lower odds of being adherent to their COPD maintenance medications in the 365-day follow-up period compared to non-opioid users independent of other factors. Insurance plan type, D-CCI, number of pain conditions, type of index maintenance medication, mail-order index maintenance medication and total all-cause healthcare expenditures were retained in the backwards elimination model at $p<0.20$.

**Sample for Specific Aims 2, 3 and 4**

Specific Aims 2, 3 and 4 were answered using long-term prescription opioid users and non-opioid users among COPD patients. Baseline characteristics of long-term prescription opioid users and non-users among COPD patients are presented in Table 31.

A total of 566 COPD patients on maintenance medications were classified as long-term prescription opioid users, representing 10.2% of all the matched prescription opioid users. Long-term prescription opioid users were similar to non-opioid users in terms of baseline sex, age, MSA, insurance plan type, type of index maintenance medication, mail-order index maintenance medication, adherence in the pre-index period, pre-index moderate COPD exacerbations, and pulmonary physician visit. Similar to prescription opioid users, long-term prescription opioid users had significantly higher number of mean comorbid conditions compared to non-opioid users. The mean D-CCI score among long-term prescription opioid users was significantly higher compared to

**Table 31: Baseline characteristics of long-term and non-users of prescription opioids in one-year follow-up period for Specific Aims 2, 3, and 4**

| Variable | | Non-Opioid users (n=5,541) | | Long-term opioid users (n=566) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col % Row % | N | Col % Row % | |
| **Sociodemographic characteristics** | | | | | | |
| Sex | Male | 2,537 | 45.8 | 267 | 47.2 | 0.53 |
| | | | 90.5 | | 9.5 | |
| | Female | 3,004 | 54.2 | 299 | 52.8 | |
| | | | 90.9 | | 9.1 | |
| | | | | | | |
| Age | *mean (±sd)* | 57.2 years (±5.4) | | 57.3 years (±5.2) | | 0.73 |
| | 40 – 49 years | 604 | 10.9 | 50 | 8.8 | 0.31 |
| | | | 92.4 | | 7.6 | |
| | 50 – 59 years | 2,555 | 46.1 | 269 | 47.5 | |
| | | | 90.5 | | 9.5 | |
| | ≥60 years | 2,382 | 43.0 | 247 | 43.6 | |
| | | | 90.6 | | 9.4 | |
| Metropolitan Statistical Area | Urban | 4,408 | 79.6 | 441 | 77.9 | 0.32 |
| | | | 90.9 | | 9.1 | |
| | Rural | 1,106 | 20.0 | 123 | 21.7 | |
| | | | 90.0 | | 10.0 | |
| | | | | | | |
| Region | Northeast | 910 | 16.4 | 52 | 9.2 | <0.0001 |
| | | | 94.6 | | 5.4 | |
| | North Central | 2,084 | 37.6 | 232 | 41.0 | |
| | | | 90.0 | | 10.0 | |
| | South | 1,808 | 32.6 | 213 | 37.6 | |
| | | | 89.5 | | 10.5 | |
| | West | 708 | 12.8 | 67 | 11.8 | |
| | | | 91.4 | | 8.6 | |
| | | | | | | |
| Insurance Plan Type | HMO | 879 | 15.9 | 92 | 16.3 | 0.96 |
| | | | 90.5 | | 9.5 | |
| | PPO | 1,518 | 27.4 | 153 | 27.0 | |
| | | | 90.8 | | 9.2 | |
| | Other | 3118 | 56.3 | 319 | 56.4 | |
| | | | 90.7 | | 9.3 | |
| **Clinical characteristics** | | | | | | |
| Deyo-Charlson Comorbidity Index | *mean (±sd)* | 1.7 (±1.2) | | 2.4 (±1.8) | | <0.0001 |
| | | | | | | |
| | | | | | | |

| Variable | | Non-Opioid users (n=5,541) | | Long-term opioid users (n=566) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col % Row % | N | Col % Row % | |
| Number of pain conditions | 0 | 1624 | 29.3 | 37 | 6.5 | <0.0001 |
| | | | 97.8 | | 2.2 | |
| | 1 | 2,515 | 45.4 | 116 | 20.5 | |
| | | | 95.6 | | 4.4 | |
| | 2 | 1,402 | 25.3 | 413 | 73.0 | |
| | | | 77.2 | | 22.8 | |
| | | | | | | |
| Number of comorbid conditions | 0 | 1,312 | 23.7 | 76 | 13.4 | <0.0001 |
| | | | 94.5 | | 5.5 | |
| | 1 | 2,168 | 39.1 | 169 | 29.9 | |
| | | | 92.8 | | 7.2 | |
| | 2 | 2,061 | 37.2 | 321 | 56.7 | |
| | | | 86.5 | | 13.5 | |
| | | | | | | |
| Type of index maintenance medication | ICS+LABA | 2,904 | 52.4 | 284 | 50.2 | 0.3 |
| | | | 91.1 | | 8.9 | |
| | LAMA+LABA or LAMA+ICS | 56 | 1.0 | 10 | 1.8 | |
| | | | 84.8 | | 15.2 | |
| | ICS+LABA+LAMA | 538 | 9.7 | 60 | 10.6 | |
| | | | 90.0 | | 10.0 | |
| | ICS or LABA or LAMA | 2043 | 36.9 | 212 | 37.5 | |
| | | | 90.6 | | 9.4 | |
| Mail-order index maintenance medication prescription | No | 3,353 | 60.5 | 324 | 57.2 | 0.13 |
| | | | 91.2 | | 8.8 | |
| | Yes | 2,188 | 39.5 | 242 | 42.8 | |
| | | | 90.0 | | 10.0 | |
| | | | | | | |
| Adherence to COPD-maintenance medications in the pre-index period | Non-adherent if PDC < 80% | 1,734 | 31.3 | 170 | 30.0 | 0.54 |
| | | | 91.1 | | 8.9 | |
| | Adherent if PDC ≥ 80% | 3,807 | 68.7 | 396 | 70.0 | |
| | | | 90.6 | | 9.4 | |
| | | | | | | |

| Variable | | Non-Opioid users (n=5,541) | | Long-term opioid users (n=566) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col % Row % | N | Col % Row % | |
| **COPD severity indicators** | | | | | | |
| Supplemental oxygen use in the pre-index period | No | 4,425 | 79.9 | 407 | 71.9 | <0.0001 |
| | | | 91.6 | | 8.4 | |
| | Yes | 1,116 | 20.1 | 159 | 28.1 | |
| | | | 87.5 | | 12.5 | |
| | | | | | | |
| SABA use in the pre-index period | No | 2,590 | 46.7 | 232 | 41.0 | 0.009 |
| | | | 91.8 | | 8.2 | |
| | Yes | 2,951 | 53.3 | 334 | 59.0 | |
| | | | 89.8 | | 10.2 | |
| | | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | 5,380 | 97.1 | 536 | 94.7 | 0.002 |
| | | | 90.9 | | 9.1 | |
| | ≥1 | 161 | 2.9 | 30 | 5.3 | |
| | | | 84.3 | | 15.7 | |
| | | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | 4,777 | 86.2 | 473 | 83.6 | 0.08 |
| | | | 91.0 | | 9.0 | |
| | ≥1 | 764 | 13.8 | 93 | 16.4 | |
| | | | 89.1 | | 10.9 | |
| | | | | | | |
| **Physician characteristics** | | | | | | |
| Pulmonologist visit in the pre-index period | No | 4,072 | 73.5 | 406 | 71.7 | 0.37 |
| | | | 90.9 | | 9.1 | |
| | Yes | 1,469 | 26.5 | 160 | 28.3 | |
| | | | 90.2 | | 9.8 | |
| | | | | | | |
| **Prior utilization characteristics** | | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | *mean (±sd) [median interquartile range]* | 6,988.4 (±11,358.8) | [4,059 (5059)] | 15,427.4 (±27,780.0) | [7,774 (11,074)] | <0.0001 |

| Variable | | Non-Opioid users (n=5,541) | | Long-term opioid users (n=566) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col % Row % | N | Col % Row % | |
| | <$2,844 | 1874 | 33.8 | 70 | 12.4 | <0.0001 |
| | | | 96.4 | | 3.6 | |
| | $2,844 - $9,838 | 2752 | 49.7 | 269 | 47.5 | |
| | | | 91.1 | | 8.9 | |
| | >$9,838 | 915 | 16.5 | 227 | 40.1 | |
| | | | 80.1 | | 19.9 | |

*sd denotes standard deviation; Col, column; HMO, health maintenance organization; PPO, preferred provider organization; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.

[a] adjusted to 2010 US $

non-users of prescription opioids (2.4 ± 1.8 vs 1.7 ± 1.2, $p<0.0001$). Similarly, a higher proportion of long-term prescription opioid users had presence of one or more comorbid chronic conditions (86.6% vs 76.3%, $p<0.0001$) and comorbid pain conditions (93.5% vs 70.7%, $p<0.0001$). Also, significantly higher percentage of long-term prescription opioid users had pre-index supplemental oxygen use (28.1% vs 20.1%, $p<0.0001$), SABA use (59% vs 53.3%, $p<0.009$), severe COPD exacerbations (5.3% vs 2.9%, $p=0.002$), and higher mean total all-cause healthcare costs (Table 31).

**Results for Specific Aim 2**

**Baseline characteristics as per Specific Aim 2:**

Specific Aim 2 was to examine the impact of long-term prescription opioid use (≥90-day supply in a one-year period) compared to no-opioid use on adherence to COPD maintenance medications among a real-world, large sample of COPD patients after adjusting for other confounders. Table 32 provides baseline characteristics of the included sample of long-term and non-opioid users among COPD patients according to adherence to COPD maintenance medications in one-year follow-up period. Overall, 49.1% of the included sample of COPD patients were adherent (defined as PDC ≥0.8) to their COPD maintenance medications in the one-year follow-up period after the index date. A smaller percentage of long-term prescription opioid users were adherent to their COPD maintenance medications as compared to non-opioid users (42.6% vs 49.7%, $p=0.001$). A higher percentage of patients who had comorbid conditions were non-adherent to their COPD maintenance medications than patients who did not have comorbid conditions. A significantly higher percentage of non-adherent patients had

### Table 32: Baseline characteristics for specific aim 2

| Variable | | Non-Adherent in 365 days (n=3,110) | | Adherent in 365 days (n=2,997) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| **Sociodemographic characteristics** | | | | | | |
| Sex | Male | 1,372 | 44.1 | 1,432 | 47.8 | 0.004 |
| | | | 48.9 | | 51.1 | |
| | Female | 1,738 | 55.9 | 1,565 | 52.2 | |
| | | | 52.6 | | 47.4 | |
| | | | | | | |
| Age | *mean (±sd)* | 56.4 years (±5.7) | | 58.1 years (±4.9) | | <0.0001 |
| | 40 – 49 years | 434 | 14.0 | 220 | 7.3 | <0.0001 |
| | | | 66.4 | | 33.6 | |
| | 50 – 59 years | 1,526 | 49.1 | 1,298 | 43.3 | |
| | | | 54.0 | | 46.0 | |
| | ≥60 years | 1,150 | 37.0 | 1,479 | 49.3 | |
| | | | 43.7 | | 56.3 | |
| | | | | | | |
| Metropolitan Statistical Area | Urban | 2,471 | 79.5 | 2,378 | 79.3 | 0.97 |
| | | | 51.0 | | 49.0 | |
| | Rural | 627 | 20.2 | 602 | 20.1 | |
| | | | 51.0 | | 49.0 | |
| | | | | | | |
| Region | Northeast | 492 | 15.8 | 470 | 15.7 | <0.0001 |
| | | | 51.1 | | 48.9 | |
| | North Central | 1,086 | 34.9 | 1,230 | 41.0 | |
| | | | 46.9 | | 53.1 | |
| | South | 1,113 | 35.8 | 908 | 30.3 | |
| | | | 55.1 | | 44.9 | |
| | West | 403 | 13.0 | 372 | 12.4 | |
| | | | 52.0 | | 48.0 | |
| | | | | | | |
| Insurance Plan Type | HMO | 546 | 17.6 | 425 | 14.2 | 0.001 |
| | | | 56.2 | | 43.8 | |
| | PPO | 1,723 | 55.4 | 1,714 | 57.2 | |
| | | | 50.1 | | 49.9 | |
| | Other | 823 | 26.5 | 848 | 28.3 | |
| | | | 49.3 | | 50.7 | |
| | | | | | | |
| **Clinical characteristics** | | | | | | |
| **Prescription opioid use** | Non user | 2785 | 89.5 | 2756 | 92.0 | 0.001 |
| | | | 50.3 | | 49.7 | |
| | Long-term user | 325 | 10.5 | 241 | 8.0 | |
| | | | 57.4 | | 42.6 | |
| | | | | | | |
| Deyo-Charlson Comorbidity Index | *mean (±sd)* | 1.8 (±1.3) | | 1.7 (±1.2) | | 0.297 |
| | | | | | | |

| Variable | | Non-Adherent in 365 days (n=3,110) | | Adherent in 365 days (n=2,997) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| Number of pain conditions | 0 | 814 | 26.2 | 847 | 28.3 | <0.0001 |
| | | | 49.0 | | 51.0 | |
| | 1 | 1,264 | 40.6 | 1,367 | 45.6 | |
| | | | 48.0 | | 52.0 | |
| | 2 | 1,032 | 33.2 | 783 | 26.1 | |
| | | | 56.9 | | 43.1 | |
| | | | | | | |
| Number of comorbid conditions | 0 | 654 | 21.0 | 734 | 24.5 | 0.004 |
| | | | 47.1 | | 52.9 | |
| | 1 | 1,203 | 38.7 | 1,134 | 37.8 | |
| | | | 51.5 | | 48.5 | |
| | 2 | 1,253 | 40.3 | 1,129 | 37.7 | |
| | | | 52.6 | | 47.4 | |
| | | | | | | |
| Type of index maintenance medication | ICS+LABA | 1,871 | 60.2 | 1317 | 43.9 | <0.0001 |
| | | | 58.7 | | 41.3 | |
| | LAMA+LABA or LAMA+ICS | 19 | 0.6 | 47 | 1.6 | |
| | | | 28.8 | | 71.2 | |
| | ICS+LABA+LAMA | 203 | 6.5 | 395 | 13.2 | |
| | | | 33.9 | | 66.1 | |
| | ICS or LABA or LAMA | 1017 | 32.7 | 1238 | 41.3 | |
| | | | 45.1 | | 54.9 | |
| | | | | | | |
| Mail-order index maintenance medication prescription | No | 2,172 | 69.8 | 1,505 | 50.2 | <0.0001 |
| | | | 59.1 | | 40.9 | |
| | Yes | 938 | 30.2 | 1,492 | 49.8 | |
| | | | 38.6 | | 61.4 | |
| | | | | | | |
| Adherence to COPD-maintenance medications in the pre-index period | Non-adherent if PDC < 80% | 1,487 | 47.8 | 417 | 13.9 | <0.0001 |
| | | | 78.1 | | 21.9 | |
| | Adherent if PDC ≥ 80% | 1,623 | 52.2 | 2,580 | 86.1 | |
| | | | 38.6 | | 61.4 | |
| | | | | | | |
| **COPD severity indicators** | | | | | | |

| Variable | | Non-Adherent in 365 days (n=3,110) | | Adherent in 365 days (n=2,997) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col %<br>Row % | N | Col %<br>Row % | |
| Supplemental oxygen use in the pre-index period | No | 2,609 | 83.9 | 2,223 | 74.2 | <0.0001 |
| | | | 54.0 | | 46.0 | |
| | Yes | 501 | 16.1 | 774 | 25.8 | |
| | | | 39.3 | | 60.7 | |
| | | | | | | |
| SABA use in the pre-index period | No | 1,427 | 45.9 | 1,395 | 46.5 | 0.6 |
| | | | 50.6 | | 49.4 | |
| | Yes | 1,683 | 54.1 | 1,602 | 53.5 | |
| | | | 51.2 | | 48.8 | |
| | | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | 3,025 | 97.3 | 2,891 | 96.5 | 0.07 |
| | | | 51.1 | | 48.9 | |
| | ≥1 | 85 | 2.7 | 106 | 3.5 | |
| | | | 44.5 | | 55.5 | |
| | | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | 2,703 | 86.9 | 2,547 | 85.0 | 0.03 |
| | | | 51.5 | | 48.5 | |
| | ≥1 | 407 | 13.1 | 450 | 15.0 | |
| | | | 47.5 | | 52.5 | |
| | | | | | | |
| **Physician characteristics** | | | | | | |
| Pulmonologist visit in the pre-index period | No | 2,359 | 75.9 | 2,119 | 70.7 | <0.0001 |
| | | | 52.7 | | 47.3 | |
| | No | 751 | 24.1 | 878 | 29.3 | |
| | | | 46.1 | | 53.9 | |
| | | | | | | |
| **Prior utilization characteristics** | | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | *mean (±sd) [median ± interquartile range]* | 7,672.5 (±15,023.7) | [3,847 (5,545)] | 7,872.4 (±12,731) | [4,678 (5,393)] | <0.0001 |
| | <$2,844 | 1153 | 37.1 | 791 | 26.4 | <0.0001 |
| | | | 59.3 | | 40.7 | |
| | $2,844 - $9,838 | 1396 | 44.9 | 1625 | 54.2 | |
| | | | 46.2 | | 53.8 | |
| | >$9,838 | 561 | 18.0 | 581 | 19.4 | |

| Variable | | Non-Adherent in 365 days (n=3,110) | | Adherent in 365 days (n=2,997) | | P value |
|---|---|---|---|---|---|---|
| | | N | Col % Row % | N | Col % Row % | |
| | | | 49.1 | | 50.9 | |

*sd denotes standard deviation; Col, column; HMO, health maintenance organization; PPO, preferred provider organization; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

comorbid chronic conditions (79% vs 75.5%, $p<0.001$) and comorbid pain conditions (73.8% vs 71.7%, $p<0.0001$). However, the mean D-CCI scores were not significantly different between adherent and non-adherent COPD patients (1.8 ± 1.3 vs 1.7 ± 1.2, $p=0.297$).

