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Medication Use Behavior and Outcomes among Chronic Obstructive Pulmonary Disease Patients

by

Jeetvan G. Patel, MS

A dissertation submitted in partial fulfillment of

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Medication Use Behavior and Outcomes among Chronic Obstructive Pulmonary Disease Patients

To the Faculty of the University of Houston, College of Pharmacy:

The members of the committee appointed to examine the dissertation of *Jeetvan G. Patel* find it satisfactory and recommend that it be accepted on 05/20/2015.

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Dedicated to my family and Dr. J

Abstract

Objectives: (1) Characterize the Chronic Obstructive Pulmonary Disease (COPD) patients and estimate medication adherence (2) Estimate the association between medication adherence and exacerbation risk and COPD-related costs (3) Develop and validate a risk equation to identify medication non-adherence among COPD patients.

Methods: The study used Truven commercial and claims encounter database to identify COPD patients initiating maintenance therapy identified over a 12 month identification period (January 1, 2011 to Dec 31, 2011). The initiation of maintenance medication therapy was classified as the index date. After a 12-month baseline period (January 1, 2010 to Dec 31, 2010), beneficiaries were followed over a two year rolling index period through to December 31, 2013. Medication adherence was assessed using proportion of days covered (PDC). The association of adherence with exacerbations and healthcare expenditure were estimated using logistic regression and γ generalized linear models, respectively, adjusting for socio-demographics, comorbidities, comedication use and proxy measures of disease severity. Risk factors were added to a logistic regression model employing a backward elimination process to develop the final model. Sensitivity, specificity, false positive and false negative rates were specified for the final model. Model performance was also described using c-statistic, percent concordant pairs and percent discordant pairs. To estimate the predictive validity of the final model, the final selection of variables were added in a GLM model and predicted adherence rates were estimated assuming a normal distribution of PDC scores.

Results: Only 58% of newly diagnosed COPD patients were adherent (PDC>0.80) in the first year of maintenance medication use and the adherence rates fell down to 28% (PDC>0.80)

during the second year. After controlling for baseline exacerbation rates and healthcare expenditure, patients with PDC <0.80 exhibited higher risk of exacerbations (OR = 1.55, 95% CI: 1.35 – 1.79) and higher total ($784.06) and pharmacy expenditure ($543.12), compared with patients with PDC ≥0.80. Medical expenditure was not different across adherent and non-adherent patients with a new diagnosis of COPD. **:** The final model included 13 variables which were below the inclusion p-value criteria of p<0.35 and had a c-statistic of 0.799. The newly developed model had a specificity of 81.70% and a sensitivity of 75.20% with a 79.60% concordance in the final model. The concordant validity of the final model was estimated by predicting out adherence values using the final model.The model estimated the adherence level in the COPD population at 55.84% as compared to the actual adherence level of 61.85%.

Conclusions: Only 1 in 4 COPD patients remained adherent to maintenance medication treatment during the second year. Improved adherence in the first year of maintenance therapy use was significantly associated with reduced risk of exacerbation and lower healthcare expenditure. Findings suggest need to identify barriers associated with continued maintenance medication use among newly diagnosed COPD patients. Using information available from healthcare claims data only, predictive models can reliably identify COPD medication non-adherence. Prior medication adherence was the best predictor of the future medication adherence among COPD patients.

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Manuscript 1

Development and Validation of a Predictive model to identify medication non-adherence among COPD patients within a managed care setting.

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Key words: adherence, chronic obstructive pulmonary disease, costs, exacerbations, maintenance medications

ABSTRACT

Objective: The aim of the study was to construct predictive models of COPD medication non-adherence, using primarily demographics, comorbid conditions, and COPD treatment claims data as covariates

Methods: Using the Truven commercial and claims encounter database, this retrospective longitudinal study included 44,393 COPD patients initiating maintenance therapy identified over a 12 month identification period (January 1, 2011 to Dec 31, 2011). The initiation of maintenance medication therapy was classified as the index date. After a 12-month baseline period (January 1, 2010 to Dec 31, 2010), beneficiaries were followed over a two year rolling index period through to December 31, 2013. Medication adherence was assessed using proportion of days covered (PDC). Risk factors were added to a logistic regression model employing a backward elimination process to develop the final model. Sensitivity, specificity, false positive and false negative rates were specified for the final model. Model performance was also described using c-statistic, percent concordant pairs and percent discordant pairs. To estimate the predictive validity of the final model, the final selection of variables were added in a GLM model and predicted adherence rates were estimated assuming a normal distribution of PDC scores.

Results: The final model included 13 variables which were below the inclusion p-value criteria of $p<0.35$ and had a c-statistic of 0.799. The newly developed model had a specificity of 81.70% and a sensitivity of 75.20% with a 79.60% concordance in the final model. The concordant validity of the final model was estimated by predicting out adherence values using the final

model. The model estimated the adherence level in the COPD population at 55.84% as compared to the actual adherence level of 61.85%.

Conclusions: Using information available from healthcare claims data only, predictive models can reliably identify COPD medication non-adherence. Prior medication adherence was the best predictor of the future medication adherence among COPD patients.

INTRODUCTION

COPD being a progressive disorder, smoking cessation for a long time was the only intervention affecting the progression of the disease by reducing the rate of decline of FEV1 and mortality.[1,2] In the last decade, the availability of novel pharmacotherapy for the management of COPD as shown by the TORCH and UPLIFT trials has given new hope for patients with COPD.[3,4] The GOLD guidelines recommend maintenance medication use to reduce symptoms, reduce exacerbation frequency and severity, improve health status and exercise tolerance.[5] Medications in COPD are effective in improving health outcomes and reducing mortality if they are used appropriately by patients, however, only 40 – 60% of individuals with COPD adhere to pharmacotherapy.[6,7]

Non-adherence to COPD medication is high and all the stakeholders within the healthcare delivery system experience an impact of medication non-adherence. When patients do not use medications appropriately, they reduce the drug's effectiveness and as a result experience poor health outcomes leading to healthcare resource utilization. Providers work within a fragmented healthcare delivery network and have neither been equipped to monitor and modify patients' health behaviors, nor are accountable towards it.[8] A recent study shows that nearly one in three prescriptions written by healthcare providers are not filled by their patients.[9] From a payer perspective, medication adherence plays an important role with an increasing focus on quality ratings and corresponding bonus payments.[10] Prescription drugs when used appropriately are proven to be the most cost-effective component of the healthcare delivery process.[11]

Identification of medication non-adherence is a big challenge. Patients who are non-adherent to their medications are generally reluctant to discuss their medication use behavior and admit about it. Physicians in such a scenario often assume that their patients are taking medications appropriately. A study comparing electronic monitoring of patient medication use behavior and physician report of patient medication use found that physicians underestimated medication non-adherence.[12] Several factors predispose patients to be non-adherent to medications. Studies have identified that type of disease, treatment, patient and physician characteristics and cost of treatments are determinants to medication non-adherence.[13]

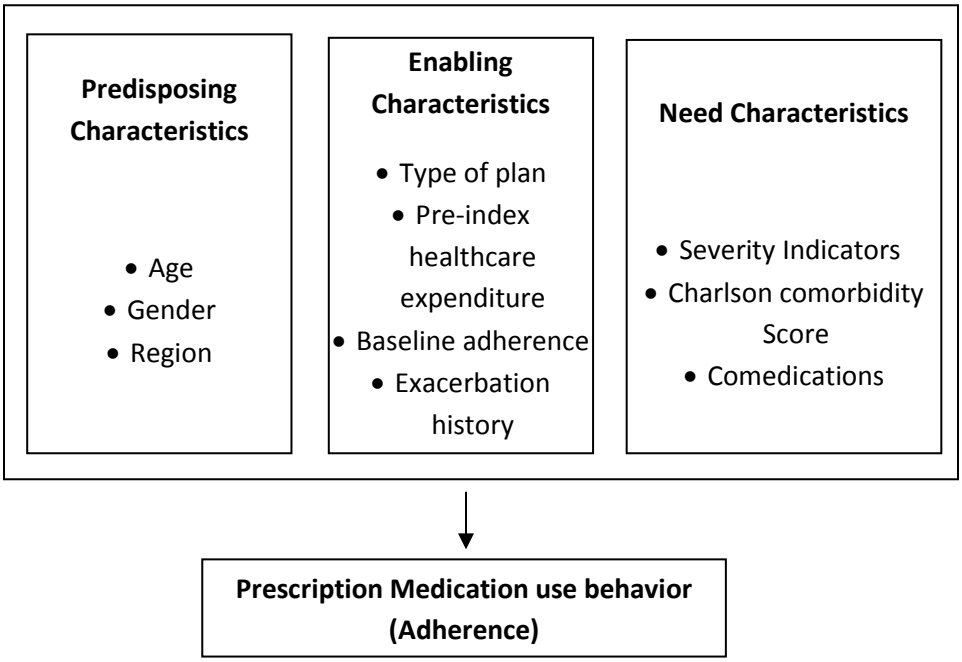
Claims data routinely collected to administer patient health benefits contain several of the risk factors associated with medication non-adherence. Retrospective evaluations conducted on such databases have also been used to detect medication non-adherence and identify risk-factors associated with non-adherence. However, very few studies have used such databases to identify and predict future medication non-adherence. Identification of individuals at risk of medication non-adherence could help target appropriate patient interventions for improving medication adherence in-turn reducing overall cost burden. The goal of this study is to develop a risk equation based on data captured from claims databases to predict medication non-adherence among patients with COPD. The study will also validate of the predicted adherence values to actual adherence estimates to demonstrate concurrent validity to facilitate application of the final risk equation of medication non-adherence.