**Unadjusted logistic regression analyses:**

Table 33 provides the results of the unadjusted logistic regression analysis of the odds of being adherent to COPD maintenance medications in one-year follow-up period for Specific Aim 2. In the unadjusted logistic regression analysis, long-term prescription opioid users were found to have 0.68 times (95% CI 0.52-0.88, $p=0.003$) significantly lower odds of being adherent to their COPD maintenance medications in the one-year follow-up period as compared to non-opioid users. D-CCI, number of comorbid pain conditions, and total all-cause healthcare expenditures were found significant at $p<0.2$ and were considered in the multiple logistic regression analysis.

**Multiple logistic regression analyses:**

Table 34 provides the results of the adjusted multiple logistic regression analysis of the odds of being adherent to COPD maintenance medications in one-year follow-up period, for Specific Aim 2. The overall model was statistically significant (Wald's $x^2=26.3$, df=7, $p=0.0004$). The significant impact of long-term prescription opioid use in the unadjusted logistic regression analysis persisted in the multiple logistic regression analysis after adjusting for other factors. Long-term prescription opioid users were found to have 0.63 times (95% CI 0.46-0.88, $p=0.005$) significantly lower odds of being adherent to their COPD maintenance medications in one-year follow-up period as compared to non-opioid users, independent of other predictors. D-CCI, type of index

**Table 33: Unadjusted logistic regression predicting the odds of being adherent to COPD maintenance medications in one-year follow-up**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Metropolitan Statistical Area | Rural | Reference | | | |
| | Urban | 0.79 | 0.51 | 1.21 | 0.28 |
| | | | | | |
| Region | Northeast | Reference | | | |
| | North Central | 0.79 | 0.45 | 1.39 | 0.41 |
| | South | 0.71 | 0.40 | 1.23 | 0.22 |
| | West | 0.55 | 0.26 | 1.20 | 0.22 |
| | | | | | |
| Insurance Plan Type | Health maintenance organization | Reference | | | |
| | Preferred provider organization | 0.80 | 0.46 | 1.38 | 0.42 |
| | Other | 1.30 | 0.71 | 2.40 | 0.4 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Long-term | 0.68 | 0.52 | 0.88 | 0.003 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.88 | 0.77 | 1.00 | 0.05 |
| | | | | | |
| Number of pain conditions | 0 | Reference | | | |
| | 1 | 1.05 | 0.64 | 1.74 | 0.84 |
| | 2 | 0.70 | 0.44 | 1.12 | 0.14 |
| | | | | | |
| Number of comorbid conditions | 0 | Reference | | | |
| | 1 | 0.86 | 0.49 | 1.51 | 0.6 |
| | 2 | 0.79 | 0.44 | 1.42 | 0.43 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 2.42 | 0.56 | 10.50 | 0.24 |
| | ICS+LABA+LAMA | 2.11 | 1.13 | 3.97 | 0.02 |
| | ICS or LABA or LAMA | 2.02 | 1.31 | 3.10 | 0.001 |
| | | | | | |
| Mail-order index | No | Reference | | | |

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| maintenance medication prescription | | | | | |
| | Yes | 1.12 | 0.77 | 1.63 | 0.56 |
| | | | | | |
| **Physician characteristics** | | | | | |
| Type of physician visited in the pre-index period | Other | Reference | | | |
| | Pulmonologist | 1.28 | 0.83 | 1.98 | 0.27 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 1.32 | 0.83 | 2.11 | 0.19 |
| | >$9,838 | 0.87 | 0.52 | 1.46 | 0.6 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

**Table 34: Multiple logistic regression predicting the odds of being adherent to COPD maintenance medications in one-year follow-up**

| Variable | | Point Estimate | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Long-term use | 0.63 | 0.46 | 0.88 | 0.005 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.89 | 0.76 | 1.04 | 0.14 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 3.33 | 0.68 | 16.42 | 0.14 |
| | ICS+LABA+LAMA | 2.37 | 1.21 | 4.61 | 0.01 |
| | ICS or LABA or LAMA | 2.18 | 1.39 | 3.42 | 0.0007 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 2.03 | 1.18 | 3.5 | 0.01 |
| | >$9,838 | 1.64 | 0.85 | 3.16 | 0.14 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

maintenance medication, and total all-cause healthcare expenditures were retained in the backwards elimination model at $p<0.20$.

COPD patients having an index fill of ICS+LABA+LAMA combination had 2.37 times (95% CI 1.21-4.61, $p=0.01$) higher odds of being adherent to COPD maintenance medications compared to having an index fill of ICS+LABA combination, independent of other factors. Similarly, patients having an index fill of either ICS or LABA or LAMA alone had 2.18 times (95% CI 1.39-3.42, $p=0.0007$) significantly higher odds of being adherent to COPD maintenance medications compared to patients having an index fill of ICS+LABA combination, independent of other factors. Having pre-index all cause healthcare expenditures between $2,844 to $9,838 was associated with 2.0 times (95% CI 1.18-3.5, $p=0.01$) higher odds of being adherent to COPD maintenance medications compared to having pre-index all cause healthcare expenditures less than $2,844, independent of other factors.

**Results for Specific Aim 3**

Specific Aim 3 was to examine the impact of long-term prescription opioid use (≥90-day supply in a one-year period) compared to no prescription opioid use on COPD exacerbations among a real-world, large sample of COPD patients after adjusting for other confounders.

**Results for Specific Aim 3 A**

**Baseline characteristics as per Specific Aim 3A:**

Specific Aim 3A was to examine the impact of long-term prescription opioid use (≥90-day supply in a one-year period) compared to no-opioid use on the number of severe COPD exacerbations among a real-world, large sample of COPD patients after

**Table 35: Baseline characteristics for Specific Aim 3A**

| Variable | | Severe COPD exacerbations | No severe COPD exacerbations (n=5,842) | | Severe COPD exacerbations (n=265) | | P value |
|---|---|---|---|---|---|---|---|
| | | mean (±sd) | N | Col % Row % | N | Col % Row % | |
| **Sociodemographic characteristics** | | | | | | | |
| Sex | Male | 0.05 (±0.28) | 2,700 | 46.2 | 104 | 39.2 | 0.03 |
| | | | | 96.3 | | 3.7 | |
| | Female | 0.06 (±0.28) | 3,142 | 53.8 | 161 | 60.8 | |
| | | | | 95.1 | | 4.9 | |
| | | | | | | | |
| Age | *mean (±sd)* | | 57.1 years (±5.4) | | 58.6 years (±4.7) | | <0.0001 |
| | 40 – 49 years | 0.02 (±0.15) | 643 | 11.0 | 11 | 4.2 | <0.0001 |
| | | | | 98.3 | | 1.7 | |
| | 50 – 59 years | 0.05 (±0.28) | 2,719 | 46.5 | 105 | 39.6 | |
| | | | | 96.3 | | 3.7 | |
| | ≥60 years | 0.07 (±0.3) | 2,480 | 42.5 | 149 | 56.2 | |
| | | | | 94.3 | | 5.7 | |
| Metropolitan Statistical Area | Urban | 0.05 (±0.28) | 4,648 | 79.6 | 201 | 75.8 | 0.132 |
| | | | | 95.9 | | 4.1 | |
| | Rural | 0.06 (±0.27) | 1,166 | 20.0 | 63 | 23.8 | |
| | | | | 94.9 | | 5.1 | |
| | | | | | | | |
| Region | Northeast | 0.06 (±0.28) | 918 | 15.7 | 44 | 16.6 | 0.032 |
| | | | | 95.4 | | 4.6 | |
| | North Central | 0.06 (±0.29) | 2,197 | 37.6 | 119 | 44.9 | |
| | | | | 94.9 | | 5.1 | |
| | South | 0.05 (±0.27) | 1,942 | 33.2 | 79 | 29.8 | |
| | | | | 96.1 | | 3.9 | |
| | West | 0.03 (±0.28) | 753 | 12.9 | 22 | 8.3 | |
| | | | | 97.2 | | 2.8 | |
| | | | | | | | |
| Insurance Plan Type | HMO | 0.04 (±0.28) | 936 | 16.0 | 35 | 13.2 | 0.41 |
| | | | | 96.4 | | 3.6 | |
| | PPO | 0.05 (±0.28) | 3,280 | 56.1 | 157 | 59.2 | |

| Variable | | Severe COPD exacerbations | No severe COPD exacerbations (n=5,842) | | Severe COPD exacerbations (n=265) | | P value |
|---|---|---|---|---|---|---|---|
| | | mean (±sd) | N | Col % Row % | N | Col % Row % | |
| | | | | 95.4 | | 4.6 | |
| | Other | 0.06 (±0.29) | 1,601 | 27.4 | 70 | 26.4 | |
| | | | | 95.8 | | 4.2 | |
| **Clinical characteristics** | | | | | | | |
| Prescription opioid use | No use | 0.05 (±0.26) | 5,321 | 91.1 | 220 | 83.0 | <0.0001 |
| | | | | 96.0 | | 4.0 | |
| | Long-term use | 0.11 (±0.41) | 521 | 8.9 | 45 | 17.0 | |
| | | | | 92.0 | | 8.0 | |
| | | | | | | | |
| Deyo-Charlson Comorbidity Index | *mean (±sd)* | | 1.7 (±1.2) | | 2.3 (±1.4) | | <0.0001 |
| | | | | | | | |
| Number of pain conditions | 0 | 0.01 (±0.08) | 1,650 | 28.2 | 11 | 4.2 | <0.0001 |
| | | | | 99.3 | | 0.7 | |
| | 1 | 0.06 (±0.29) | 2,488 | 42.6 | 143 | 54.0 | |
| | | | | 94.6 | | 5.4 | |
| | 2 | 0.08 (±0.35) | 1,704 | 29.2 | 111 | 41.9 | |
| | | | | 93.9 | | 6.1 | |
| | | | | | | | |
| Number of comorbid conditions | 0 | 0.03 (±0.19) | 1,351 | 23.1 | 37 | 14.0 | <0.0001 |
| | | | | 97.3 | | 2.7 | |
| | 1 | 0.03 (±0.20) | 2,272 | 38.9 | 65 | 24.5 | |
| | | | | 97.2 | | 2.8 | |
| | 2 | 0.09 (±0.36) | 2,219 | 38.0 | 163 | 61.5 | |
| | | | | 93.2 | | 6.8 | |
| | | | | | | | |
| Type of index maintenance medication | ICS+LABA | 0.04 (±0.22) | 3,069 | 52.5 | 119 | 44.9 | 0.08 |
| | | | | 96.3 | | 3.7 | |

| Variable | | Severe COPD exacerbations | No severe COPD exacerbations (n=5,842) | | Severe COPD exacerbations (n=265) | | P value |
|---|---|---|---|---|---|---|---|
| | | mean (±sd) | N | Col % Row % | N | Col % Row % | |
| | LAMA+LABA or LAMA+ICS | 0.09 (±0.38) | 62 | 1.1 | 4 | 1.5 | |
| | | | | 93.9 | | 6.1 | |
| | ICS+LABA+LAMA | 0.07 (±0.32) | 565 | 9.7 | 33 | 12.5 | |
| | | | | 94.5 | | 5.5 | |
| | ICS or LABA or LAMA | 0.06 (±0.33) | 2,146 | 36.7 | 109 | 41.1 | |
| | | | | 95.2 | | 4.8 | |
| | | | | | | | |
| Mail-order index maintenance medication prescription | No | 0.05 (±0.28) | 3,536 | 60.5 | 141 | 53.2 | 0.02 |
| | | | | 96.2 | | 3.8 | |
| | Yes | 0.06 (±0.27) | 2,306 | 39.5 | 124 | 46.8 | |
| | | | | 94.9 | | 5.1 | |
| | | | | | | | |
| Adherence to COPD-maintenance medications in the pre-index period | Non-adherent if PDC < 80% | 0.04 (±0.24) | 1,831 | 31.3 | 73 | 27.5 | 0.19 |
| | | | | 96.2 | | 3.8 | |
| | Adherent if PDC ≥ 80% | 0.06 (±0.29) | 4,011 | 68.7 | 192 | 72.5 | |
| | | | | 95.4 | | 4.6 | |
| | | | | | | | |
| **COPD severity indicators** | | | | | | | |
| Supplemental oxygen use in the pre-index period | No | 0.03 (±0.17) | 4,722 | 80.8 | 110 | 41.5 | <0.0001 |
| | | | | 97.7 | | 2.3 | |
| | Yes | 0.16 (±0.49) | 1,120 | 19.2 | 155 | 58.5 | |
| | | | | 87.8 | | 12.2 | |

| Variable | | Severe COPD exacerbations | No severe COPD exacerbations (n=5,842) | | Severe COPD exacerbations (n=265) | | P value |
|---|---|---|---|---|---|---|---|
| | | mean (±sd) | N | Col % Row % | N | Col % Row % | |
| | | | | | | | |
| SABA use in the pre-index period | No | 0.03 (±0.23) | 2,741 | 46.9 | 81 | 30.6 | <0.0001 |
| | | | | 97.1 | | 2.9 | |
| | Yes | 0.07 (±0.32) | 3,101 | 53.1 | 184 | 69.4 | |
| | | | | 94.4 | | 5.6 | |
| | | | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | 0.05 (±0.26) | 5,686 | 97.3 | 230 | 86.8 | <0.0001 |
| | | | | 96.1 | | 3.9 | |
| | ≥1 | 0.26 (±0.63) | 156 | 2.7 | 35 | 13.2 | |
| | | | | 81.7 | | 18.3 | |
| | | | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | 0.04 (±0.23) | 5,063 | 86.7 | 187 | 70.6 | <0.0001 |
| | | | | 96.4 | | 3.6 | |
| | ≥1 | 0.13 (±0.48) | 779 | 13.3 | 78 | 29.4 | |
| | | | | 90.9 | | 9.1 | |
| | | | | | | | |
| **Physician characteristics** | | | | | | | |
| Pulmonologist visit in the pre-index period | No | 0.05 (±0.26) | 4,312 | 73.8 | 166 | 62.6 | <0.0001 |
| | | | | 96.3 | | 3.7 | |
| | Yes | 0.08 (±0.33) | 1,530 | 26.2 | 99 | 37.4 | |
| | | | | 93.9 | | 6.1 | |
| | | | | | | | |
| **Prior utilization characteristics** | | | | | | | |

| Variable | | Severe COPD exacerbations | No severe COPD exacerbations (n=5,842) | | Severe COPD exacerbations (n=265) | | P value |
|---|---|---|---|---|---|---|---|
| | | mean (±sd) | N | Col % Row % | N | Col % Row % | |
| Total all-cause healthcare expenditures in the pre-index period[a] | *mean (±sd)* | | 7,538.6 (±13,592.2) | | 12,884.8 (±19,569.2) | | <0.0001 |
| | <$2,844 | 0.03 (±0.21) | 1,891 | 32.4 | 53 | 20.0 | <0.0001 |
| | | | | 97.3 | | 2.7 | |
| | $2,844 - $9,838 | 0.05 (±0.25) | 2,893 | 49.5 | 128 | 48.3 | |
| | | | | 95.8 | | 4.2 | |
| | >$9,838 | 0.1 (±0.40) | 1,058 | 18.1 | 84 | 31.7 | |
| | | | | 92.6 | | 7.4 | |

*sd denotes standard deviation; Col, column; HMO, health maintenance organization; PPO, preferred provider organization; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

adjusting for other confounders. Table 35 provides baseline characteristics of the included sample of long-term and non-opioid users among COPD patients as per evidence of severe COPD exacerbation in a one-year follow-up period. Overall, 4.3% of the included sample of COPD patients experienced a severe COPD exacerbation in a one-year follow-up period after the index date. A higher percentage of long-term prescription opioid users experienced a severe COPD exacerbation in a one-year follow-up period compared to non-opioid users (8% vs 4%, $p<0.0001$). Also, long-term prescription opioid users had a higher mean number of severe COPD exacerbation compared to non-opioid users ($0.11 \pm 0.41$ vs $0.05 \pm 0.26$, $p<0.001$). A greater proportion of females, patients older than 50 years, patients having a mail-order index maintenance medication, patients who used supplemental oxygen, had previous SABA use, had pre-index severe or moderate exacerbations, had visited a pulmonologist, and had higher baseline healthcare costs experienced a severe COPD exacerbation in one-year follow-up period. A higher proportion of patients who had comorbid conditions experienced a severe COPD exacerbation in one-year follow-up period than patients who did not have comorbid conditions. Patients who experienced a severe COPD exacerbation in a one-year follow-up period had higher mean D-CCI scores compared to patients who did not experience a severe COPD exacerbation ($2.3 \pm 1.4$ vs $1.7 \pm 1.2$, $p<0.0001$). A greater percentage of patients who had comorbid chronic ($p>0.0001$) or comorbid pain conditions ($p>0.0001$) experienced a severe COPD exacerbation in one-year follow-up period compared to patients who did not have comorbid chronic or pain conditions.

**Negative binomial regression: Number of severe COPD exacerbation in one-year follow-up:**

In the univariate negative binomial regression analysis, long-term prescription opioid users were found to have 2.0 times (95% CI, 1.45-2.76, $p<0.0001$) significantly higher rate of severe COPD exacerbations in one-year follow-up period. Age group, sex, metropolitan statistical area, region of residence, comorbid pain and chronic conditions, type of index COPD maintenance medication, mail-order index maintenance medication, pulmonologist visit, D-CCI, cost quartile, supplemental oxygen use, SABA use, and pre-index moderate and severe exacerbation variables were found significantly associated with the number of severe COPD exacerbation in one-year follow up period at $p<0.2$ and were included in the final adjusted multiple negative binomial regression analysis.

Table 36 presents the results of the final adjusted multiple negative binomial regression analysis model. After adjusting for other covariates, long-term prescription opioid use was not significantly associated with number of severe COPD exacerbations in one-year follow-up period (incidence rate ratio 1.32, 95% CI 0.93-1.87, $p=0.12$). Patients ≥60 years old had 2.06 times (95% CI 1.10-3.85, $p=0.02$) higher rate of severe COPD exacerbations compared to patients who were 40-49 years old. Patients residing in the west had 0.57 times (95% CI 0.34-0.96, $p=0.04$) lower rate of severe COPD exacerbations compared to patients who resided in the northeast. Patients having 1 or ≥2 number of comorbid pain conditions had 6.0 times (95% CI 3.13-11.47, $p<0.0001$) and 6.09 times (95% CI 3.13-11.85, $p<0.0001$) higher rate of severe COPD exacerbations compared to patients who did not have any comorbid pain conditions,

**Table 36: Adjusted negative binomial regression: Number of severe COPD exacerbation in one-year follow-up**

| Variable | | Incidence Rate Ratios | 95% Confidence Interval | | P value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Sex | Male | Reference | | | |
| | Female | 1.13 | 0.87 | 1.45 | 0.36 |
| | | | | | |
| | | | | | |
| Age | 40 – 49 years | Reference | | | |
| | 50 – 59 years | 1.48 | 0.79 | 2.79 | 0.22 |
| | ≥60 years | 2.06 | 1.10 | 3.85 | 0.02 |
| | | | | | |
| Metropolitan Statistical Area | Rural | Reference | | | |
| | Urban | 0.85 | 0.64 | 1.13 | 0.26 |
| | | | | | |
| Region | Northeast | Reference | | | |
| | North Central | 0.95 | 0.67 | 1.34 | 0.76 |
| | South | 0.78 | 0.54 | 1.14 | 0.21 |
| | West | 0.57 | 0.34 | 0.96 | 0.04 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Long-term use | 1.32 | 0.93 | 1.87 | 0.12 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 1.04 | 0.95 | 1.14 | 0.43 |
| | | | | | |
| Number of pain conditions | 0 | Reference | | | |
| | 1 | 6.00 | 3.13 | 11.47 | <0.0001 |
| | 2 | 6.09 | 3.13 | 11.85 | <0.0001 |
| | | | | | |
| Number of comorbid conditions | 0 | Reference | | | |
| | 1 | 0.95 | 0.63 | 1.43 | 0.81 |
| | 2 | 1.65 | 1.10 | 2.47 | 0.02 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 1.04 | 0.38 | 2.85 | 0.94 |
| | ICS+LABA+LAMA | 1.02 | 0.69 | 1.51 | 0.92 |
| | ICS or LABA or LAMA | 1.14 | 0.87 | 1.48 | 0.34 |

| Variable | | Incidence Rate Ratios | 95% Confidence Interval | | P value |
|---|---|---|---|---|---|
| | | | | | |
| **COPD severity indicators** | | | | | |
| Supplemental oxygen use in the pre-index period | No | Reference | | | |
| | Yes | 3.55 | 2.71 | 4.65 | <.0001 |
| | | | | | |
| SABA use in the pre-index period | No | Reference | | | |
| | Yes | 1.50 | 1.15 | 1.97 | 0.003 |
| | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | Reference | | | |
| | ≥1 | 2.21 | 1.45 | 3.37 | 0.0002 |
| | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | Reference | | | |
| | ≥1 | 1.45 | 1.09 | 1.94 | 0.01 |
| | | | | | |
| **Physician characteristics** | | | | | |
| Pulmonologist visit in the pre-index period | No | Reference | | | |
| | Yes | 1.09 | 0.84 | 1.43 | 0.51 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 0.79 | 0.57 | 1.11 | 0.18 |
| | >$9,838 | 0.56 | 0.37 | 0.87 | 0.009 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

respectively. Patients having ≥2 number of comorbid chronic conditions had 1.6 times (95% CI 1.10-2.47, $p=0.02$) higher rate of severe COPD exacerbations compared to patients who did not have any comorbid chronic conditions. Patients who had supplemental oxygen use had 3.55 times (95% CI 2.71-4.65, $p<0.0001$) higher rate of severe COPD exacerbations as patients who did not have any supplemental oxygen use in the pre-index period. Patients who had SABA use had 1.5 times (95% CI 1.15-1.97, $p=0.003$) higher rate of severe COPD exacerbations as patients who did not have any SABA use in the pre-index period. Patients who had high pre-index total healthcare costs (>$9,838) had 0.56 times (95% CI 0.37-0.8, $p=0.009$) lower rate of severe COPD exacerbations as patients who lowest pre-index total healthcare costs (<$2,844) in the pre-index period. Presence of pre-index COPD exacerbation either severe or moderate was associated with 2.21 times (95% CI 1.45-3.37, $p=0.0002$) and 1.45 times (95% CI 1.09-1.94, $p=0.01$) significantly higher rate of severe COPD exacerbations in the one-year follow-up compared to not having a pre-index severe or moderate COPD exacerbation, respectively.

**Results for Specific Aim 3B**

**Baseline characteristics as per Specific Aim 3B:**

Specific Aim 3B was to examine the impact of long-term prescription opioid use (≥90-day supply in a one-year period) compared to no prescription opioid use on the number of moderate and severe COPD exacerbations among a real-world, large sample of COPD patients after adjusting for other confounders. Table 37 provides baseline characteristics of the included sample of long-term and non-opioid users among COPD patients according to total moderate and severe COPD exacerbations in

### Table 37: Baseline characteristics for specific aim 3B

| Variable | | Total COPD exacerbations | No COPD exacerbations (n=4,881) | | Total COPD exacerbations (n=1,226) | | P value |
|---|---|---|---|---|---|---|---|
| | | mean (±sd) | N | Col % Row % | N | Col % Row % | |
| **Sociodemographic characteristics** | | | | | | | |
| Sex | Male | 0.29 (±0.84) | 2,296 | 47.0 | 508 | 41.4 | 0.0004 |
| | | | | 81.9 | | 18.1 | |
| | Female | 0.35 (±0.87) | 2,585 | 53.0 | 718 | 58.6 | |
| | | | | 78.3 | | 21.7 | |
| | | | | | | | |
| Age | *mean (±sd)* | | 57.0 years (±5.5) | | 57.9 years (±5.0) | | <0.0001 |
| | 40 – 49 years | 0.20 (±0.55) | 559 | 11.5 | 95 | 7.7 | <0.0001 |
| | | | | 85.5 | | 14.5 | |
| | 50 – 59 years | 0.32 (±0.86) | 2,270 | 46.5 | 554 | 45.2 | |
| | | | | 80.4 | | 19.6 | |
| | ≥60 years | 0.36 (±0.90) | 2,052 | 42.0 | 577 | 47.1 | |
| | | | | 78.1 | | 21.9 | |
| Metropolitan Statistical Area | Urban | 0.32 (±0.86) | 3,896 | 79.8 | 953 | 77.7 | 0.14 |
| | | | | 80.3 | | 19.7 | |
| | Rural | 0.34 (±0.85) | 964 | 19.8 | 265 | 21.6 | |
| | | | | 78.4 | | 21.6 | |
| | | | | | | | |
| Region | Northeast | 0.32 (±0.88) | 779 | 16.0 | 183 | 14.9 | 0.08 |
| | | | | 81.0 | | 19.0 | |
| | North Central | 0.35 (0.89) | 1,824 | 37.4 | 492 | 40.1 | |
| | | | | 78.8 | | 21.2 | |
| | South | 0.32 (±0.87) | 1,612 | 33.0 | 409 | 33.4 | |
| | | | | 79.8 | | 20.2 | |
| | West | 0.30 (±0.66) | 642 | 13.2 | 133 | 10.8 | |
| | | | | 82.8 | | 17.2 | |
| | | | | | | | |
| Insurance Plan Type | HMO | 0.32 (±0.85) | 780 | 16.0 | 191 | 15.6 | 0.67 |
| | | | | 80.3 | | 19.7 | |
| | PPO | 0.32 (±0.82) | 2,735 | 56.0 | 702 | 57.3 | |

| Variable | | Total COPD exacerbations | No COPD exacerbations (n=4,881) | | Total COPD exacerbations (n=1,226) | | P value |
|---|---|---|---|---|---|---|---|
| | | **mean (±sd)** | N | Col % Row % | N | Col % Row % | |
| | | | | 79.6 | | 20.4 | |
| | Other | 0.33 (±0.86) | 1,347 | 27.6 | 324 | 26.4 | |
| | | | | 80.6 | | 19.4 | |
| **Clinical characteristics** | | | | | | | |
| Prescription opioid use | No use | 0.31 (±0.82) | 4,465 | 91.5 | 1,076 | 87.8 | <0.0001 |
| | | | | 80.6 | | 19.4 | |
| | Long-term use | 0.50 (±1.14) | 416 | 8.5 | 150 | 12.2 | |
| | | | | 73.5 | | 26.5 | |
| | | | | | | | |
| Deyo-Charlson Comorbidity Index | *mean (±sd)* | | 1.7 (±1.2) | | 1.9 (±1.3) | | 0.0002 |
| | | | | | | | |
| Number of pain conditions | 0 | 0.16 (±0.50) | 1,461.00 | 29.9 | 200 | 16.3 | <0.0001 |
| | | | | 88.0 | | 12.0 | |
| | 1 | 0.36 (±0.85) | 2,033.00 | 41.7 | 598 | 48.8 | |
| | | | | 77.3 | | 22.7 | |
| | 2 | 0.43 (±1.07) | 1,387.00 | 28.4 | 428 | 34.9 | |
| | | | | 76.4 | | 23.6 | |
| | | | | | | | |
| Number of comorbid conditions | 0 | 0.24 (±0.70) | 1,166 | 23.9 | 222 | 18.1 | <0.0001 |
| | | | | 84.0 | | 16.0 | |
| | 1 | 0.27 (±0.73) | 1,917 | 39.3 | 420 | 34.3 | |
| | | | | 82.0 | | 18.0 | |
| | 2 | 0.42 (±1.02) | 1,798 | 36.8 | 584 | 47.6 | |
| | | | | 75.5 | | 24.5 | |
| | | | | | | | |
| Type of index maintenance medication | ICS+LABA | 0.28 (±0.71) | 2,592 | 53.1 | 596 | 48.6 | 0.03 |

| Variable | | Total COPD exacerbations | No COPD exacerbations (n=4,881) | | Total COPD exacerbations (n=1,226) | | P value |
|---|---|---|---|---|---|---|---|
| | | mean (±sd) | N | Col % Row % | N | Col % Row % | |
| | | | | 81.3 | | 18.7 | |
| | LAMA+LABA or LAMA+ICS | 0.53 (±1.08) | 49 | 1.0 | 17 | 1.4 | |
| | | | | 74.2 | | 25.8 | |
| | ICS+LABA+LAMA | 0.42 (±1.09) | 466 | 9.5 | 132 | 10.8 | |
| | | | | 77.9 | | 22.1 | |
| | ICS or LABA or LAMA | 0.36 (±0.95) | 1,774 | 36.3 | 481 | 39.2 | |
| | | | | 78.7 | | 21.3 | |
| | | | | | | | |
| Mail-order index maintenance medication prescription | No | 0.33 (±0.88) | 2,949 | 60.4 | 728 | 59.4 | 0.51 |
| | | | | 80.2 | | 19.8 | |
| | Yes | 0.32 (±0.80) | 1,932 | 39.6 | 498 | 40.6 | |
| | | | | 79.5 | | 20.5 | |
| | | | | | | | |
| Adherence to COPD-maintenance medications in the pre-index period | Non-adherent if PDC < 80% | 0.27 (±0.70) | 1,547 | 31.7 | 357 | 29.1 | 0.08 |
| | | | | 81.3 | | 18.8 | |
| | Adherent if PDC ≥ 80% | 0.35 (±0.91) | 3,334 | 68.3 | 869 | 70.9 | |
| | | | | 79.3 | | 20.7 | |
| | | | | | | | |
| **COPD severity indicators** | | | | | | | |
| Supplemental oxygen use in the pre-index period | No | 0.20 (±0.58) | 4,112 | 84.2 | 720 | 58.7 | <0.0001 |
| | | | | 85.1 | | 14.9 | |