CONCEPTUAL FRAMEWORK

The conceptual framework presented here describes how patient factors affect medication use behavior.

Andersen Behavior Model for Healthcare Resource Use Behavior: Andersen and Newman conceptualized that medical care utilization could be explained by societal and individual determinants.[14] The medical care utilization of interest for this particular study is medication adherence. Hence, for the purpose of identifying individual and societal factors associated with maintenance medication use behavior among patients diagnosed with COPD, Andersen and Newman's behavior model framework of predisposing, enabling and need characteristics will be used.

This model has been cited by previous studies focusing on health services utilization among COPD patients.[15] This model captures health services utilization behavior as a function of their 1) predisposition to use; 2) enabling resources to use; and 3) need to use the health services. The model is adapted from the original model that was developed by Andersen and colleagues to study medication use behavior in older adults with COPD. The modified Andersen Behavior model proposed here emphasizes the dynamic and recursive nature of health services used after taking into account the health outcomes of an individual.



Predisposing characteristics: Predisposing characteristics are unique attributes of every individual who has a different propensity to use health care resources. Demographic characteristics, social structure and attitudinal differences are broad categories of such attributes that are unique to each individual under the predisposing factors. Demographic variables such as age, gender and region have been shown to have an impact on the health of an individual. In general, COPD is a disease of the elderly and with increase in age, severity of COPD usually increases. Use of healthcare services also varies across gender and regional groups. Another important predisposing characteristic that will be included in this study is prior medication use behavior. Prior medication use has been shown to predict future medication use, healthcare resource use and costs which may account for significant variation in predicting future utilization events.

Enabling resources: Higher predisposition to utilization may not result into actual utilization of the healthcare services. Adequate resources may be required to translate the predisposition into

actual use. There are two major categories of enabling resources, personal/ family and community. The enabling resources include variables such as income, cost-sharing liabilities on all utilization conducted, provider type and prior healthcare expenditure. All these factors affect the ability of an individual to have future healthcare resource utilization. Enabling resources play a key role by providing necessary means to obtain the health care services by the patients.

Need: Need describes the perception that an individual is falling ill, or the disease is severe to seek medical attention. Other than the predisposition to use and availability of enabling resources, presence of an illness and degree of it is also important in predicting health services use. Illness level represents the most immediate cause to use any health services. The presence of other comorbidities and co-medications are also predictive of resource use. Together, severity, comorbidites and comedications describe the need that an individual may have for healthcare resource use for a particular disease condition.

The factors identified from the Andersen Behavioral Model as being associated with medication adherence will be used to develop an algorithm to predict future medication adherence. The goal will be to develop the best predicting parsimonious model.

METHODS

Data Source

This study used the Truven Commercial Claims and Encounters Database. The Commercial database contains integrated medical and pharmacy claims data that is sourced directly from health plans and employers, representing over 35 million commercial lives annually. They include detailed cost, use, and outcomes data for healthcare services performed in inpatient and outpatient settings, prescription drug claims, as well as information on patient enrollment.

Study Design

The first long acting maintenance medication dispensing during the year 2011 be called the index date and will mark the beginning of the observation period. The pre-index period will consist of the 12 months prior to the index date. During these 12 months, the patients should have at least one diagnosis of COPD defined using an ICD-9-CM code of [491.xx, 492.xx, 496.xx] at any position. Baseline period (year 1) consisted of 12 months post the index date when demographic characteristics, comorbidities, comedications and baseline adherence rates and baseline exacerbations and costs were obtained. Medication adherence in year 2 was the dependent variable. Figure 1 describes the overall study design of this study.

Sample

- At least one long-acting inhaled therapy prescription in 2011 (see Appendix A for the complete list of medications) with the first prescription defined as the index date.
- At least one hospitalization or emergency department visit with at any position diagnosis of COPD (ICD-9-CM codes: 491.xx, 492.xx, and 496.xx) or two outpatient visits with a primary or secondary diagnosis of COPD during the 12-month pre-index period.
- At least 12 months of continuous enrollment before the index date and 24 months of continuous enrollment after the index date
- Aged 40 or older at the index date

Adherence

Adherence was measured using Proportion of days covered (PDC). PDC assesses how many days do individuals have medication in their possession. COPD medications included inhaled

corticosteroids (alone or in combination with long acting beta-agonists (LABA)), anticholinergics, LABA only and methylxanthines. This study did not differentiate adherence across therapeutic class or individual drugs. PDC values ranged from 0 to 1 and were calculated as the number of days with drug on hand as measured by the 'days' supply' from the data (numerator). The days' supply was divided by 365 days (denominator) to come up with the final PDC scores.[16] Switching and augmentation from the initial medication at index was not considered as end of therapy. Patients with a PDC of ≥0.80 were classified as adherent to maintenance medication, otherwise, patients were considered non-adherent. Two yearly PDC assessments were conducted. PDC measured in the first year of follow up (year 1) was considered baseline adherence and included as an independent variable in the model. PDC measured in the year 2 was the dependent variable in the model and was used to predict out adherence rates in the second year of follow-up (year 2).

Other Study Variables

1. Demographic characteristics: Patient demographics were assessed at the COPD index date. Age, gender and region (Northeast, North Central, South, and West), health plan type were obtained from the eligibility files.
2. Comorbidity: The Charlson comorbidity index was calculated for each patient based on the presence of ICD-9-CM codes in the 12-month baseline period. Asthma, Depression and Cardiovascular diseases, lower respiratory tract diseases (LRTI), upper respiratory tract diseases (URTI) were identified using ICD-9-CM codes and a binary indicator variable was created for these comorbid conditions.
3. Comedications: Rescue medication use – specifically Oral corticosteroids (OCS), short acting beta agonists (SABA), Ipratropium weres identified and a binary indicator variable

was created. The total number of fills for rescue medication use was also estimated. Use of home oxygen therapy was identified using a medical claim with a procedure code for home oxygen therapy.

4. Exacerbations: COPD related exacerbations are defined based on visits. A visit will be defined as a unique date of service. For hospitalizations, a unique admission and discharge date were identified. Two exacerbations occurring within 14 days of the first one were classified as one event in order to identify discrete events. COPD-related exacerbation were defined as:

    - Hospitalization with a primary discharge diagnosis of COPD.
    - ED visit with a primary diagnosis of COPD.
    - COPD-related physician visit with a primary diagnosis of COPD and receipt of oral corticosteroid or antibiotic prescription within 7 days of physician visit (abbreviated as Phy+Rx).

5. Healthcare expenditure: Healthcare expenditure was estimated using the costs paid to the provider for the service after applicable discounts and also any deductibles, coinsurance, and copayment.

    - COPD-related medical costs: Defined as the costs for claims with a primary diagnosis of COPD; for hospitalizations, all claims of a hospitalization with a primary discharge diagnosis of COPD will be used.
    - COPD-related pharmacy costs: Defined as the costs for claims for COPD medications – both maintenance and rescue (See Appendix A).

Statistical Analyses

Descriptive statistics examined sociodemographic and clinical characteristics of the study sample. Univariate associations for the independent variables were estimated using chi-sq test for categorical variables and t-test for continuous variables. All independent variables were added to a logistic regression model. Backward elimination process was employed to develop the final model. The analysis used a significance level of .35 to retain variables in the model (slstay=.35). The ctable option was specified to produce classification of input observations based on the final selected model. The classification table summarized the sensitivity, specificity, false positive and false negative rates for the final model. Model performance was also described using c-statistic, percent concordant pairs and percent discordant pairs. To estimate the predictive validity of the final model, the final selection of variables were added in a GLM model and predicted adherence rates were estimated assuming a normal distribution of PDC scores. Predicted estimates of PDC scores were categorized into adherence levels based on a PDC cut-off of 0.8. The predicted estimates were then compared to the actual PDC estimates. All analyses were performed using PROC LOGISTIC and GLM (SAS version 9.2; SAS Institute Inc, Cary, North Carolina).

RESULTS

A steady state sample of 44,393 beneficiaries with COPD who had at least one maintenance medication prescription claim and one ICD-9-CM based medical claim were identified during the 12-month identification period. This sample was predominantly female (59.79%), with a mean age of 55 years. Majority of the population had an insurance from a PPO plan (51.76%) and were identified in the winter season (50.58%) (**Table 1**). Cardiovascular disorders were the most common comorbid condition (46.23%), followed by asthma (33.92%). About 1 in 4 patients had a comorbid diagnosis of an upper or a lower respiratory tract infection. Over 60% of beneficiaries used COPD rescue medications during the baseline period and the mean number of

fills for rescue medications was 3.46 (SD 4.62). Majority of the population did not have an exacerbation during the baseline period (92.46%), 2.22% of the population was classified as an infrequent exacerbator (1 exacerbation/year) and 5.32% of the population were classified as a frequent exacerbator (atleast 2 eacerbations/year). Medication adherence for the patient population was 53.51% during the first year with a mean PDC=0.73 (SD = 0.29).

Unadjusted Results

Table 2 presents univariate associations on the demographic characteristics, baseline adherence rates, prevalence of exacerbations and healthcare expenditure by medication adherence status in the second year. COPD patients who were adherent in year 2 were more likely to be adherent during the baseline period (75.19% vs 18.36%, p<0.001). Adherent individuals were more likely to have a comprehensive plan (9.97% vs 7.74%). Adherent patients were also less likely to have comorbid diseases such as asthma (30.63% vs 39.25%, p<0.0001), depression (17.10% vs 18.95%, p<0.0001), lower respiratory tract infection (22.49% vs 24.07%) and upper respiratory tract infection (24.95% vs 27.11%, p<0.0001). Adherent individuals were also less likely to use short acting medications: SABAs (58.01% vs 65.02%), OCS (43.54% vs 48.67%, p<0.0001), Ipratropium (4.32% vs 4.92%, P=0.0026) and were less likely to refill rescue medications (mean 3.30 vs 3.72, p<0.0001). No differences were observed in the baseline exacerbation rates and medical costs across adherent and non-adherent individuals. Adherent patients were less likely to have baseline pharmacy costs ($3,533 vs. 3846, p<0.0001).

Modeling results

A total of 20 risk factors (specified before) for medication non-adherence were added into the backward selection process for logistic regression. The final model included 13 variables which

were below the inclusion p-value criteria of $p<0.35$. The final selection of variables and the model performance characteristics are shown in **Table 3** and **Table 4**, respectively. The final model with 13 variables had a c-statistic of 0.799 and adding the remaining 7 variables increased the c-statistic by 0.001. Exploratory analyses of the interactions of risk factors revealed that the contribution of these interactions did not significantly improve the model. They were, therefore, not included in the final models considered. The model had a specificity of 81.70% and a sensitivity of 75.20% with a 79.60% concordance in the final model.

The concordant validity of the final model was estimated by predicting out adherence values using the final model. As shown in Figure 2, the model estimated the adherence level in the COPD population at 55.84% as compared to the actual adherence level of 61.85%.

DISCUSSION

The current study used data routinely collected in claims processing to develop a risk equation to identify medication non-adherence. Prior medication adherence was the best predictor of future medication use behavior among patients with COPD. The study was also able to demonstrate concurrent validity between predicted values of medication adherence and actual PDC scores of patients with COPD. To authors' knowledge, this study is one of the first risk equations to be published in a publically available forum.

Typically C-statistics of 0.7 to 0.8 show acceptable discrimination, 0.8 to 0.9 indicate excellent discrimination, and ≥ 0.9 show outstanding discrimination.[17] The final model developed by the authors had a discriminant validity of 0.799. Adherence intervention programs that target the entire patient population are unnecessary and not cost effective. Proactive identification of

patients at risk for future non-adherence can allow managed care organizations to target the right patients in need of drug adherence intervention programs.

With the advent of newer payment models such as patient-centered medical homes, accountable care organizations (ACOs), and episode-based payments, payers hope to slow the spending and achieve better quality of care.[8,18,19] These initiatives drive the current reimbursement initiatives away from a traditional volume based healthcare delivery to a value based system where outcomes become most important. In such a system, medication use is seen as a means to achieve better outcomes leading to incentives to facilitate medication adherence.

There are important limitations associated with both over-specification and under-specification of a regression model. Over-specification (or over-fitting) of regression models arises whenever a large number of correlated explanatory variables can be related to a single response. In other words, when using regression analysis to identify empirical relationships, there is a risk of identifying relationships in a particular sample studied that do not hold in general. Ignoring the problem may lead to unstable estimates of regression coefficients and thus to large errors for prediction of future observations. There is, therefore, an arbitrage between, on one hand, a very detailed model that is less likely to be applicable to other samples and, on the other hand, a more parsimonious model with a greater generalizability, but which can overlook certain important factors, thus affecting the predictive performance of the model. Using a large administrative health care claims database, the current study has the advantage of including a large sample. The risk model we developed are therefore unlikely to be driven by a few outlier patients. The large sample used also helped improve the generalizability of the models, as confirmed by the relatively high C-statistic.

Conclusions: Using information available from healthcare claims data only, predictive models can reliably identify COPD medication non-adherence. Prior medication adherence was the best predictor of the future medication adherence among COPD patients.

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TABLES MANUSCRIPT 1

Table 1: Sample characteristics of COPD patients prescribed long acting maintenance medication during the one year baseline period.

Variable	Initial Maintenance Rx (n=44,393)
Adherent at baseline (%)	53.51%
Age, yr (mean (SE))	55.25 (5.93)
Sex (%)	
Male (sex=1)	40.21%
Female (sex=2)	59.79%
Region	
North East (region =1)	16.05%
North Central (region =2)	27.70%
South (region =3)	35.40%
West (region =4)	20.38%
Unknown (region =5)	0.48%
Season	
Spring (season =1)	26.41%
Summer (season =2)	12.24%
Fall (season =3)	10.78%
Winter (season =4)	50.58%
Plan Type, (%)	
Comprehensive (plan =1)	9.12%
HMO (plan =2)	21.80%
PPO (plan =3)	51.76%
POS (plan =4)	1.24%
Other (plan =5)	16.08%
Charlson Comorbidity Index (mean (SE))	1.62 (1.47)
Comorbidities, (%)	
Asthma	33.92%
Depression	17.81%
Cardiovascular Disorders	46.23%
LTRI	23.09%
UTRI	25.77%
Comedications (%)	
SABA	61.27%
OCS	45.92%
Ipratropium	4.60%
Antibiotics	69.26%
O_2 Therapy	12.42%
Count of rescue medication fills (mean (SE))	3.46 (4.62)
COPD Related HCRU (%)	
COPD Related Exacerbation	7.54%
Non-exacerbator	92.46%
Infrequent exacerbation	2.22%
Frequent Exacerbations	5.32%