| Variable | | Total COPD exacerbations | No COPD exacerbations (n=4,881) | | Total COPD exacerbations (n=1,226) | | P value |
|---|---|---|---|---|---|---|---|
| | | mean (±sd) | N | Col % Row % | N | Col % Row % | |
| | Yes | 0.78 (±1.40) | 769 | 15.8 | 506 | 41.3 | |
| | | | | 60.3 | | 39.7 | |
| | | | | | | | |
| SABA use in the pre-index period | No | 0.22 (±0.65) | 2,401 | 49.2 | 421 | 34.3 | <0.0001 |
| | | | | 85.1 | | 14.9 | |
| | Yes | 0.41 (±0.99) | 2,480 | 50.8 | 805 | 65.7 | |
| | | | | 75.5 | | 24.5 | |
| | | | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | 0.31 (±0.80) | 4,775 | 97.8 | 1,141 | 93.1 | <0.0001 |
| | | | | 80.7 | | 19.3 | |
| | ≥1 | 1.20 (±1.77) | 106 | 2.2 | 85 | 6.9 | |
| | | | | 55.5 | | 44.5 | |
| | | | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | 0.22 (±0.60) | 4,396 | 90.1 | 854 | 69.7 | <0.0001 |
| | | | | 83.7 | | 16.3 | |
| | ≥1 | 0.94 (±1.60) | 485 | 9.9 | 372 | 30.3 | |
| | | | | 56.6 | | 43.4 | |
| | | | | | | | |
| **Physician characteristics** | | | | | | | |
| Pulmonologist visit in the pre-index period | No | 0.29 (±0.80) | 3,625 | 74.3 | 853 | 69.6 | 0.0009 |
| | | | | 81.0 | | 19.0 | |
| | Yes | 0.41 (±0.98) | 1,256 | 25.7 | 373 | 30.4 | |
| | | | | 77.1 | | 22.9 | |

| Variable | | Total COPD exacerbations | No COPD exacerbations (n=4,881) | | Total COPD exacerbations (n=1,226) | | P value |
|---|---|---|---|---|---|---|---|
| | | **mean (±sd)** | N | Col % Row % | N | Col % Row % | |
| | | | | | | | |
| **Prior utilization characteristics** | | | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | *mean (±sd)* | | 7,397.7 (±13,872.3) | | 9,255.1 (±14,139.3) | | <0.0001 |
| | <$2,844 | 0.22 (±0.57) | 1,618 | 33.1 | 326 | 26.6 | <0.0001 |
| | | | | 83.2 | | 16.8 | |
| | $2,844 - $9,838 | 0.31 (±0.84) | 2,437 | 49.9 | 584 | 47.6 | |
| | | | | 80.7 | | 19.3 | |
| | >$9,838 | 0.54 (±1.19) | 826 | 16.9 | 316 | 25.8 | |
| | | | | 72.3 | | 27.7 | |

*sd denotes standard deviation; Col, column; HMO, health maintenance organization; PPO, preferred provider organization; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

a one-year follow-up period. Overall, 20.1% of the included sample of COPD patients experienced either a moderate or severe COPD exacerbation in a one-year follow-up period after the index date. A higher percentage of long-term prescription opioid users experienced a moderate or severe COPD exacerbation in a one-year follow-up compared to non-opioid users (26.5% vs 19.4%, $p<0.0001$). Long-term prescription opioid users had a higher mean number of moderate and severe COPD exacerbations compared to non-opioid users ($0.50\pm1.14$ vs $0.31\pm0.82$, $p=0.0003$). A higher percentage of females, patients older than 50 years, patients who used supplemental oxygen, had previous SABA use, had pre-index severe or moderate exacerbations, had visited a pulmonologist, and had higher baseline healthcare costs experienced a moderate or severe COPD exacerbation in one-year follow-up period. A higher proportion of patients who had comorbid conditions experienced a moderate or severe COPD exacerbation in one-year follow-up period than patients who did not have comorbid conditions. Patients who experienced a moderate or severe COPD exacerbation in a one-year follow-up had higher mean D-CCI scores compared to patients who did not experience a moderate or severe COPD exacerbation ($1.9 \pm 1.3$ vs $1.7 \pm 1.2$, $p=0.0002$). A higher percentage of patients who had comorbid chronic ($p>0.0001$) or comorbid pain conditions ($p>0.0001$) experienced a moderate or severe COPD exacerbation in one-year follow-up period compared to patients who did not have comorbid chronic or pain conditions.

**Negative binomial regression: Number of moderate and severe COPD exacerbations in one-year follow-up**

In the univariate negative binomial regression analysis, long-term prescription opioid users were found to have 1.36 times (95% CI, 1.15-1.62, $p=0.0004$) higher number of moderate and severe COPD exacerbations in one-year follow-up period. Age group, sex, metropolitan statistical area, comorbid pain and chronic conditions, type of index COPD maintenance medication, pulmonologist visit, D-CCI, cost quartile, pre-index maintenance medication adherence, supplemental oxygen use, SABA use, and pre-index moderate and severe exacerbation variables were found statistically significantly associated with number of moderate and severe COPD exacerbation in one-year follow up at $p<0.2$. These variables were included in the final adjusted multiple negative binomial regression analysis.

Table 38 presents the results of the final multiple negative binomial regression analysis model. After adjusting for other covariates, long-term prescription opioid use was not significantly associated with number of moderate and severe COPD exacerbations in one-year follow-up period (incidence rate ratio 1.12, 95% CI 0.93-1.35, $p=0.23$). Patients having 1 or ≥2 number of comorbid pain conditions had 1.53 times (95% CI 1.30-1.81, $p<0.0001$) and 1.51 times (95% CI 1.26-1.82, $p<0.0001$) higher rate of moderate and severe COPD exacerbations as patients who did not have any comorbid pain conditions, respectively. Patients having ≥2 number of comorbid chronic conditions had 1.34 times (95% CI 1.12-1.60, $p=0.002$) higher rate of moderate and severe COPD exacerbations as patients who did not have any comorbid chronic conditions. Patients who had supplemental oxygen use had 2.12 times (95% CI 1.87-2.41, $p<0.0001$) higher rate of moderate and severe COPD exacerbations as patients who did not have any supplemental oxygen use in the pre-index period. Patients who had SABA use had 1.35 times (95% CI 1.20-1.53, $p<0.0001$) higher rate of moderate and severe COPD exacerbations as patients who did not have any SABA use in the

**Table 38: Adjusted negative binomial regression: Number of moderate and severe COPD exacerbation in one-year follow-up**

| Variable | | Incidence Rate Ratios | Confidence Interval | | P value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Sex | Male | Reference | | | |
| | Female | 1.09 | 0.97 | 1.23 | 0.15 |
| | | | | | |
| Age | 40 – 49 years | Reference | | | |
| | 50 – 59 years | 1.14 | 0.91 | 1.42 | 0.25 |
| | ≥60 years | 1.22 | 0.98 | 1.53 | 0.08 |
| | | | | | |
| Metropolitan Statistical Area | Rural | Reference | | | |
| | Urban | 0.96 | 0.84 | 1.11 | 0.6 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Long-term use | 1.12 | 0.93 | 1.35 | 0.23 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.97 | 0.92 | 1.02 | 0.2 |
| | | | | | |
| Number of pain conditions | 0 | Reference | | | |
| | 1 | 1.53 | 1.30 | 1.81 | <.0001 |
| | 2 | 1.51 | 1.26 | 1.82 | <.0001 |
| | | | | | |
| Number of comorbid conditions | 0 | Reference | | | |
| | 1 | 1.07 | 0.91 | 1.27 | 0.4 |
| | 2 | 1.34 | 1.12 | 1.60 | 0.002 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 1.06 | 0.65 | 1.73 | 0.8 |
| | ICS+LABA+LAMA | 0.98 | 0.81 | 1.19 | 0.83 |
| | ICS or LABA or LAMA | 1.09 | 0.96 | 1.23 | 0.17 |
| | | | | | |
| **COPD severity indicators** | | | | | |
| Supplemental oxygen use in the pre-index period | No | Reference | | | |

| Variable | | Incidence Rate Ratios | Confidence Interval | | P value |
|---|---|---|---|---|---|
| | Yes | 2.12 | 1.87 | 2.41 | <.0001 |
| | | | | | |
| SABA use in the pre-index period | No | Reference | | | |
| | Yes | 1.35 | 1.20 | 1.53 | <.0001 |
| | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | Reference | | | |
| | ≥1 | 1.21 | 0.95 | 1.55 | 0.13 |
| | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | Reference | | | |
| | ≥1 | 2.03 | 1.78 | 2.32 | <.0001 |
| | | | | | |
| **Physician characteristics** | | | | | |
| Pulmonologist visit in the pre-index period | No | Reference | | | |
| | Yes | 0.94 | 0.83 | 1.07 | 0.36 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 0.85 | 0.73 | 0.98 | 0.02 |
| | >$9,838 | 0.82 | 0.68 | 0.99 | 0.04 |

* ICS denotes inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.
[a] adjusted to 2010 US $

pre-index period. Patients who had moderate ($2,844-$9,838) and high (>$9,838) pre-index total healthcare costs had 0.85 times (95% CI 0.73-0.98, p=0.02) and 0.82 times (95% CI 0.68-0.99, p=0.04) lower rate of moderate and severe COPD exacerbations as patients who lowest pre-index total healthcare costs (<$2,844) in the pre-index period. Patients who had pre-index moderate COPD exacerbation were associated with 2.03 times (95% CI 1.78-2.32, p<0.0001) higher rate of moderate and severe COPD exacerbations in the one-year follow-up compared to patients not having a pre-index moderate COPD exacerbation.

**Results for Specific Aim 4**

Specific Aim 4 was to examine the impact of long-term prescription opioid use (≥90-day supply in a one-year period) compared to no prescription opioid use on all-cause total healthcare costs (prescription medication and medical costs) among a real-world, large sample of COPD patients after adjusting for other confounders. Table 40 provides the unadjusted all-cause total healthcare costs for long-term prescription opioid users and non-opioid users. The unadjusted costs for long-term prescription opioid users were significantly higher than non-opioid users (p<0.0001).

In the unadjusted univariate regression analysis type of health insurance plan, number of comorbid pain and chronic conditions, type of index maintenance medication, whether mail-order index maintenance medication, D-CCI, visit to a pulmonologist, cost quartiles, age groups, pre-index adherence to maintenance medications, supplemental oxygen use, SABA use, and history of severe and moderate COPD exacerbations were found significant at p<0.20 and were included in the multiple regression analysis.

**Table 39: Unadjusted all-cause total healthcare costs for long-term prescription opioid users and non-opioid users**

| | Non-opioid user | Long-term opioid user | p-value |
|---|---|---|---|
| Mean (SD) | 14,686.09 (21,229.42) | 37,402.29 (40,537.40) | <0.0001 |
| Median (IQR) | 9,794 (10,283) | 24,501.50 (28,956) | <0.0001 |

Generalized linear model with a gamma distribution and a log link function was used to calculate adjusted all-cause total healthcare costs for long-term prescription opioid users and non-opioid users. The adjusted all-cause total healthcare costs were significantly higher for long-term prescription opioid users compared to non-opioid users [23,996 (1,106.22) vs 13,947 (512.67), p<0.0001]. Results of adjusted regression analysis for all-cause total healthcare costs are presented in Table 41.

**Table 40: Adjusted all-cause total healthcare costs using generalized linear model with a gamma distribution and log-link function**

| Variable | | Coefficient | Confidence Interval | | P value |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Sex | Male | Reference | | | |
| | Female | | | | |
| | | | | | |
| Age | 40 – 49 years | Reference | | | |
| | 50 – 59 years | 0.11 | 0.0468 | 0.1687 | 0.0005 |
| | ≥60 years | 0.14 | 0.0760 | 0.2011 | <0.0001 |
| | | | | | |
| Metropolitan Statistical Area | Rural | Reference | | | |
| | Urban | | | | |
| | | | | | |
| Insurance Plan Type | HMO | Reference | | | |
| | PPO | -0.01 | -0.0650 | 0.0375 | 0.60 |
| | Other | 0.06 | 0.0053 | 0.1191 | 0.03 |
| | | | | | |
| **Clinical characteristics** | | | | | |
| Prescription opioid use | No use | Reference | | | |
| | Long-term use | 0.57 | 0.5034 | 0.6345 | <0 0001 |
| | | | | | |
| Deyo-Charlson Comorbidity Index | | 0.11 | 0.0926 | 0.1285 | <0.0001 |
| | | | | | |
| Number of pain conditions | 0 | Reference | | | |
| | 1 | 0.18 | 0.1365 | 0.2261 | <0.0001 |
| | 2 | 0.32 | 0.2646 | 0.3679 | <0.0001 |
| | | | | | |
| Number of comorbid conditions | 0 | Reference | | | |
| | 1 | 0.15 | 0.1049 | 0.2003 | <0.0001 |
| | 2 | 0.40 | 0.3444 | 0.4540 | <0.0001 |
| | | | | | |
| Type of index maintenance medication | ICS+LABA | Reference | | | |
| | LAMA+LABA or LAMA+ICS | 0.24 | 0.0621 | 0.4104 | 0.008 |
| | ICS+LABA+LAMA | 0.01 | -0.0580 | 0.0680 | 0.88 |
| | ICS or LABA or LAMA | -0.00 | -0.0397 | 0.0379 | 0.96 |

| Variable | | Coefficient | Confidence Interval | | P value |
|---|---|---|---|---|---|
| | | | | | |
| Mail-order index maintenance medication | No | Reference | | | |
| | Yes | 0.10 | 0.0605 | 0.1376 | <0.0001 |
| | | | | | |
| **COPD severity indicators** | | | | | |
| Supplemental oxygen use in the pre-index period | No | Reference | | | |
| | Yes | 0.31 | 0.27 | 0.36 | <0.0001 |
| | | | | | |
| Adherent to maintenance medication in the pre-index period | No | Reference | | | |
| | Yes | 0.07 | 0.03 | 0.11 | 0.0006 |
| | | | | | |
| SABA use in the pre-index period | No | Reference | | | |
| | Yes | 0.05 | 0.01 | 0.08 | 0.009 |
| | | | | | |
| COPD-related severe exacerbations in the pre-index period | 0 | Reference | | | |
| | ≥1 | -0.26 | -0.37 | -0.15 | <0.0001 |
| | | | | | |
| COPD-related moderate exacerbations in the pre-index period | 0 | Reference | | | |
| | ≥1 | 0.02 | -0.03 | 0.08 | 0.38 |
| | | | | | |
| **Physician characteristics** | | | | | |
| Pulmonologist visit in the pre-index period | No | Reference | | | |
| | Yes | 0.04 | -0.0032 | 0.0807 | 0.07 |
| | | | | | |
| **Prior utilization characteristics** | | | | | |
| Total all-cause healthcare expenditures in the pre-index period[a] | <$2,844 | Reference | | | |
| | $2,844 - $9,838 | 0.33 | 0.2885 | 0.3728 | <0.0001 |

| Variable | | Coefficient | Confidence Interval | | P value |
|---|---|---|---|---|---|
| | >$9,838 | 0.76 | 0.698 | 0.8180 | <0.0001 |

* HMO denotes health maintenance organization; PPO, preferred provider organization; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; and PDC, proportion of days covered.