Table 2: Univariate associations of risk factors measured during the baseline period with the adherence levels measured during follow up period			
Variable	**Non-Adherent (46%)**	**Adherent (54%)**	**p-value**
Adherent at baseline (%)	18.36%	75.19%	**<0.0001***
Age, yr (mean (SE))	54.98 (5.91)	55.41 (5.94)	**<0.0001***
Sex, %			
Male (sex=1)	39.91%	40.39%	**0.0153***
Female (sex=2)	60.09%	59.61%	
Region			
North East (region =1)	15.32%	16.49%	
North Central (region =2)	27.07%	28.08%	
South (region =3)	37.47%	34.12%	**<0.0001***
West (region =4)	19.74%	20.77%	
Unknown (region =5)	0.39%	0.54%	
Season			
Spring (season =1)	26.41%	26.19%	
Summer (season =2)	12.48%	12.09%	**<0.0001***
Fall (season =3)	9.71%	11.43%	
Winter (season =4)	51.05%	50.29%	
Plan Type, (%)			
Comprehensive (plan =1)	7.74%	9.97%	
HMO (plan =2)	22.34%	21.47%	
PPO (plan =3)	52.46%	51.32%	**<0.0001***
POS (plan =4)	1.29%	1.21%	
Other (plan =5)	16.18%	16.02%	
Charlson Comorbidity Index (mean (SE))	1.63 (1.46)	1.62 (1.49)	0.8425
Comorbidities, (%, p-value)			
Asthma	39.25%	30.63%	**<0.0001***
Depression	18.95%	17.10%	**0.0004***
Cardiovascular Disorders	46.35%	45.16%	0.6887
LRTI	24.07%	22.49%	**<0.0001***
URTI	27.11%	24.95%	**<0.0001***
Comedications (%, p-value)			
SABA	65.02%	58.01%	**<0.0001***
OCS	48.67%	43.54%	**<0.0001***
Ipratropium	4.92%	4.32%	**0.0026***
Antibiotics	70.28%	68.37%	**0.0409***
O_2 Therapy	11.47%	13.24%	**<0.0001***
Count of rescue medication fills (mean (SD))	3.72 (4.65)	3.30 (4.59)	**<0.0001***
COPD Related HCRU (n, %)			
COPD Related Exacerbation	7.48%	7.59%	0.6665
Non-exacerbator	92.52%	92.41%	0.9015
Infrequent exacerbation	2.21%	2.23%	0.9013
Frequent Exacerbations	5.26%	5.36%	0.6493
COPD Related Costs (mean)			
Medical Costs	1705.4	1683.4	0.7871
Pharmacy Costs	3843.6	3533.8	**<0.0001***
Total Costs	5548.9	5217.2	**0.0018***

Table 3: Input and output variables from the backward selection process.	
Input Variables	**Final Selection**
Age	Age
Gender	Gender
Region	Region
Season	Season
Plan Type	Plan Type
Asthma	Asthma
Depression	Depression
Cardiovascular Disorders	URTI
LRTI	OCS
URTI	Antibiotics
SABA	Count of rescue medications*
OCS	Baseline Adherence*
Ipratropium	Oxygen Therapy Use*
Antibiotics	
Count of rescue medications	
Charlson Comorbidity Index	
Exacerbation	
Frequency of exacerbations	
Baseline Adherence	
Oxygen Therapy Use	

***p<0.05**

Table 4: Model Performance statistics for logistic regression model

Model Fit Criteria	Value
Percent Concordance	79.60%
Percent Discordance	19.70%
c-statistic	0.799
Sensitivity	75.20%
Specificity	81.70%
False Positive	13.10%
False Negative	33.00%

FIGURES MANUSCRIPT 1

Figure 1: Study Design

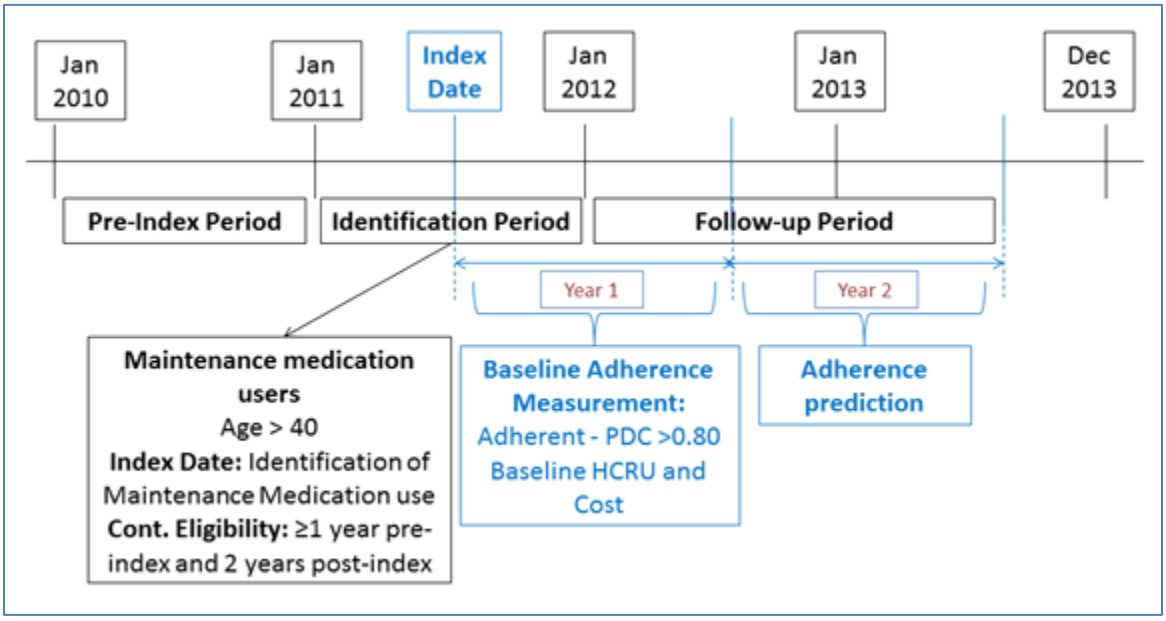
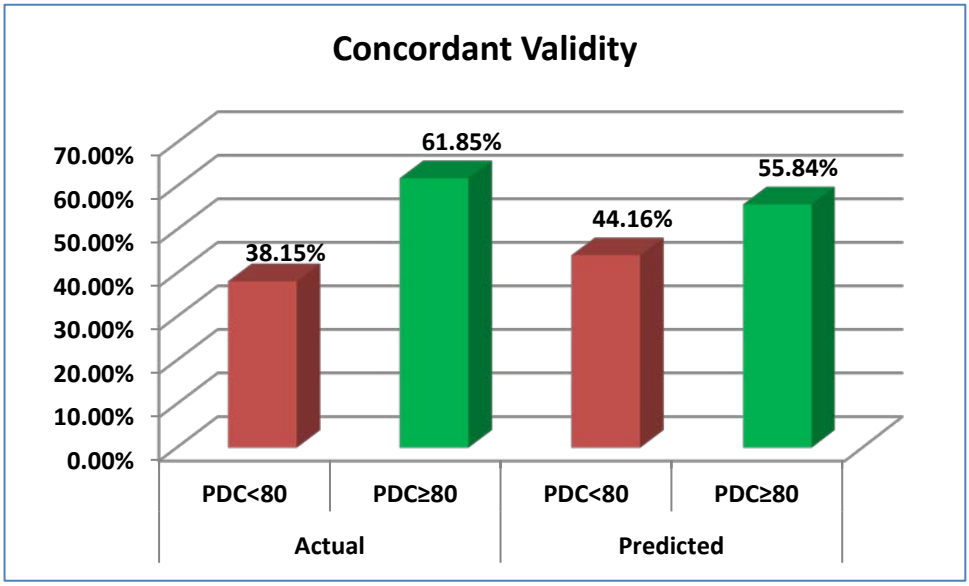


Figure 2: Concordance across predicted and actual adherence



		Percent	Number	Total
Actual	**PDC<80**	38.15%	16936	44393
	PDC≥80	61.85%	27457	
Predicted	**PDC<80**	44.16%	19604	44393
	PDC≥80	55.84%	24789	

Manuscript 2

Initial Maintenance Therapy Use Behavior and Outcomes Among Chronic Obstructive Pulmonary Disease Patients Within a Managed Care Setting.

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Key words: adherence, chronic obstructive pulmonary disease, costs, exacerbations, maintenance medications

ABSTRACT

Objective: To characterize maintenance medication use behavior among newly diagnosed commercially insured COPD patients and quantify impact on subsequent healthcare resource use and costs.

Methods: Using the Truven commercial and claims encounter database, this retrospective longitudinal study included 17,785 COPD patients newly imitating maintenance therapy identified over a 12 month identification period (January 1, 2011 to Dec 31, 2011). The initiation of maintenance medication therapy was classified as the index date. After a 12-month baseline period (January 1, 2010 to Dec 31, 2010), beneficiaries were followed over a two year rolling index period through to December 31, 2013. Medication adherence was assessed using proportion of days covered (PDC). PDC values ranged from 0 to 1 which were calculated yearly over a two year rolling index follow-up period. The association of adherence with exacerbations and healthcare expenditure were estimated using logistic regression and γ generalized linear models, respectively, adjusting for socio-demographics, comorbidities, comedication use and proxy measures of disease severity.

Results: Only 58% of newly diagnosed COPD patients were adherent (PDC>0.80) in the first year of maintenance medication use and the adherence rates fell down to 28% (PDC>0.80) during the second year. After controlling for baseline exacerbation rates and healthcare expenditure, patients with PDC <0.80 exhibited higher risk of exacerbations (OR = 1.55, 95% CI: 1.35 – 1.79) and higher total ($784.06) and pharmacy expenditure ($543.12), compared with patients with PDC ≥0.80. Medical expenditure was not different across adherent and non-adherent patients with a new diagnosis of COPD.

Conclusions: Only 1 in 4 COPD patients remained adherent to maintenance medication treatment during the second year. Improved adherence in the first year of maintenance therapy use was significantly associated with reduced risk of exacerbation and lower healthcare expenditure. Findings suggest need to identify barriers associated with continued maintenance medication use among newly diagnosed COPD patients.

Abbreviations

COPD, chronic obstructive pulmonary disease

ICD-9-CM, *International Classification of Diseases, 9th Edition, Clinical Modification*

INTRODUCTION

COPD is a progressive chronic disease, characterized by an irreversible decline in lung function which starts occurring many years before a diagnosis is actually made.[1,2] Approximately 12 million Americans are currently diagnosed with COPD and another 12 million individuals remain undiagnosed.[3] In 2008 in the United States, COPD become the third leading cause of death (behind heart disease and cancer) accounting for more than 140,000 deaths. The number of deaths due to COPD is increasing while most other causes of death are on the decline.[4] COPD also has a significant economic burden. The aggregate costs associated with COPD have been well documented. The total economic burden of COPD in 2010 was estimated at $49.9 billion, which included $29.5 billion in direct health care expenditures, $8.0 billion in indirect morbidity costs, and $12.4 billion in indirect mortality costs.[5]

Medications in COPD can be effective in improving health outcomes and reducing costs if they are used appropriately by patients. Only 40 – 60% of individuals with COPD adhere to pharmacotherapy.[6] The most common type of non-adherence to therapy is underuse; which is previously shown to be associated with worse outcomes.[7] The issue is more serious among patients who are newly diagnosed with COPD. Previous studies conducted in the US have shown that 23–52% of patients did not receive any COPD-related pharmacotherapy following diagnosis.[8-10] Identification and maintenance pharmacologic treatment of COPD patients earlier in the course of their disease could help manage disease progression and reduce incidence of outcomes such as exacerbations.[1]

To our knowledge, no currently published study describes the extent and type of maintenance therapy use among newly diagnosed COPD patients within a managed care setting. Data is missing on medication use behavior among patients who are newly diagnosed with COPD. It is important to understand which maintenance therapies do COPD patients initiate at the time of diagnosis and how adherent these newly diagnosed patients are to maintenance medications. The goal of this study is to describe medication use over a two year follow-up period post their diagnosis and describe health outcomes, specifically - exacerbations and healthcare expenditure among newly diagnosed COPD patients.

METHODS

Data Source

This study used the Truven Commercial Claims and Encounters Database. The Commercial database contains integrated medical and pharmacy claims data that is sourced directly from health plans and employers, representing over 35 million commercial lives annually. They include detailed cost, use, and outcomes data for healthcare services performed in inpatient and outpatient settings, prescription drug claims, as well as information on patient enrollment.

Study Design

The first long acting maintenance medication dispensing during the year 2011 be called the index date and will mark the beginning of the observation period. The pre-index period will consist of the 12 months prior to the index date. During these 12 months, the patients should have at least one diagnosis of COPD defined using an ICD-9-CM code of [491.xx, 492.xx, 496.xx] at any

position. Patients with a history of long acting maintenance medication (Appendix 1) were excluded from the study to ensure identification of new initiators of maintenance therapy. Baseline period consisted of 12 months post the index date when demographic characteristics, comorbidities, comedications and baseline adherence rates and baseline exacerbations and costs were obtained. For outcomes assessment, exacerbation events and healthcare expenditure (total, medical and pharmacy) were measured over a 12-month follow-up period after the baseline period. Figure 1 describes the overall study design of this study.

Sample

1. At least one long-acting inhaled therapy prescription in 2011 (see Appendix for the complete list of medications) with the first prescription defined as the index date.
2. At least one hospitalization or emergency department visit with at any position diagnosis of COPD (ICD-9-CM codes: 491.xx, 492.xx, and 496.xx) or two outpatient visits with a primary or secondary diagnosis of COPD in the 12-month baseline period (in 2011).
3. At least 12 months of continuous enrollment before the index date and 24 months of continuous enrollment after the index date
4. Aged 40 or older at the index date

Adherence

Adherence was measured using proportion of days covered (PDC). PDC assesses how many days do individuals have medication in their possession. COPD medications included inhaled corticosteroids (alone or in combination with long acting beta-agonists (LABA)), anticholinergics, LABA only and methylxanthines. This study did not differentiate adherence

across therapeutic class or individual drugs. PDC values ranged from 0 to 1 and were calculated as the number of days with drug on hand divided by 365 days. Switching and augmentation from the initial medication at index was not considered as end of therapy. Patients with a PDC of ≥0.80 were classified as adherent to maintenance medication, otherwise, patients were considered non-adherent.

Dependent Variables

1. Exacerbations: COPD related exacerbations are defined based on visits. A visit was defined as a unique date of service. For hospitalizations, a unique admission and discharge date were identified. Two exacerbations occurring within 14 days of the first one were classified as one event in order to identify discrete events. COPD-related exacerbation were defined as:
    - Hospitalization with a primary discharge diagnosis of COPD.
    - ED visit with a primary diagnosis of COPD.
    - COPD-related physician visit with a primary diagnosis of COPD and receipt of oral corticosteroid or antibiotic prescription within 7 days of physician visit (abbreviated as Phy+Rx).
2. Healthcare expenditure: Healthcare expenditure was estimated using the costs paid to the provider for the service after applicable discounts and also any deductibles, coinsurance, and copayment.
    - COPD-related medical costs: Defined as the costs for claims with a primary diagnosis of COPD; for hospitalizations, all claims of a hospitalization with a primary discharge diagnosis of COPD will be used.

- COPD-related pharmacy costs: Defined as the costs for claims for COPD medications – both maintenance and rescue (See Table 1).
- Total COPD-related costs: Sum of COPD-related medical and pharmacy costs.

Other Study Variables

Patient demographics were assessed at the COPD index date. Age, gender and region (Northeast, North Central, South, and West) were obtained from the eligibility files. The Charlson comorbidity index was calculated for each patient based on the presence of ICD-9-CM codes in the 12-month baseline period. Asthma, Depression and Cardiovascular diseases were identified using ICD-9-CM codes and a binary indicator variable was created for these three comorbid conditions. Use of home oxygen therapy was identified using a medical claim with a procedure code for home oxygen therapy.

Statistical Analyses

Descriptive statistics examined sociodemographic and clinical characteristics of the study sample. Unadjusted all-cause exacerbation prevalence (over 1.5 years) and Healthcare expenditure (means [SDs]) were reported overall, and by adherence status. After adjustment for covariates, the associations of COPD maintenance medication adherence (primary independent variables) with exacerbation (dependent variable) were estimated by using logistic regression models. Adjusted Odds ratios (RRs) with 95% CIs were reported. To estimate the influence of the independent adherence measure on healthcare expenditure, the other dependent measure, generalized linear models (GLMs) with a beta distribution and a log-link function, were used to approximate the highly right-skewed distribution of cost data.35,36 Stratifications were conducted across patients with or without comorbid asthma. Predicted probabilities of

exacerbation were estimated to show differential effects of adherence on risk of exacerbations across asthmatic and non-asthmatic individuals. These predicted probabilities of exacerbation were estimated using a logistic regression model after adjusting for confounders (shown above). Predicted probabilities were estimated across age groups and counts of rescue medications. All analyses were performed using PROC LOGISTIC and GENMOD (SAS version 9.2; SAS Institute Inc, Cary, North Carolina) and LOGIT (STATA version 11.1; Stata Corp, College Station, Texas).

RESULTS

A sample of 17,785 beneficiaries with COPD who had at least one maintenance medication prescription claim and one ICD-9-CM based medical claim were identified during the 12-month identification period. This sample was predominantly female (60.28%), with a mean age of 55 years (**Table 1**). Cardiovascular disorders were the most common comorbid condition (48.29%), followed by asthma (32.22%). Over 60% of beneficiaries used COPD rescue medications during the baseline period, and 6.06% of the population had an exacerbation event in the baseline period. COPD patients who experienced an exacerbation in the 12 month outcomes period had a higher mean age, were less likely to have comorbid asthma, more likely to have comorbid CV diseases, higher baseline comedication use, were more likely to have an exacerbation and had higher medication adherence during the 12-month pre-index period.

Medication adherence for COPD newly diagnosed COPD patients was 58.49% during the first year with a mean PDC=0.74 (SD = 0.31) (**Figure 2**). However, the adherence rates fell down to 27.61% during the second year (follow-up period).