[a] adjusted to 2010 US $

# CHAPTER 5 DISCUSSION

This chapter provides a discussion on the findings of the study. Results of the study are discussed as per the specific aims. The discussion of the results is followed by the limitations of the study along with proposals on how future studies should be conducted based on the strengths and limitations of the current study. Finally, the implications and final conclusions of the study results are discussed.

## Discussion for Specific Aim 1

Prescription opioid users and non-users differed significantly in terms of their baseline characteristics prior to matching. The mean age of prescription opioid users was significantly lower than non-opioid users (Table 13), and a greater percentage of prescription opioid users were females. The variables sex, age, metropolitan statistical area (MSA), region, Deyo-Charlson Comorbidity Index (D-CCI), number of pain and chronic comorbid conditions, mail-order index maintenance medications, adherence to maintenance medications in the pre-index period, supplemental oxygen use, moderate COPD exacerbations, pulmonologist visits in the pre-index period and pre-index total all-cause healthcare expenditures were all statistically significantly different between prescription opioid users and non-users prior to matching (Table 13).

After matching, the matched variables, age, sex, adherence to maintenance medications in the pre-index period, supplemental oxygen use, SABA use, moderate and severe COPD exacerbations, and comorbid asthma were similar between prescription opioid users and non-users (Table 14). Most of the baseline characteristics were equally distributed between matched groups of prescription opioid users and non-users among COPD patients. However, there were certain important difference between prescription opioid users and non-users after matching. The significant difference between prescription opioid users and non-users in terms of the number of comorbid conditions persisted after matching. The mean D-CCI score among prescription opioid users was significantly higher compared to non-opioid users ($2.0 \pm 1.5$ vs $1.7 \pm 1.2$, $p<0.0001$) after matching (Table 14). Higher mean D-CCI score signifies that prescription opioid users had higher number of comorbid conditions at baseline compared to non-opioid users. Similarly, a significantly higher percentage of prescription opioid users had ≥1 comorbid chronic condition (82% vs 76.3%, $p<0.0001$) and ≥1 comorbid pain condition (86% vs 70.7%, $p<0.0001$) compared to non-opioid users. Higher mean number of comorbid conditions may signify that prescription opioid users were overall more complex patients and these differences may translate into poor health care outcomes such as higher healthcare resource utilization and its associated costs, and higher mortality as compared to non-opioid users. Significantly different variables between prescription opioid users and non-users, after matching, were considered in the multiple regression models for all specific aims to adjust for their impact on the study outcomes.

Specific Aim 1 was to examine the impact of prescription opioid use compared to no prescription opioid use on adherence to COPD maintenance medications, over four different time periods, among a real-world, large sample of COPD patients after adjusting for other confounders. Adherence to COPD maintenance medications was assessed over 90 days, 180 days, 270 days and 365 days follow-up periods.

Overall, 59.4% of the included matched sample of COPD patients were adherent (defined as PDC ≥0.8) to their COPD maintenance medications in the 90-day follow-up period after the index date. However, as the follow-up period increased from 90 days up to 365 days the number of people adherent to their COPD maintenance medications decreased. Nearly half (50.9%) of the included matched sample of COPD patients were adherent to their COPD maintenance medications in the 180-day follow-up period after the index date. In the 270-day follow-up period, this number decreased to less than half (47.3%) of the included matched sample of all COPD patients. About 54% of the included matched sample of COPD patients were found to be non-adherent to COPD maintenance medications in the 365-day follow-up period after the index date which is high, however not surprising. This means that about 54% of COPD patients were not receiving optimal long-term controller medication therapy to manage their COPD symptoms. Previous studies have reported that about 60% of COPD patients exhibit poor adherence to COPD treatment and even more do not use their inhalers correctly[46–48,143,144]. Thus, the high non-adherence to controller medication among COPD patients observed in the current study is comparable to previous studies among COPD patients. Also, COPD patients commonly have chronic comorbidities which may lower the adherence to COPD maintenance medications[8,44,45]. Similarly, in the current study about 79% of the overall COPD patients had at least one comorbid chronic condition.

In the current study, prescription opioid users were found to have lower adherence to COPD maintenance medications compared to non-opioid users in all the four follow-up time periods (Table 41) and the differences were statistically significant. As the follow-up time increased from 90 days up to 365 days the adherence levels decreased for both prescription opioid users and non-opioid users. When prescription

**Table 41: Adherence to COPD maintenance medications among prescription opioid users and non-opioid users among COPD patients in the four different follow-up periods**

| | Adherent to COPD Maintenance Medications (PDC≥0.8) | | |
|---|---|---|---|
| **Follow-up period** | **Prescription opioid user (n=5,541)** | **Non-opioid user (n=5,541)** | **P-Value** |
| *90-day follow-up period* | 49.2% | 69.5% | **<0.0001** |
| *180-day follow-up period* | 45.3% | 56.6% | **<0.0001** |
| *270-day follow-up period* | 43.3% | 51.2% | **<0.0001** |
| *365-day follow-up period* | 42.1% | 49.7% | **<0.0001** |

opioid use was further classified as >30-day supply of prescription opioids and ≤30-day supply of prescription opioids (sub-group analyses), the adherence levels for both the groups of prescription opioid users remained lower than non-opioid users in all the four follow-up time periods (Table 42). The classification of prescription opioid use as >30-day supply and ≤30-day supply has been utilized in a previously published peer-review study conducted among a sample of VA patients[145].

In the multivariate regression analyses, prescription opioid users were found to have significantly lower odds of being adherent to their COPD maintenance medications in the 90-day follow-up period as compared to non-opioid users, independent of other predictors. This association remained significant when other follow-up times were assessed as well (Table 43). Similar results were observed in the sub-group analyses for Specific Aim 1 where use of prescription opioids was further classified as > 30-day supply of prescription opioids and ≤ 30-day supply of prescription opioids (Table 44).

Although we matched prescription opioid users and non-opioid users on various confounders reported in Table 10, it is important to consider that there were certain baseline characteristics that varied significantly between prescription opioid users and non-opioid users. Prescription opioid users and non-opioid users differed significantly on the presence of baseline comorbidities. Overall, a higher percentage of prescription opioid users were found to have comorbidities as compared to non-opioid users. The mean D-CCI score among prescription opioid users was significantly higher compared to non-opioid users (2.0 ± 1.5 vs 1.7 ± 1.2, $p<0.0001$). Significantly different baseline characteristics between prescription opioid users and non-users among COPD patients

**Table 42: Adherence to COPD maintenance medications among prescription opioid users and non-opioid users among COPD patients in the four different follow-up periods as per Specific Aim 1 sub group analyses**

| | **Adherent to COPD Maintenance Medications (PDC≥0.8)** | | | |
|---|---|---|---|---|
| **Follow-up period** | **≤ 30-day supply of prescription opioids** | **> 30-day supply of prescription opioids** | **Non-opioid user** | **P-Value** |
| *90-day follow-up period* | 49.1% | 50.2% | 69.5% | **<0.0001** |
| *180-day follow-up period* | 45.2% | 45.7% | 56.6% | **<0.0001** |
| *270-day follow-up period* | 43.3% | 43.4% | 51.2% | **<0.0001** |
| *365-day follow-up period* | 42.3% | 41.4% | 49.7% | **<0.0001** |

**Table 43: Summary of the logistic regression results of the odds of being adherent to COPD maintenance medications among prescription opioid users and non-opioid users among COPD patients in the four different follow-up periods**

| **Prescription Opioid use** | **Point estimate** | **95% Confidence interval** | **P-Value** |
|---|---|---|---|
| No Use | Reference | | |
| Use in the following periods: | | | |
| *90-day follow-up period* | 0.29 | (0.26 – 0.37) | **<0.0001** |
| *180-day follow-up period* | 0.55 | (0.50 – 0.61) | **<0.0001** |
| *270-day follow-up period* | 0.66 | (0.60 – 0.73) | **<0.0001** |
| *365-day follow-up period* | 0.69 | (0.63 – 0.76) | **<0.0001** |

*Adjusted for other covariates

**Table 44: Summary of the logistic regression results of the odds of being adherent to COPD maintenance medications among prescription opioid users and non-opioid users among COPD patients in the four different follow-up periods as per Specific Aim 1 sub group analyses**

| **Prescription Opioid use** | | **Point estimate** | **95% Confidence interval** | **P-Value** |
|---|---|---|---|---|
| No Use | | Reference | | |
| Use in the following periods: | | | | |
| *90-day follow-up period* | *≤ 30-day supply of prescription opioids* | 0.30 | (0.26 – 0.34) | **<0.0001** |
| | *> 30-day supply of prescription opioids* | 0.32 | (0.23 – 0.44) | **<0.0001** |
| *180-day follow-up period* | *≤ 30-day supply of prescription opioids* | 0.55 | (0.50 – 0.61) | **<0.0001** |
| | *> 30-day supply of prescription opioids* | 0.58 | (0.46 – 0.72) | **<0.0001** |
| *270-day follow-up period* | *≤ 30-day supply of prescription opioids* | 0.66 | (0.59 – 0.73) | **<0.0001** |
| | *> 30-day supply of prescription opioids* | 0.68 | (0.56 – 0.83) | **0.0001** |
| *365-day follow-up period* | *≤ 30-day supply of prescription opioids* | 0.69 | (0.62 – 0.77) | **<0.0001** |
| | *> 30-day supply of prescription opioids* | 0.71 | (0.59 – 0.85) | **0.0003** |

*Adjusted for other covariates

were adjusted in the multivariate regression analyses.

Similarly, a significantly higher percentage of prescription opioid users had ≥1 comorbid chronic condition (82% vs 76.3%, p<0.0001) and ≥1 comorbid pain condition (86% vs 70.7%, p<0.0001) compared to non-opioid users. Having a higher number of comorbid chronic conditions and specifically pain conditions could translate into higher need for prescription opioids to alleviate pain among these patients. In the 2015 Medicare Payment Advisory Commission report, the committee reported that concurrent use of prescription opioids may have adverse effects including unintentional overdoses which may interfere with treatment of comorbid conditions[146]. Along with having a high number of comorbid conditions and use of prescription opioids for treatment of pain conditions the use of prescription opioids may translate into lower adherence among COPD patients using prescription opioids as observed in this study.

In summary, concurrent prescription opioid use among COPD patients using maintenance medications was found to be associated with lower medication adherence to COPD-related maintenance medications compared to non-opioid users. This association was significant in all the four follow-up time periods (90 days, 180 days, 270 days, and 365 days).

**Discussion for Specific Aim 2**

Specific Aim 2 was to examine the impact of long-term prescription opioid use (≥90-day supply in a one-year period) compared to no prescription opioid use on adherence to COPD maintenance medications among a real-world, large sample of COPD patients after adjusting for other confounders. For Specific Aims 2 to 4, only long-term prescription opioid users among COPD patients were included in the analyses, and COPD patients with <90-day supply of prescription opioids in a one-year follow-up period were excluded. The control group of non-opioid users among COPD patients however, remained the same.

Although long-term prescription opioid users had similar characteristics as overall prescription opioid users among COPD patients there were certain characteristics which differed between long-term prescription opioid users and non-opioid users which were not significantly different in the matched sample of overall prescription opioid users and non-opioid users. Supplemental oxygen use, SABA use and severe COPD exacerbations in the pre-index period which were similar between overall prescription opioid users and non-opioid users among COPD patients were however, significantly different between long-term prescription opioid user and non-opioid users among COPD patients (Table 31). A higher percentage of long-term prescription opioid users had supplemental oxygen use (28.1% vs 20.1%, $p<0.0001$), SABA use (59% vs 53.3%, $p=0.009$), and severe COPD exacerbations (5.3% vs 2.9%, $p=0.002$) compared to non-opioid users among COPD patients.

Similar to any prescription opioid users, long-term prescription opioid users had a significantly higher number of mean comorbid conditions compared to non-opioid users. The mean D-CCI score among long-term prescription opioid users was significantly higher compared to non-users of prescription opioids ($2.4 \pm 1.8$ vs $1.7 \pm 1.2$, $p<0.0001$). Similarly, a higher proportion of long-term prescription opioid users had presence of one or more comorbid chronic conditions (86.6% vs 76.3%, $p<0.0001$) and comorbid pain conditions (93.5% vs 70.7%, $p<0.0001$).

Similar to any prescription opioid users in Specific Aim 1, a smaller percentage of long-term prescription opioid users were adherent to their COPD maintenance medications as compared to non-opioid users (42.6% vs 49.7%, p=0.001) (Table 32). Long-term prescription opioid users were found to have 0.63 times (95% CI 0.46-0.88, p=0.005) significantly lower odds of being adherent to their COPD maintenance medications in one-year follow-up period as compared to non-opioid users, independent of other predictors (Table 34).

Rose A et al, 2009 conducted a study among patients with diabetes mellitus to assess the impact of chronic prescription opioid use versus no use of prescription opioids on clinical end-points associated with treatment of diabetes[147]. Older diabetes patients were identified from the Veteran Affairs (VA) Medicare database from 2004. The authors defined chronic prescription opioid use as ≥ 6 fills of prescription opioid in a one-year period. Rose A and colleagues reported that diabetes patients using prescription opioids on a chronic basis had 0.90 (95% CI, 0.84 – 0.96) significantly lower odds of having glycosylated hemoglobin (A1C) control compared to diabetes patients who had not received any prescription opioids[147]. Similarly, the odds of low-density lipoprotein cholesterol (LDL-C) control was also statistically significantly lower (OR 0.87; 95% CI, 0.82 – 0.94) among diabetes patients using prescription opioids on a chronic basis compared to diabetes patients not using prescription opioids. The authors believed that diabetes patients concurrently using prescription opioids on a chronic basis are likely to be distracted and concerned about their use of prescription opioids which may affect their diabetes performance[147]. Their reasoning was based on a previous study by Krein et al which showed that presence of chronic pain among patient with diabetes may distract them from adhering to medications[148]. Although Rose A et al, 2009 study did not assess the impact of prescription opioid use on adherence to diabetes medications, the association of long-term prescription opioid use and poor medication adherence among COPD patients, as observed in the current study, may likely be explained by distraction due to prescription opioid use as proposed by Krein et al and Rose A et al[147,148].

Jeevanjee S and colleagues conducted a study to identify the association between prescription opioid use and misuse and adherence to antiretrovirals (ARV) among HIV-infected patients[149]. The authors interviewed 258 HIV-infected patients and classified opioid use as self-reported use of physician prescribed opioids and further identified misuse of prescription opioids. Adherence to ARVs was reported in the 7 days before the study interview. The authors reported that receipt of prescription opioids among HIV-infected patients was not significantly associated with adherence to ARVs. However, misuse of prescription opioids was associated with statistically significantly higher odds (OR 1.47; 95% CI 1.06 – 2.03; p 0.022) of suboptimal adherence to ARVs[149]. It is important to consider that study was conducted among lower income HIV patients recruited from homeless shelters, free meal program and single room occupancy hotels. Medication adherence was reported and measure over a period of 7 days. The current study was conducted among commercially insured patients enrolled in employer sponsored healthcare plans and adherence to COPD maintenance medications was assessed over 365-day follow-up period after the initiation of prescription opioids. Due to the administrative claims nature of the data utilized in the current study prescription opioid misuse could not be assessed. Also, patients are more likely to misuse prescription opioids when taken on a long-term basis as assessed in the current study[27]. COPD patients taking prescription opioids on a long-term basis may likely misuse prescription opioids which may explain the non-adherence to COPD maintenance medications observed in the study.