Unadjusted Results

Table 2 presents data on the prevalence of exacerbations and healthcare expenditure by medication adherence status. Exacerbations were observed less frequently (4.76%) in COPD patients who were adherent as compared with patients who had a lower medication adherence (7.90%). Patients who were adherent to maintenance medications also were less likely to be infrequent (1.29%) and frequent exacerbators (3.47%) as compared patients who were non-adherent (2.28% and 5.62%, respectively). Adherent patients also had lower total COPD-related healthcare expenditure as compared to non-adherent patients ($4172.2 vs $5090.81), as well as lower medical ($347.93 vs $537.25) and pharmacy ($3824.27 vs $4553.55) spending. Similar findings were seen in all-cause expenditure across adherent and non-adherent individuals.

Adjusted Results

After adjusting for covariates, patients non adherent to COPD maintenance medications had a significantly higher exacerbation risk (OR = 1.55; 95% CI, 1.35– 1.79) relative to adherent COPD patients (**Table 3**). Prior history of exacerbation during the baseline period was an important predictor of an exacerbation during the 12 month follow-up period. (OR = 4.73; 95% CI, 3.94 – 5.66). Other factors associated with exacerbations include increasing age (OR = 1.05, 95% CI, 1.03 – 1.06) and presence of rescue medication use: SABA (OR = 1.44; 95% CI, 1.23 – 1.69); OCS (OR = 1.48; 95% CI, 1.26 – 1.75); Ipratropium (OR = 1.59; 95% CI, 1.21– 2.11) or oxygen therapy utilization (OR = 2.63; 95% CI, 2.22 – 3.13) during the baseline period.

Adherent COPD patients also exhibited significantly lower total health care expenditure (– $784.06; $P<0.001$) compared non-adherent patients, with total healthcare expenditure driven by

decreases in pharmacy cost (–$543.12; *P*< 0.001) (**Figure 3**). Medical expenditure was not different across adherent and non-adherent patients with a new diagnosis of COPD.

Stratification for comorbid asthma

As shown in Table1, 32% of the population had a diagnosis of comorbid asthma during the baseline period. The adjusted logistic regression model showed that presence of asthma has a protective effect on the risk of exacerbation (OR = 0.65; 95% CI, 0.55–0.77). Stratified analyses were conducted across patients with and without comorbid asthma to estimate the risk of exacerbations across adherent and non-adherent patients. The predicted probabilities of exacerbations are described across age-groups and counts of rescue medication refills (**Figure 4**). Higher age and increasing rescue medication use were associated with a higher risk of exacerbations. Lower adherence was associated with a higher risk of exacerbations among both the stratified populations with or without comorbid asthma.

DISCUSSION

Results of this study demonstrated that among newly diagnosed COPD patients higher adherence to maintenance medications of proven benefit in COPD appeared to be significantly associated with reduced exacerbation rates and total healthcare expenditure. Increased adherence to maintenance medications at baseline also resulted in significant decreases in reduced pharmacy expenditure during the 12 month outcomes period. For newly diagnosed COPD patients, no study has characterized medication use behavior especially adherence over two subsequent years. Among newly diagnosed COPD patients, medication adherence rates during the second year of COPD management fell down to 27.61% (PDC>0.80).

Current recommendation for management of COPD includes a combination of non-pharmacologic treatment with vaccines, physical activity and smoking cessation along with pharmacologic treatment. Several randomized trials and real world studies suggest greater benefit with early Pharmacologic intervention.[11-13] Analysis of UPLIFT study indicates that patients with GOLD Stage II COPD had greatest improvements in FEV_1 than the other study populations.[11] TORCH study also demonstrated greatest FEV_1 improvements in Stage II COPD as compared to patients with GOLD Stage III or IV COPD.[12] These improvements in lung function translated into lower rates of hospitalizations among these patients.[11] Early intervention with initial maintenance treatment and adherence to those medications could play an important role for management of non-severe COPD patients.

Several previous studies have examined the relationship between adherence and healthcare resource utilization and cost. A literature review conducted by Muszbek et al. found 23 studies across diabetes, hypertension, heart disease/failure, and dyslipidemia, patients. In these studies, higher adherence was generally found to be associated with lower overall healthcare cost.[14] Wastila and colleagues looked at maintenance medication use among Medicare beneficiaries within a prevalent COPD patient population.[15] Their study demonstrated that medication use over an extended time period was associated with a lower risk of hospitalizations and better economic outcomes. The present study extends this literature to show that the inverse relationship between adherence and exacerbations and cost is observed in the context of newly initiated COPD treatments within a managed care setting.

Administrative claims data lack clinical laboratory data and other information needed to assess COPD severity.[16,17] This study used baseline supplemental oxygen use and baseline COPD short acting medication use to address this limitation. Supplemental oxygen use is indicative of Stage IV COPD, and has been used as a proxy for COPD severity in multiple other studies.[16,18-20] Short acting medication use was controlled for as an independent variable in all the adjusted analysis. Short acting medication use can be considered a marker of COPD severity because individuals who do not use and/or adhere to maintenance medications often use rescue drugs to treat exacerbations.[19]

COPD and asthma can be difficult to differentiate using just claims data and so subpopulation analyses were conducted by restricting analyses to beneficiaries with no evidence of asthma.[15] The logistic regression model showed that patients with asthma had a protective effect on the risk of exacerbation. In order to explore the extent to which asthma was driving the association between adherence and future risk of exacerbation, a stratified analysis was conducted across patients with and without comorbid asthma. Predicted probabilities for exacerbations were estimated for COPD patients across these two sub-groups. These analyses found no differences in interpretation of association between medication adherence and risk of a future exacerbation. Asthma is a disease prevalent among younger patients. Because of years of managing asthma related respiratory symptoms, these patients could potentially identify acute worsening of the disease early and manage their symptoms better leading to a potential protective effect among COPD patients with comorbid asthma.

This study also is an important first step in looking at adherence rates across multiple year periods. An important insight that the study provides is a large reduction in adherence levels during the second year of maintenance medication use among newly diagnosed COPD patients. No other study to authors' knowledge has previously demonstrated a two year trend in adherence among with a COPD patient population. Understanding medication use behavior over extended period of time is important in the context of maintenance medications. These medications need to be taken over an extended period of time to help ensure appropriate management of COPD patients.

Several limitations exist in this study. First, adherence to COPD treatments was measured using administrative claims data. A claim for a prescription refill does not necessarily mean that a patient is taking the medication as prescribed. There are several possible situations where patients may obtain refills before a prescription runs out; patients may not be using inhalers correctly. Several measures exist to demonstrate medication use be behavior. PDC was selected as a measure of choice because of its increasing relevance in the US health policy environment and its direct applicability to health plans. Pharmacy Quality Alliance also published a review of adherence measures and identified PDC as a measure of choice to look at medication use behavior from claims databases.[21] Second, claims databases typically do not contain severity information for COPD patients (i.e., based on spirometry tests). COPD severity is correlated with resource utilization, adherence, and treatment choice, and therefore can act as a confounding factor in the analysis. However, the regression analysis of resource utilization included a variety of covariates that are indirect measures for COPD severity. This statistical approach reduces the potential for bias. Third, our analysis is limited to patients that are newly initiating treatment of COPD and therefore is unlikely to include patients with severe COPD. These results may not be

generalized to other settings or patient groups. This study demonstrates that as patients gain more experience with inhaled treatments, their medication use behavior changes and that needs to be taken into account while interpreting results of this study.

CONCLUSION

This study demonstrated that COPD maintenance medication use was associated with a reduced risk of future exacerbations and total healthcare expenditure among COPD patients newly initiating maintenance medications. The results also show a large reduction in adherence during the second year of medication use. The findings from this study have health policy relevance and highlight the need for interventions to improve medication adherence over prolonged period of time.

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Tables Manuscript 2

Table 1: Baseline demographic characteristics of patients newly initiating maintenance medications of COPD				
Variable	**Initial Maintenance Rx (n=17,785)**	**Non-exacerbator**	**Exacerbator**	**p-value**
Age, yr (mean (SE))	54.65 (5.68)	54.01 (5.78)	55.37 (5.47)	**<0.0001***
Sex, %				
Male (sex=1)	39.72%	39.67%	40.67%	0.5509
Female (sex=2)	60.28%	60.33%	59.33%	
Region				
North East (region =1)	15.04%	15.05%	14.78%	
North Central (region =2)	26.49%	26.17%	32.56%	
South (region =3)	35.66%	35.36%	41.33%	**<0.0001***
West (region =4)	22.34%	22.94%	11.00%	
Unknown (region =5)	0.47%	0.47%	0.33%	
Season				
Spring (season =1)	27.77%	27.76%	27.89%	
Summer (season =2)	20.36%	20.26%	22.22%	**<0.0001***
Fall (season =3)	22.07%	22.08%	22.00%	
Winter (season =4)	29.79%	29.90%	27.89%	
Charlson Comorbidity Index (mean (SE))	1.64 (1.51)	1.57 (1.51)	1.72 (1.51)	**<0.0001***
Comorbidities (%, p-value)				
Asthma	32.22%	32.58%	25.44%	**<0.0001***
Depression	19.52%	19.68%	19.34%	0.5666
Cardiovascular Disorders	48.29%	47.26%	49.46%	**0.0035***
Comedications (%, p-value)				
SABA	57.94%	51.52%	65.26%	**<0.0001***
OCS	44.30%	39.84%	49.40%	**<0.0001***
Ipratropium	3.77%	3.15%	4.47%	**<0.0001***
Antibiotics	69.87%	69.34%	70.48%	0.0967
O_2 Therapy	8.93%	6.27%	11.97%	**<0.0001***
Adherence in Pre-Index	58.49%	41.93%	72.99%	**<0.0001***
Exacerbation History	6.06%	4.06%	8.35%	**<0.0001***

Table 2: Unadjusted healthcare expenditure and prevalence of exacerbations across adherent and non-adherent individuals with COPD			
	Overall	**Non-adherent (42%)**	**Adherent (58%)**
COPD Related HCRU (n, %)			
COPD Related Exacerbation	1078 (6.06%)	583 (7.90%)	495 (4.76%)
Non-exacerbator	16707 (93.94%)	6800 (92.10%)	9907 (95.24%)
Infrequent exacerbation	168 (1.70%)	134 (2.28%)	135 (1.29%)
Frequent Exacerbations	776 (4.36%)	415 (5.62%)	361 (3.47%)
COPD-related Costs (mean(SE))			
Medical Costs	426.52 (3135.73)	537.25 (3110.65)	347.93 (3151.21)
Pharmacy Costs	4127.01 (8903.53)	4553.55 (8366.18)	4172.2 (8132.92)
Total Costs	4553.54 (8238.10)	5090.81 (9042.93)	3824.27 (8783.92)
All-cause Costs (mean(SE))			
Medical Costs	7457.80 (27853.15)	8118.19 (26688.72)	6995.2 (28632.78)
Pharmacy Costs	2867.11 (5182.12)	3139.82 (5145.52)	2676.07 (5199.33)
Total Costs	10324.91 (28824.40)	11258.01 (27662.05)	9671.28 (29595.19)

Table 3: Associations of maintenance medication adherence and risk of exacerbations among patients with COPD			
Variable	**Odds Ratio (e^{β})**	**Confidence Interval (95%)**	**p-value**
Non-Adherence in the Prior Year (pdc<0.8)	1.55	1.35 - 1.79	**<0.0001***
History of exacerbation	4.73	3.94 - 5.66	**<0.0001***
Age, yr (mean (SE))	1.05	1.03 - 1.06	**<0.0001***
Sex, %			
Male (sex=1)	1.01	0.87 - 1.16	0.5026
Female (sex=2)	Reference	Reference	
Region			
North East (region =1)	Reference	Reference	
North Central (region =2)	0.969	0.78 - 1.21	
South (region =3)	0.918	0.74 - 1.14	**<0.0001***
West (region =4)	0.46	0.35 - 0.61	
Unknown (region =5)	0.61	0.19 - 2.02	
Season			
Spring (season =1)	Reference	Reference	
Summer (season =2)	1.07	0.88 - 1.31	0.7173
Fall (season =3)	0.98	0.80 - 1.19	
Winter (season =4)	0.69	0.79 - 1.15	
Charlson Comorbidity Index (mean (SE))	1.04	0.99 - 1.09	0.0822
Comorbidities (%, p-value)			
Asthma	0.65	0.55 - 0.77	**<0.0001***
Depression	1.19	1.00 - 1.41	0.0504
Cardiovascular Disorders	0.81	0.69 - 0.93	**0.0038***
Comedications			
SABA	1.44	1.23 - 1.69	**<0.0001***
OCS	1.48	1.26 - 1.75	**<0.0001***
Ipratropium	1.59	1.21 - 2.11	**0.0011***
Antibiotics	0.91	0.77 - 1.08	0.2717
O2 Therapy	2.63	2.22 - 3.13	**<0.0001***

Figures Manuscript 2

Figure 1: Study Design

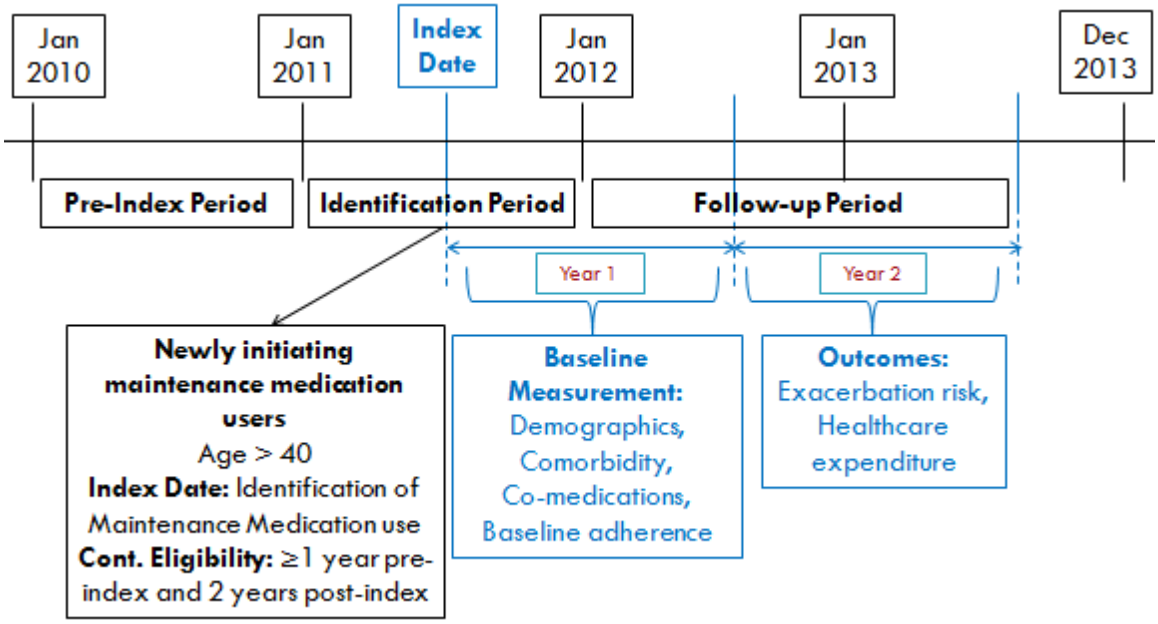


Figure 2: Adherence levels among COPD patients newly initiating maintenance medications