Although there is established validity for the use of prescription opioids acutely, there is little evidence for their use on a long-term basis for conditions other than cancer[12–15]. A Cochrane literature review of studies assessing safety, efficacy and effectiveness of long-term prescription opioid use in chronic non-cancer pain (CNCP) patients reported that there was very limited evidence for clinically meaningful amount of alleviation of pain associated with long-term use of prescription opioids[13]. Despite lacking evidence for effectiveness, the use of prescription opioids on a long-term basis is highly prevalent in the US population. Overall, about 11 million people in 2005 were prescribed long-term prescription opioid therapy[17]. In the current study, a total of 566 COPD patients on maintenance medications were classified as long-term prescription opioid users, representing 10.2% of all matched COPD prescription opioid users. Vozoris et al, 2016 have warned that COPD patients using prescription opioids may suffer from adverse respiratory effects from opioid use expressed through various mechanisms such as “respiratory depression, reduced mucous clearance through cough suppression, and immunosuppressive effects”[64].

In the current study long-term use of prescription opioids was found to be significantly associated with lower adherence to COPD maintenance medications, independent of other factors. This association could be explained due to various theories mentioned above. Use of prescription opioids on a long-term basis may distract patients from adhering to COPD maintenance medications as hypothesized by Krein et al and Rose A et al among diabetes patients using prescription opioids[147,148]. COPD patients taking prescription opioids on a long-term basis may likely misuse prescription opioids, as reported by Jeevanjee S et al among HIV patients, which may explain the non-adherence to COPD maintenance medications observed in the study[149]. Also, COPD patients taking prescription opioids on a long-term basis may suffer from adverse respiratory effects from opioid use expressed through various mechanisms such as "respiratory depression, reduced mucous clearance through cough suppression, and immunosuppressive effects" which may impact their medication adherence[64]. As this is the first study to assess the impact of prescription opioid use and long-term prescription opioid use on adherence to COPD maintenance medications among a sample of COPD patients, future studies are needed to replicate the methods from the current study in other COPD populations to test the reproducibility of the results in other COPD patient populations.

**Discussion for Specific Aim 3**

Specific Aim 3 was to examine the impact of long-term prescription opioid use (≥90-day supply in a one-year period) compared to no prescription opioid use on COPD exacerbations among a real-world, large sample of COPD patients after adjusting for other confounders. Only about 4.3% (n=265) of the included sample of COPD patients using maintenance medications in specific aim 3 experienced a severe COPD exacerbation in a one-year follow-up period. About 20.1% (n=1,226) of the overall sample of COPD patients using maintenance medications experienced either a severe or moderate COPD exacerbation in a one-year follow-up period. The low rates of COPD exacerbations observed in the current study are comparable to rates reported in published studies. A study by Stanford RH and colleagues in 2016 which used a similar set of criteria for identification of severe and moderate COPD exacerbations as the current study, found incidence of COPD exacerbation rates similar to rates found in the current study[140]. About 13.8% of COPD patients were classified as having one or more moderate COPD exacerbations and 8.5% were classified as having one or more severe COPD exacerbation in a one-year follow-up period[141]. Patients having either a moderate or severe COPD exacerbations were 22.3% in the Stanford RH et al study compared to 20.1% in this study[140].

The mean number of severe exacerbations in the overall sample of COPD patients using maintenance medications was 0.05 (± 0.28) in a one-year follow-up period. When both severe and moderate exacerbations were measured the mean increased to 0.20 (± 0.40). It is however, important to consider that many COPD exacerbations experienced by COPD patients cannot be captured when using secondary datasets such as administrative claims which require patients to have an interaction with the healthcare system. Studies in the past have shown that nearly 50% of COPD exacerbations go unreported as COPD patients may not always interact with healthcare systems when experiencing exacerbations of their COPD symptoms[147,148]. These unreported exacerbations are identified only when assessment of patients' recording of COPD symptoms in daily diaries are analyzed[143]. Wedzicha J, et al 2003 suggest that COPD patients commonly experience changes in symptoms, and along with having comorbid symptoms of depression and anxiety COPD patients accept their symptoms as part of their disease and do not seek treatment[147–150] Previously published studies have reported the mean rate of exacerbations among COPD patients to range from 0.6 to 3.0 annually [148,151–153]. However, these studies varied from the current study on various parameters such as patients maintaining a daily diary to report symptoms, studies including mostly older COPD patients >65 years old, and combining mild, moderate and severe COPD exacerbations, utilization of various methods of classifying exacerbations, variable follow-up times, and study samples belonging to various countries.

A significantly higher percentage of long-term prescription opioid users experienced severe exacerbations (8% vs. 4%, $p<0.0001$; Table 35) in a one-year follow-up period compared to non-opioid users. Long-term prescription opioid users also had a higher mean number of severe COPD exacerbation compared to non-opioid users ($0.11 \pm 0.41$ vs $0.05 \pm 0.26$, $p<0.001$; Table 35). Similarly, a significantly higher percentage of long-term prescription opioid users experienced either a severe or moderate exacerbation (26.5% vs 19.4%, $p<0.0001$; Table 37) in a one-year follow-up period compared to non-opioid users. Long-term prescription opioid users also had a significantly higher mean number of moderate and severe COPD exacerbations compared to non-opioid users ($0.50\pm1.14$ vs $0.31\pm0.82$, $p=0.0003$; Table 37).

After adjusting for confounders, the impact of long-term prescription opioid use on the number of the severe COPD exacerbations in a one-year follow-up period was not found to be significant (Table 36). The non-significant result persisted when the sum of moderate and severe COPD exacerbations was evaluated (Table 38). In separate analysis the impact of long-term prescription opioid use versus no use was assessed on the likelihood of having a severe COPD exacerbation and either moderate or severe

COPD exacerbation using conditional logistic regression analysis (not reported here). The non-significant results from Specific Aims 3A and 3B persisted in the conditional logistic regression analysis. History of COPD exacerbations has been established as a significant predictor of future COPD exacerbations[79]. After adjusting for the effect of pre-index COPD exacerbations the impact of long-term prescription opioid use was not significant on adherence to COPD controller medications.

Vozoris N et al, 2016 conducted a study to identify the impact of prescription opioid use on adverse respiratory outcomes, including exacerbations, among COPD patients[64]. Vozoris N et al, 2016 study reported no significant association between incident prescription opioid use and COPD-related hospitalizations (hazard ratio 1.08, 95% CI 1.00 – 1.29; p=0.15), which translate into severe COPD exacerbations in the current study. Similarly, in the current study long-term use of prescription opioids was not significantly associated with severe COPD exacerbations (Table 36). However, the authors found that incident prescription opioid use was associated with decreased outpatient COPD exacerbations (hazard ratio 0.88, 95% CI 0.83 – 0.94; p<0.001). When the analysis was conducted among users of more potent opioid-only agents, the use of opioids was associated with significantly increased outpatient COPD exacerbations (hazard ratio 1.27, 95% CI 1.14 – 1.41; p<0.0001). The current study combined moderate and severe COPD exacerbations in Specific Aim 3B and found no association between long-term prescription opioid use and the sum of severe and moderate COPD exacerbations.

There are however various differences between the current study and the Vozoris N et al, 2016 study which should be considered when comparing the results from the two studies. Vozoris N et al, 2016 measured only outpatient COPD exacerbations which corresponds to moderate COPD exacerbations in the current study. However, in the current study emergency room visits were also included in the classification of moderate COPD exacerbations whereas Vozoris N et al, 2016 excluded emergency COPD visits in the classification of outpatient COPD exacerbations. In the current study moderate COPD exacerbation were not assessed stand-alone as an outcome variable, as in the Vozoris N et al, 2016 study, but were combined with severe COPD-exacerbations. In the Vozoris N et al, 2016 study outpatient COPD exacerbations and COPD-related hospitalizations were measured only within 30 days of incident prescription opioid use compared to the current study in which COPD exacerbations were measured in a one-year follow-up period. The Vozoris N et al, 2016 study was conducted only among older COPD patients above 65 years old (mean age 77.0 ± 7.0 years) whereas the current study included COPD patients between 40 to 64 years old (mean age 57.2 ± 5.4 years). The Vozoris N et al, 2016 study was conducted among a sample of Canadian COPD patients whereas the current study included COPD patients residing the US.

In summary, the current study did not find any association between long-term prescription opioid use and severe and moderate COPD exacerbations among COPD patients, after adjusting for other confounders.

**Discussion for Specific Aim 4**

Specific Aim 4 was to examine the impact of long-term prescription opioid use (≥90-day supply in a one-year period) compared to no prescription opioid use on all-cause total healthcare costs (prescription medication and medical costs) among a real-world, large sample of COPD patients after adjusting for other confounders. The adjusted mean all-cause total healthcare costs were significantly higher for long-term prescription opioid users compared to non-opioid users [$23,996 (± $1,106.22) vs. $13,947 (± $512.67), p<0.0001] (Table 40).

The adjusted prescription drug costs among long-term prescription opioid users was statistically significantly higher [$7,782 (± $301) vs. $6,686 (± $205), p<0.0001] compared to non-opioid users. The higher adjusted prescription drug costs among long-term prescription opioid users despite having statistically significantly lower medication adherence to COPD maintenance medications compared to non-opioid users is not surprising. Long-term prescription opioid users had significantly higher mean number of comorbid medical conditions as compared to non-opioid users. With higher mean comorbid conditions, long-term prescription opioid users may fill higher number of prescriptions attributed to conditions other than COPD. Also, the costs associated with using prescription opioids may be reflected in the higher total prescription drug costs among long-term prescription opioid users. The significantly higher all-cause total healthcare costs among long-term prescription opioid users as compared to non-opioid users is likely driven by higher total medical costs (sum of costs associated with inpatient, outpatient and emergency room visits). The adjusted total medical costs among long-term prescription opioid users was statistically significantly higher [$15,684 (± $1,197) vs. $6,679 (± $401), p<0.0001] compared to non-opioid users.

This is the first study to assess the impact of prescription opioid use on healthcare costs among patients with COPD. It is important to consider that the current study assessed all-cause total healthcare costs among COPD patients. This higher all-cause total healthcare costs among COPD patients may be related to higher healthcare resource utilization associated with management of COPD or higher healthcare utilization associated with management of other comorbid conditions among COPD patients. The current study however, did not assess COPD-related costs independently, but rather assessed all-cause total healthcare costs. It was found that long-term prescription opioid users had significantly higher number of mean comorbid conditions compared to non-opioid users (Table 31). The mean D-CCI score among long-term prescription opioid users was significantly higher compared to non-users of prescription opioids ($2.4 \pm 1.8$ vs $1.7 \pm 1.2$, $p<0.0001$). Similarly, a higher proportion of long-term prescription opioid users had presence of one or more comorbid chronic conditions (86.6% vs 76.3%, $p<0.0001$) and comorbid pain conditions (93.5% vs 70.7%, $p<0.0001$). D-CCI score, number of comorbid conditions and number of comorbid pain conditions were all significantly associated with higher all-cause total healthcare costs among COPD patients in the generalized linear model with a gamma distribution and log-link function (Table 40). These differences in the presence of comorbidities among long-term prescription opioid users and non-opioid users could translate into higher all-cause total healthcare costs among COPD patients.

In summary, long-term prescription opioid use was significantly associated with all-cause total healthcare costs among COPD patients, after adjusting for other confounders. Long-term prescription opioid use may be associated with higher all-cause total healthcare costs among COPD patients. As this is the first study to assess the impact of long-term prescription opioid use on healthcare costs among COPD patients, future studies are needed to provide evidence on the reproducibility of these results among similar or different population of COPD patients.

**Study limitations**

Limitations associated with the use of administrative claims database are applicable to this study[157]. Medication adherence when assessed using administrative claims data is unable to ascertain whether the patient is taking the right prescribed quantity of dose or whether the doses were taken in a timely prescribed manner. Patients may refill their prescriptions on time but may be non-adherent to their regimen by not taking their medications as prescribed and this is not captured in the analysis. However, filling a prescription is a necessary step which leads to utilization of the prescribed drug and PDC has been utilized on a wide scale by researchers, and validated and recommended by the Pharmacy Quality Alliance (PQA) and the National Quality Forum (NQF) as a measure of medication adherence[121].

Just observing a refill of a prescription in an administrative claims data may not be a good indicator of medication adherence. Patients in the study may also have other sources of acquiring medications which may not be captured by the dataset. Including only patients who have a prescription fill for a COPD maintenance medication has the potential to exclude patients who do not fill any prescribed maintenance medications, thus missing on important non-adherent patients. When a patient discontinues a therapy for COPD maintenance medication, it is possible that the patient discontinued the therapy due to physician’s recommendations, however according to the PDC method the patient is assumed to be non-adherent.

Many factors may have an impact on medication adherence such as social support, perceived susceptibility to adverse events and others; however, these factors are not captured in the dataset and thus cannot be adjusted for their impact on medication adherence. Medication adherence is also impacted by the severity of a disease[158,159]. Proxy values for the severity of COPD such as history of COPD-related moderate or severe exacerbations, use of short acting beta agonists, oral corticosteroids, and oxygen therapy were used in the analyses. These measures although predictive of future COPD exacerbation and health care utilization may not always accurately predict the level of airflow limitation and may be subject to measurement bias. As administrative datasets do not capture clinical information, spirometry information cannot be measured and therefore COPD exacerbations history are used as proxy measures for COPD symptom severity.

An important limitation of the study relates to the inability to identify diagnosis associated with the use of prescription opioids among COPD patients. COPD patients who use prescription opioids for chronic non-cancer pain (CNCP) may have significantly different characteristics compared to patients using prescription opioids for dyspnea or patients using opioids for acute pain conditions. Although, baseline characteristics were adjusted in the multiple regression analyses there may be certain unobservable factors such as diet, exercise, smoking status, not captured due to the administrative claims nature of the Truven MarketScan Commercial Claims and Encounters database which may introduce bias in the studied outcomes.

Certain factors are related to the use of prescription opioids such as the daily dosage of prescription opioids measured using morphine equivalent dosing, use of either long-acting or short-acting prescription opioids, and long-term or short-term use of prescription opioids. As these factors are exclusively applicable only to patients who use prescription opioids and not applicable to non-opioid users, they cannot be adjusted for in the analyses as they are not present in the unexposed group (non-opioid users) of COPD patients.

A major limitation of the study is based on the lack of a method to identify adverse drug-related behaviors (ADRB) using administrative claims data. One of the rationales for the study is associated with the idea that the use of prescription opioids has an ability to induce psychological behaviors such as ADRB. ADRB may influence the patients to rely heavily on prescription opioids to provide immediate symptoms relief and possibly overlook the use of long-term maintenance medications for COPD. However, identification of ADRB is challenging with the use of administrative claims data. Although ADRB could not be identified in the study a previously published study has provided evidence that patients taking prescription opioids both on a long-term and acute basis have a statistically significantly higher likelihood of developing ADRB[27]. Future studies may look at identifying ADRB and their effect on medication adherence and healthcare resource utilization among patients with COPD.

The study only includes information on privately insured patients in the age range of 40 to 64 years. The results of the study are only generalizable to the study population. The results of the study therefore may not applicable to patients who are not privately insured such as patients with Medicare, Medicaid, or patients without any health insurance coverage, or patients below 40 years of age or older patients 65 years of age and above. Middle-aged patients as included in the current study are more likely to be employed than older patients. Use of prescription opioids among employed patients may limit their ability to work and therefore these patients may likely use more discretion when using prescription opioids. As older patients are more likely to be retired then middle-aged patients the use of prescription opioids among this population may be different.

**Future research**

Future research could benefit by improving on the limitations of the study highlighted above. Future research could develop methods to identify the presence of adverse drug related behaviors (ADRB) associated with the use of prescription opioids. ADRB could impact patients' behaviors associated with prescription opioid use and may mediate the effect of the use of prescription opioids on adherence to COPD maintenance medications and total all-cause healthcare costs.

Future studies could also benefit by identifying the reasons (diagnosis) or indications for which opioids were prescribed. For example, patients using prescription opioids for acute pain or pain associated with post-surgical procedures may exhibit different characteristics than patients who receive prescription opioids for chronic non-cancer pain (CNCP) conditions. Stratified analyses in these different groups of patients may help explain whether the impact of prescription opioid use on adherence to maintenance medications and total all-cause healthcare costs persists in both the groups of patients.

Future studies could also assess characteristics associated with the use of prescription opioids such as the daily dosage of prescription opioids measured using morphine equivalent dosing, use of either long-acting or short-acting prescription opioids, and combination or opioid only agents. Quantifying prescription opioids in these categories may help facilitate a better picture of the association of prescription opioid use and adherence to COPD maintenance medications among COPD patients.

Future research could also assess if the use of prescription opioids has an impact of healthcare resource utilization such as inpatient visits, emergency room visits, and outpatient visits associated with COPD. Such analyses could help better identify the impact of prescription opioid use on healthcare resource utilization and could facilitate in quantifying the burden of prescription opioid use among COPD patients.

Since the results of the current study are generalizable only to privately insured patients in the age range of 40 to 64 years, future studies could replicate the study among older COPD patients and also among patients belonging to other healthcare plans such as Medicare Medicaid, and also uninsured COPD patients.

As this is the first study to assess the impact of prescription opioid use on adherence to COPD maintenance medications, COPD exacerbation, and total all-cause healthcare costs among COPD patients, future studies are needed to provide evidence on the reproducibility of these results among similar or different population of COPD patients.

**Study implications and conclusions**

The results of the study show that the use of prescription opioids among patients with COPD is significantly associated with lower adherence to COPD maintenance medications. This finding suggests improving the management of COPD patients to address non-adherence to maintenance therapy. Although the study results did not find prescription opioid use to have an impact on moderate or severe COPD exacerbations the impact of prescription opioid use on healthcare resource utilization such as inpatient visits, emergency room visits, and outpatient visits was not studied, and future research could help identify such impact. Also, the study results indicate higher healthcare costs for the management of COPD patients concurrently taking prescription opioids. Proper identification and management of prescription opioid therapy along with efforts to improve COPD-related adherence could potentially decrease the total healthcare costs of management of COPD patients.

Early identification of concurrent prescription opioid use and management of poor adherence to maintenance medications for COPD may lead to improved COPD symptoms and lower total healthcare costs. For COPD patients taking maintenance medications, identification of concurrent prescription opioid use might be an effective gauge of potential poor medication adherence in the future and may advocate for improved surveillance and management to attain optimum medication adherence. The results from the study could facilitate designing effective interventions that would help reduce non-adherence to maintenance medications for COPD and further help control total healthcare costs leading to better allocation of limited healthcare resources among COPD patients. The results of the current study could encourage future research to identify the effects of concurrent prescription opioid use on adherence to medications for other chronic conditions.

# References

1. GOLD 2017 Global Strategy for the Diagnosis, Management and Prevention of COPD [Internet]. Glob. Initiat. Chronic Obstr. Lung Dis. - GOLD. [cited 2016 Dec 20];Available from: http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/

2. Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. J Glob Health 2015;5(2):020415.

3. Lopez AD, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006;27(2):397–412.

4. World Health Organization. Projections of mortality and causes of death 2015 and 2030 [Internet]. WHO. [cited 2016 Dec 20];Available from: http://www.who.int/healthinfo/global_burden_disease/projections/en/

5. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Lond Engl 2015;385(9963):117–71.

6. American Lung Association. COPD [Internet]. Am. Lung Assoc. [cited 2017 Jan 16];Available from: http://www.lung.org/lung-health-and-diseases/lung-disease-lookup/copd/

7. CDC Features - Increase expected in medical care costs for COPD [Internet]. 2017 [cited 2017 Oct 20];Available from: http://www.cdc.gov/Features/ds-copd-costs/

8. Mannino DM, Higuchi K, Yu T-C, et al. Economic Burden of COPD in the Presence of Comorbidities. Chest 2015;148(1):138–50.

9. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. J Pain 2015;16(8):769–780.

10. Tsang A, Von Korff M, Lee S, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. J Pain 2008;9(10):883–891.

11. Daubresse M, Chang H-Y, Yu Y, et al. Ambulatory diagnosis and treatment of non-malignant pain in the United States, 2000–2010. Med Care [Internet] 2013 [cited 2016 Dec 19];51(10). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3845222/

12. Furlan AD, Yazdi F, Tsertsvadze A, et al. A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine for neck and low-back pain. Evid Based Complement Alternat Med [Internet] 2011 [cited 2016 Dec 19];2012. Available from: http://www.hindawi.com/journals/ecam/2012/953139/abs/

13. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev 2010;(1):CD006605.

14. Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med 2003;349(20):1943–1953.

15. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004;112(3):372–380.

16. Fredheim OMS, Borchgrevink PC, Mahic M, Skurtveit S. A pharmacoepidemiological cohort study of subjects starting strong opioids for nonmalignant pain: a study from the Norwegian Prescription Database. PAIN® 2013;154(11):2487–2493.

17. Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf 2009;18(12):1166–1175.

18. Control C for D, (CDC P, others. Vital signs: overdoses of prescription opioid pain relievers—United States, 1999–2008. MMWR Morb Mortal Wkly Rep 2011;60(43):1487.

19. International RTI, America US of, SAMHSA O of AS, America US of. Results From the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings. 2010 [cited 2016 Dec 19];Available from: https://www.ncjrs.gov/App/Publications/abstract.aspx?ID=253943

20. Factsheet on Opioids - Factsheet-opioids-061516.pdf [Internet]. [cited 2016 Dec 19];Available from: https://www.hhs.gov/sites/default/files/Factsheet-opioids-061516.pdf

21. Inocencio TJ, Carroll NV, Read EJ, Holdford DA. The Economic Burden of Opioid-Related Poisoning in the United States. Pain Med 2013;14(10):1534–1547.

22. MMWR. Morbidity and mortality weekly report, Vol. 64, no. 26, July 10, 2015 - 32001 | Morbidity and Mortality Weekly Report (MMWR) [Internet]. [cited 2016 Dec 19];Available from: https://stacks.cdc.gov/view/cdc/32001

23. Overdose Death Rates [Internet]. 2015 [cited 2016 Dec 19];Available from: https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates

24. Manchikanti L, Fellows B, Damron KS, Pampati V, McManus CD. Prevalence of illicit drug use among individuals with chronic pain in the Commonwealth of Kentucky: an evaluation of patterns and trends. J Ky Med Assoc 2005;103(2):55–62.

25. Manchikanti L, Cash KA, Damron KS, Manchukonda R, Pampati V, McManus CD. Controlled substance abuse and illicit drug use in chronic pain patients: An evaluation of multiple variables. Pain Physician 2006;9(3):215–225.

26. Ricardo Buenaventura M, Rajive Adlaka M, Nalini Sehgal M. Opioid complications and side effects. Pain Physician 2008;11:S105–S120.

27. Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic non-cancer pain: the role of opioid prescription. Clin J Pain 2014;30(7):557.

28. Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. J Pain 2008;9(1):28–36.

29. Mercadante S, Villari P, Ferrera P. Burst ketamine to reverse opioid tolerance in cancer pain. J Pain Symptom Manage 2003;25(4):302–305.

30. Byas-Smith MG, Chapman SL, Reed B, Cotsonis G. The effect of opioids on driving and psychomotor performance in patients with chronic pain. Clin J Pain 2005;21(4):345–352.

31. Swegle JM, Logemann C. Management of common opioid-induced adverse effects. Am Fam Physician [Internet] 2006 [cited 2016 Dec 19];74(8). Available from: http://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=0002838X&AN=23004458&h=%2BE54MgOiRV4V6QyZaVD040yfOy74TlkXhKSvMTxWjsUnIvUGe3xjvoNJc39KHdrWrCxNxyMOaqQZ5vBo2fHRAw%3D%3D&crl=c

32. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction 1999;94(7):961–972.

33. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother 2006;40(7–8):1280–1288.

34. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2002;36(9):1331–1336.

35. Schiff GD, Fung S, Speroff T, McNutt RA. Decompensated heart failure: symptoms, patterns of onset, and contributing factors. Am J Med 2003;114(8):625–630.

36. Senst BL, Achusim LE, Genest RP, et al. Practical approach to determining costs and frequency of adverse drug events in a health care network. Am J Health Syst Pharm 2001;58(12):1126–1132.

37. Misdrahi D, Llorca PM, Lancon C, Bayle FJ. [Compliance in schizophrenia: predictive factors, therapeutical considerations and research implications]. L'Encephale 2001;28(3 Pt 1):266–272.

38. Rodgers PT, Ruffin DM. Medication nonadherence: Part II–A pilot study in patients with congestive heart failure. Manag Care Interface 1998;11(9):67–9.

39. Levy G, Zamacona MK, Jusko WJ. Developing compliance instructions for drug labeling. Clin Pharmacol Ther 2000;68(6):586–591.

40. Berg JS, Dischler J, Wagner DJ, Raia JJ, Palmer-Shevlin N. Medication compliance: a healthcare problem. Ann Pharmacother 1993;27(9 Suppl):S1–S24.

41. Group CDPR, others. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. N Engl J Med 1980;1980(303):1038–1041.

42. LaRosa JC. Poor compliance: the hidden risk factor. Curr Atheroscler Rep 2000;2(1):1–4.

43. Horwitz RI, Horwitz SM. Adherence to treatment and health outcomes. Arch Intern Med 1993;153(16):1863–1868.

44. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J 2008;32(4):962–969.

45. Kamour A, David Mannino MD, Kanotra S, others. Prevalence and Comorbidities of Chronic Obstructive Pulmonary Disease Among Adults in Kentucky Across Gender and Area Development Districts, 2011. Chronic Obstr Pulm Dis J COPD Found 2(4):296–312.

46. Haupt D, Krigsman K, Nilsson JLG. Medication persistence among patients with asthma/COPD drugs. Pharm World Sci 2008;30(5):509–514.

47. Restrepo RD, Alvarez MT, Wittnebel LD, et al. Medication adherence issues in patients treated for COPD. Int J Chron Obstruct Pulmon Dis 2008;3(3):371–384.

48. Serra-Batlles J, Plaza V, Badiola C, Morejón E. Patient perception and acceptability of multidose dry powder inhalers: a randomized crossover comparison of Diskus/Accuhaler with Turbuhaler. J Aerosol Med 2002;15(1):59–64.

49. Rodríguez-Roisin R. The airway pathophysiology of COPD: implications for treatment. COPD J Chronic Obstr Pulm Dis 2005;2(2):253–262.

50. van Boven JF, Chavannes NH, van der Molen T, Rutten-van Mölken MP, Postma MJ, Vegter S. Clinical and economic impact of non-adherence in COPD: a systematic review. Respir Med 2014;108(1):103–113.

51. Simoni-Wastila L, Wei Y-J, Qian J, et al. Association of chronic obstructive pulmonary disease maintenance medication adherence with all-cause hospitalization and spending in a Medicare population. Am J Geriatr Pharmacother 2012;10(3):201–210.

52. Toy EL, Beaulieu NU, McHale JM, et al. Treatment of COPD: Relationships between daily dosing frequency, adherence, resource use, and costs. Respir Med [Internet] 2010 [cited 2010 Oct 18];Available from: http://www.ncbi.nlm.nih.gov/pubmed/20880687

53. Eaddy MT, Cook CL, O'Day K, Burch SP, Cantrell CR. How patient cost-sharing trends affect adherence and outcomes. Pharm Ther 2012;37(1):45–55.

54. Halpern R, Baker CL, Su J, et al. Outcomes associated with initiation of tiotropium or fluticasone/salmeterol in patients with chronic obstructive pulmonary disease. Patient Prefer Adherence 2011;5:375.

55. Vestbo J, Anderson JA, Calverley PM, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax 2009;64(11):939–943.

56. Jennings A-L, Davies AN, Higgins JPT, Gibbs JSR, Broadley KE. A systematic review of the use of opioids in the management of dyspnoea. Thorax 2002;57(11):939–44.

57. Rocker GM, Simpson AC, Horton R, et al. Opioid therapy for refractory dyspnea in patients with advanced chronic obstructive pulmonary disease: patients' experiences and outcomes. CMAJ Open 2013;1(1):E27-36.

58. Roberts MH, Mapel DW, Hartry A, Von Worley A, Thomson H. Chronic pain and pain medication use in chronic obstructive pulmonary disease. A cross-sectional study. Ann Am Thorac Soc 2013;10(4):290–8.

59. Janssen DJA, Spruit MA, Uszko-Lencer NH, Schols JMGA, Wouters EFM. Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure. J Palliat Med 2011;14(6):735–43.

60. Woodcock AA, Gross ER, Gellert A, Shah S, Johnson M, Geddes DM. Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. N Engl J Med 1981;305(27):1611–6.

61. Stark RD, O'Neill PA. Dihydrocodeine for breathlessness in "pink puffers." Br Med J Clin Res Ed 1983;286(6373):1280–1.

62. Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. BMJ 2003;327(7414):523–8.

63. Currow DC, McDonald C, Oaten S, et al. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. J Pain Symptom Manage 2011;42(3):388–99.

64. Vozoris NT, Wang X, Fischer HD, et al. Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. Eur Respir J 2016;48(3):683–93.

65. Atreja N, Fleming M, Chen H, Johnson M, Zhivan H, Todd K. Impact of long term opioid use on oral antihyperglycemic medication adherence among individuals with type 2 diabetes mellitus: a retrospective database analysis. [Internet]. [cited 2017 Jan 16];Available from: https://www.ispor.org/ScientificPresentationsDatabase/Presentation/64748

66. Ekstrom MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. BMJ 2014;348:g445.

67. Vozoris NT, Wang X, Austin PC, et al. Adverse cardiac events associated with incident opioid drug use among older adults with COPD. Eur J Clin Pharmacol 2017;

68. Babitsch B, Gohl D, von Lengerke T. Re-revisiting Andersen’s Behavioral Model of Health Services Use: a systematic review of studies from 1998-2011. Psycho-Soc Med 2012;9:Doc11.

69. Aday LA, Andersen R. A Framework for the Study of Access to Medical Care. Health Serv Res 1974;9(3):208–20.

70. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? J Health Soc Behav 1995;1–10.

71. Bhattacharya R, Shen C, Wachholtz AB, Dwibedi N, Sambamoorthi U. Depression treatment decreases healthcare expenditures among working age patients with comorbid conditions and type 2 diabetes mellitus along with newly-diagnosed depression. BMC Psychiatry 2016;16:247.

72. Hochhausen L, Le H-N, Perry DF. Community-based mental health service utilization among low-income Latina immigrants. Community Ment Health J 2011;47(1):14–23.

73. Parslow R, Jorm A, Christensen H, Jacomb P. Factors associated with young adults' obtaining general practitioner services. Aust Health Rev Publ Aust Hosp Assoc 2002;25(6):109–18.

74. Brown ER, Davidson PL, Yu H, et al. Effects of community factors on access to ambulatory care for lower-income adults in large urban communities. Inq J Med Care Organ Provis Financ 2004;41(1):39–56.

75. Chen AW, Kazanjian A, Wong H. Determinants of mental health consultations among recent Chinese immigrants in British Columbia, Canada: implications for mental health risk and access to services. J Immigr Minor Health 2008;10(6):529–40.

76. Jackson H, Hubbard R. Detecting chronic obstructive pulmonary disease using peak flow rate: cross sectional survey. BMJ 2003;327(7416):653–4.

77. Celli BR, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23(6):932–46.

78. National Heart, Lung, and Blood Institute. COPD, Learn More Breathe Better [Internet]. [cited 2017 Jan 16];Available from: https://www.nhlbi.nih.gov/health/educational/copd/

79. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363(12):1128–38.

80. Walters JA, Smith S, Poole P, Granger RH, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. Cochrane Libr [Internet] 2010 [cited 2017 Jan 16];Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001390.pub3/full

81. Poole PJ, Chacko E, Wood-Baker RWB, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Libr [Internet] 2000 [cited 2017 Jan 16];Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002733/full

82. Nici L, Lareau S, ZuWALLACK R. Pulmonary rehabilitation in the treatment of chronic obstructive pulmonary disease. Am Fam Physician 2010;82(6):655.

83. Guy GP. Vital Signs: Changes in Opioid Prescribing in the United States, 2006–2015. MMWR Morb Mortal Wkly Rep [Internet] 2017 [cited 2017 Oct 18];66. Available from: https://www.cdc.gov/mmwr/volumes/66/wr/mm6626a4.htm

84. Pain & Policy Studies Group. Global opioid consumption, 2015 [Internet]. [cited 2017 Oct 18];Available from: http://www.painpolicy.wisc.edu/global

85. Centers for Disease Control and Prevention. NVSS - National Vital Statistics System Homepage [Internet]. 2017 [cited 2017 Sep 25];Available from: https://www.cdc.gov/nchs/nvss/index.htm

86. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. Pain Med 2011;12(4):657–667.

87. Merskey HE. Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. Pain [Internet] 1986 [cited 2016 Dec 19];Available from: http://psycnet.apa.org/psycinfo/1987-31773-001

88. Simon LS. Relieving pain in America: A blueprint for transforming prevention, care, education, and research. J Pain Palliat Care Pharmacother 2012;26(2):197–198.

89. Shah A. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use—United States, 2006–2015. MMWR Morb Mortal Wkly Rep [Internet] 2017 [cited 2017 Sep 25];66. Available from: https://www.cdc.gov/mmwr/volumes/66/wr/mm6610a1.htm

90. Deyo RA, Hallvik SE, Hildebran C, et al. Association between initial opioid prescribing patterns and subsequent long-term use among opioid-naïve patients: A statewide retrospective cohort study. J Gen Intern Med 2017;32(1):21–27.

91. Paulozzi LJ, Mack KA, Hockenberry JM, others. Vital signs: variation among states in prescribing of opioid pain relievers and benzodiazepines—United States, 2012. MMWR Morb Mortal Wkly Rep 2014;63(26):563–8.

92. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA 2016;315(15):1624–1645.

93. Savage SR, Joranson DE, Covington EC, Schnoll SH, Heit HA, Gilson AM. Definitions related to the medical use of opioids: evolution towards universal agreement. J Pain Symptom Manage 2003;26(1):655–667.

94. Abuse NI on D. The Science of Drug Abuse and Addiction: The Basics [Internet]. [cited 2016 Dec 19];Available from: https://www.drugabuse.gov/publications/media-guide/science-drug-abuse-addiction-basics

95. ASAM Definition of Addiction [Internet]. [cited 2016 Dec 19];Available from: http://www.asam.org/quality-practice/definition-of-addiction

96. Corsini E, Zacharoff K. Definitions related to aberrant drug-related behavior: Is there correct terminology? [Internet]. [cited 2016 Dec 19];Available from: https://www.painedu.org/articles_timely.asp?ArticleNumber=58

97. Jones CM. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers–United States, 2002–2004 and 2008–2010. Drug Alcohol Depend 2013;132(1):95–100.

98. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. JAMA Psychiatry 2014;71(7):821–826.

99. Uniform Controlled Substances Act (1994) [Internet]. [cited 2016 Dec 19];Available from: http://www.uniformlaws.org/shared/docs/controlled%20substances/UCSA_final%20_94%20with%2095amends.pdf

100. National Institute on Drug Abuse. Misuse of prescription drugs. [Internet]. [cited 2017 Oct 18];Available from: https://www.drugabuse.gov/publications/research-reports/misuse-prescription-drugs/summary

101. Marschall U, L'hoest H, Radbruch L, Häuser W. Long-term opioid therapy for chronic non-cancer pain in Germany. Eur J Pain Lond Engl 2016;20(5):767–76.

102. Bliesener N, Albrecht S, Schwager A, Weckbecker K, Lichtermann D, Klingmuller D. Plasma testosterone and sexual function in men receiving buprenorphine maintenance for opioid dependence. J Clin Endocrinol Metab 2005;90(1):203–206.

103. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. J Pain 2002;3(5):377–384.

104. Ensrud KE, Blackwell T, Mangione CM, et al. Central nervous system active medications and risk for fractures in older women. Arch Intern Med 2003;163(8):949–957.

105. Mercadante S, Arcuri E. Hyperalgesia and opioid switching. Am J Hosp Palliat Med 2005;22(4):291–294.

106. Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. J Pain 2006;7(1):43–48.

107. Dimsdale JE, Norman D, DeJardin D, Wallace MS. The effect of opioids on sleep architecture. J Clin Sleep Med 2007;3(1):33–36.

108. Schug SA, Garrett WR, Gillespie G. Opioid and non-opioid analgesics. Best Pract Res Clin Anaesthesiol 2003;17(1):91–110.

109. Pattinson KTS. Opioids and the control of respiration. Br J Anaesth 2008;100(6):747–758.

110. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353(5):487–497.

111. De Geest S, Sabaté E. Adherence to long-term therapies: evidence for action. Eur J Cardiovasc Nurs 2003;2(4):323–323.

112. Cramer J, Rosenheck R, Kirk G, Krol W, Krystal J. Medication compliance feedback and monitoring in a clinical trial: predictors and outcomes. Value Health 2003;6(5):566–573.

113. Waeber B, Leonetti G, Kolloch R, McInnes GT, group H study, others. Compliance with aspirin or placebo in the Hypertension Optimal Treatment (HOT) study. J Hypertens 1999;17(7):1041–1045.

114. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001;23(8):1296–1310.

115. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. Am J Geriatr Pharmacother 2011;9(1):11–23.

116. Golin CE, Liu H, Hays RD, et al. A prospective study of predictors of adherence to combination antiretroviral medication. J Gen Intern Med 2002;17(10):756–765.

117. Elliott WJ, Maddy R, Toto R, Bakris G. Hypertension in patients with diabetes: overcoming barriers to effective control. Postgrad Med 2000;107(3):29–38.

118. Black HR. Will better-tolerated antihypertensive agents improve blood pressure control? JNC VI revisited. Am J Hypertens 1999;12(S9):225S–230S.

119. Ickovics JR, Meade CS. Adherence to HAART among patients with HIV: breakthroughs and barriers. AIDS Care 2002;14(3):309–318.

120. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. Value Health 2007;10(1):3–12.

121. Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. Springf VA Pharm Qual Alliance [Internet] 2012 [cited 2016 Jun 24];Available from: http://ep.yimg.com/ty/cdn/epill/pdcmpr.pdf

122. Owen JA. Medicare star ratings: Stakeholder proceedings on community pharmacy and managed care partnerships in quality: American Pharmacists Association and Academy of Managed Care Pharmacy. J Am Pharm Assoc 2014;54(3):228–240.

123. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. Jama 2002;288(4):455–461.

124. Benner JS, Pollack MF, Smith TW, Bullano MF, Willey VJ, Williams SA. Association between short-term effectiveness of statins and long-term adherence to lipid-lowering therapy. Am J Health Syst Pharm [Internet] 2005 [cited 2016 Jun 24];62(14). Available from: http://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=10792082&AN=17530677&h=4kLqY4uBugfGjL4ELZgDR6Dpcb0iB4LFpYfA0CWul9nCdr4hG7aDyZ3QveZNac6UDDXcA1CME1eHIXHaf2Jf7g%3D%3D&crl=c

125. Chapman RH, Benner JS, Petrilla AA, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med 2005;165(10):1147–1152.

126. Benner JS, Tierce JC, Ballantyne CM, et al. Follow-up lipid tests and physician visits are associated with improved adherence to statin therapy. Pharmacoeconomics 2004;22(3):13–23.

127. Curkendall SM, Thomas N, Bell KF, Juneau PL, Weiss AJ. Predictors of medication adherence in patients with type 2 diabetes mellitus. Curr Med Res Opin 2013;29(10):1275–1286.

128. Klink M, Quan SF. Prevalence of reported sleep disturbances in a general adult population and their relationship to obstructive airways diseases. Chest 1987;91(4):540–6.

129. Edmonds P, Karlsen S, Khan S, Addington-Hall J. A comparison of the palliative care needs of patients dying from chronic respiratory diseases and lung cancer. Palliat Med 2001;15(4):287–95.

130. Vozoris NT, Wang X, Fischer HD, et al. Incident opioid drug use among older adults with chronic obstructive pulmonary disease: a population-based cohort study. Br J Clin Pharmacol 2016;81(1):161–70.

131. Cicero TJ, Wong G, Tian Y, Lynskey M, Todorov A, Isenberg K. Co-morbidity and utilization of medical services by pain patients receiving opioid medications: data from an insurance claims database. Pain 2009;144(1–2):20–7.

132. Aday LA, Awe WC. Health services utilization models. Handb Health Behav Res Pers Soc Determinants 1997;153–172.

133. Hansen LG, Chang S. Health research data for the real world: the MarketScan databases. Ann Arbor Truven Health Anal Inc 2012;

134. Wurst KE, St Laurent S, Mullerova H, Davis KJ. Characteristics of patients with COPD newly prescribed a long-acting bronchodilator: a retrospective cohort study. Int J Chron Obstruct Pulmon Dis 2014;9:1021–31.

135. Albrecht JS, Park Y, Hur P, et al. Adherence to Maintenance Medications among Older Adults with Chronic Obstructive Pulmonary Disease. The Role of Depression. Ann Am Thorac Soc 2016;13(9):1497–504.

136. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45(6):613–9.

137. Choudhry NK, Shrank WH, Levin RL, et al. Measuring concurrent adherence to multiple related medications. Am J Manag Care 2009;15(7):457.

138. Rupali N. Impact of the Medicare Part D coverage gap on prescription drug utilization and medication adherence [Internet]. 2011 [cited 2017 Feb 6];Available from: https://repository.unm.edu/handle/1928/12101

139. FitzGerald JM, Haddon JM, Bradley-Kennedy C, Kuramoto L, Ford GT, Group RS. Resource use study in COPD (RUSIC): a prospective study to quantify the effects of COPD exacerbations on health care resource use among COPD patients. Can Respir J 2007;14(3):145–152.

140. Stanford RH, Nag A, Mapel DW, et al. Validation of a new risk measure for chronic obstructive pulmonary disease exacerbation using health insurance claims data. Ann Am Thorac Soc 2016;13(7):1067–1075.

141. Roberts M. Comparative effectiveness of triple therapy compared to combination or mono long-acting pharmacotherapy for COPD. 2013;

142. Rosenbaum PR. Optimal matching for observational studies. J Am Stat Assoc 1989;84(408):1024–1032.

143. Krigsman K, Nilsson JLG, Ring L. Refill adherence for patients with asthma and COPD: comparison of a pharmacy record database with manually collected repeat prescriptions. Pharmacoepidemiol Drug Saf 2007;16(4):441–8.

144. Krigsman K, Nilsson JLG, Ring L. Adherence to multiple drug therapies: refill adherence to concomitant use of diabetes and asthma/COPD medication. Pharmacoepidemiol Drug Saf 2007;16(10):1120–8.

145. Scherrer JF, Salas J, Sullivan MD, et al. The influence of prescription opioid use duration and dose on development of treatment resistant depression. Prev Med 2016;91:110–116.

146. Medicare Payment Advisory Commission. Report to the congress. Medicare and the health care delivery system [Internet]. [cited 2018 Sep 20];Available from: http://medpac.gov/docs/default-source/reports/june-2015-report-to-the-congress-medicare-and-the-health-care-delivery-system.pdf

147. Rose AJ, Hermos JA, Frayne SM, Pogach LM, Berlowitz DR, Miller DR. Does opioid therapy affect quality of care for diabetes mellitus? Am J Manag Care 2009;15(4):217–24.

148. Krein SL, Heisler M, Piette JD, Makki F, Kerr EA. The effect of chronic pain on diabetes patients' self-management. Diabetes Care 2005;28(1):65–70.

149. Jeevanjee S, Penko J, Guzman D, Miaskowski C, Bangsberg DR, Kushel MB. Opioid analgesic misuse is associated with incomplete antiretroviral adherence in a cohort of HIV-infected indigent adults in San Francisco. AIDS Behav 2014;18(7):1352–8.

150. Wedzicha JA, Donaldson GC. Exacerbations of chronic obstructive pulmonary disease. Respir Care 2003;48(12):1204–1215.

151. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157(5):1418–1422.

152. Okubadejo AA, Jones PW, Wedzicha JA. Quality of life in patients with chronic obstructive pulmonary disease and severe hypoxaemia. Thorax 1996;51(1):44–47.

153. Okubadejo AA, O'shea L, Jones PW, Wedzicha JA. Home assessment of activities of daily living in patients with severe chronic obstructive pulmonary disease on long-term oxygen therapy. Eur Respir J 1997;10(7):1572–1575.

154. Dang-Tan T, Zhang S, Tavares RV, et al. The Burden of Illness Related to Chronic Obstructive Pulmonary Disease Exacerbations in Québec, Canada. Can Respir J 2017;2017.

155. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;161(5):1608–1613.

156. Miravitlles M, Ferrer M, Pont A, et al. Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. Thorax 2004;59(5):387–395.

157. Motheral BR, Fairman KA. The use of claims databases for outcomes research: rationale, challenges, and strategies. Clin Ther 1997;19(2):346–366.

158. Peyrot M, McMurry Jr JF, Kruger DF. A biopsychosocial model of glycemic control in diabetes: stress, coping and regimen adherence. J Health Soc Behav 1999;141–158.

159. Nurymberg K, Kreitler S, Weissler K. The cognitive orientation of compliance in short-and long-term type 2 diabetic patients. Patient Educ Couns 1996;29(1):25–39.

# Appendix A: UNM Human Research Review Committee approval

UNM HEALTH SCIENCES CENTER

*Human Research Review Committee*
*Human Research Protections Office*

January 24, 2018

Matthew Borrego
mborrego@salud.unm.edu

Dear Matthew Borrego:

On 1/24/2018, the HRRC reviewed the following submission:

| | |
|---|---|
| Type of Review: | Initial Study |
| Title of Study: | ASSESSING THE IMPACT OF PRESCRIPTION OPIOID USE VERSUS NO USE ON ADHERENCE TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) MAINTENANCE MEDICATIONS, COPD EXACERBATIONS AND HEALTHCARE COSTS |
| Investigator: | Matthew Borrego |
| Study ID: | 17-484 |
| Submission ID: | 17-484 |
| IND, IDE, or HDE: | None |
| Submission Summary: | Initial Study |
| Documents Approved: | • HRP-582 -Exempt Category 4 protocol - 01-22-18 Signed.pdf<br>• FP3239 FE RIDER University of New Mexico (Kharat_Borrego) Marketscan Rider - FE - 081817.PDF |
| Review Category: | EXEMPTION: Categories (4) Data, documents, or specimen. |
| Determinations/Waivers: | Informed consent not applicable.<br>HIPAA Authorization Addendum not applicable. |
| Submission Approval Date: | 1/24/2018 |
| Approval End Date: | None |
| Effective Date: | **1/24/2018** |

The HRRC approved the study from 1/24/2018 to inclusive. If modifications were required to secure approval, the effective date will be later than the approval date. The "Effective Date" 1/24/2018 is the date the HRRC approved your modifications and, in all cases, represents the date study activities may begin.

Because it has been granted exemption, this research is not subject to continuing review.

This determination applies only to the activities described in this submission and does not apply should you make any changes to these documents. If changes are being considered and there are questions about whether HRRC review is needed, please submit a study modification to the HRRC for a determination. A change in the research may disqualify this research from the current review category. You can create a modification by clicking Create Modification / CR within the study.

In conducting this study, you are required to follow the Investigator Manual dated April 1, 2015 (HRP-103), which can be found by navigating to the IRB Library.

Sincerely,

Thomas F. Byrd, MD
*HRRC Chair*