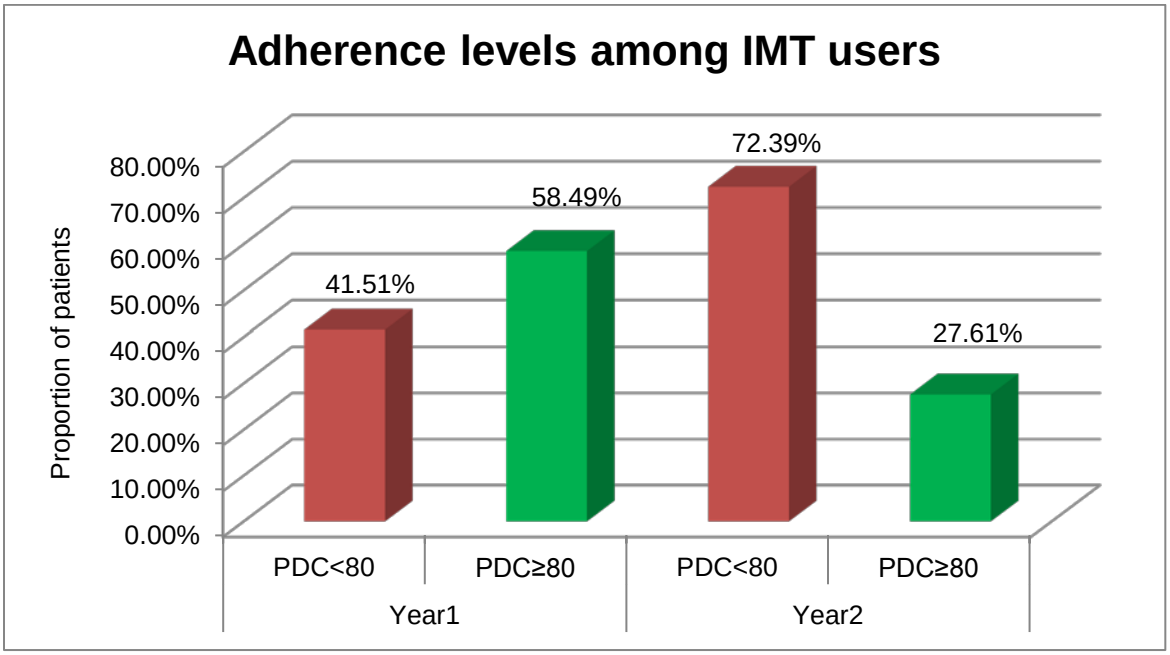
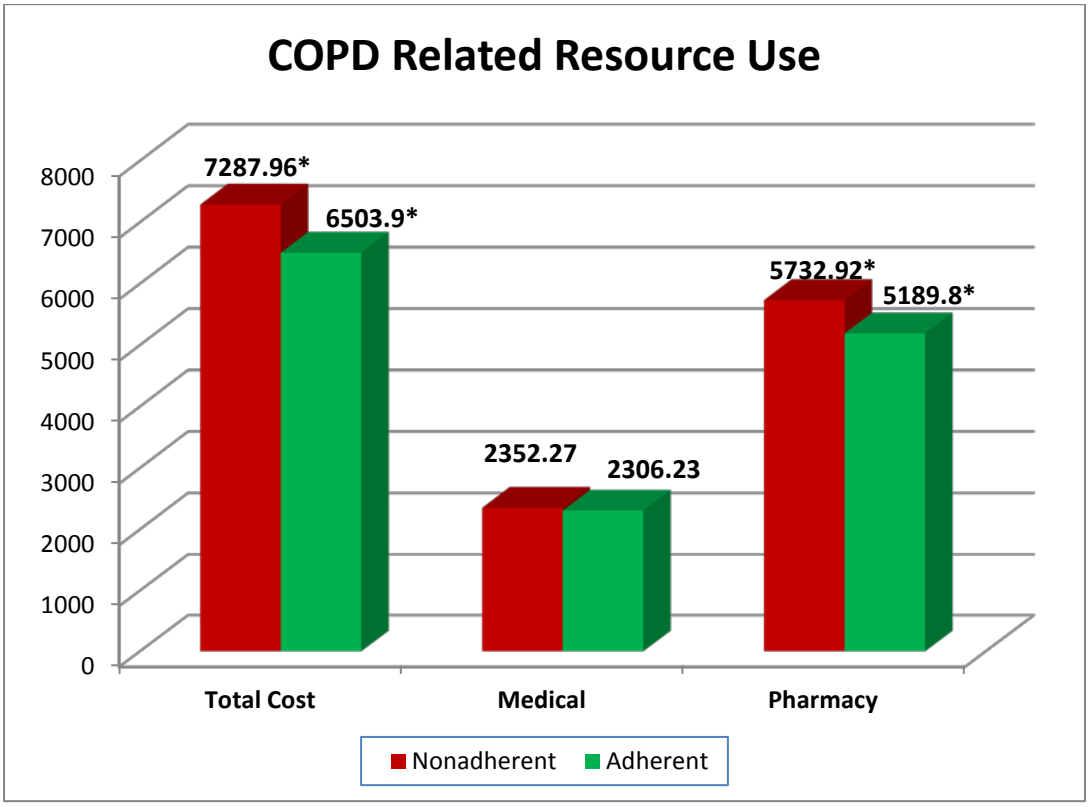
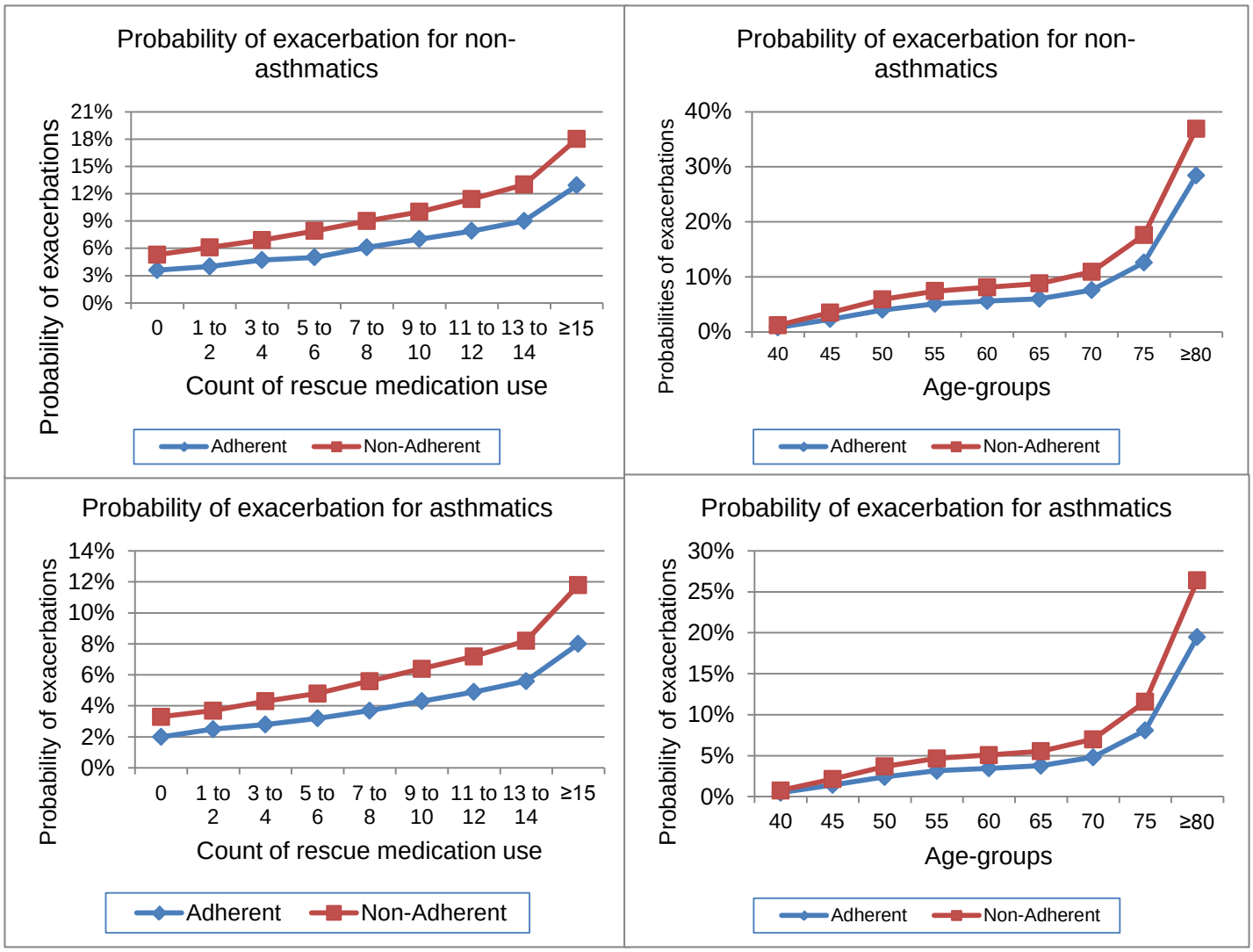


Figure 3: COPD Related costs among IMT patients who were adherent and non-adherent to maintenance treatment



*p<0.001

Figure 4: Predicted probabilities of exacerbations across adherence levels stratified across patients with or without asthma



Appendix A: List of Maintenance and Rescue medications for COPD

Maintenance Medications	
Inhaled Corticosteroids (ICS) 1) Beclomethasone 2) Budesonide 3) Flunisolide 4) Fluticasone 5) Triamcinolone	**Inhaled corticosteroid + Long-acting beta-agonist combination product (ICS+LABA)** 1) Fluticasone + Salmeterol (all doses) **2)** Budesonide + Formoterol (all doses)
Long-acting Beta-agonists (LABA) 1) Formoterol 2) Salmeterol 3) Arformoterol 4) Indacaterol	**Anticholinergics (LAMA)** 1) Tiotropium 2) Aclidinium
MethylXanthenes 1) Aminophylline 2) Dyphylline 3) Oxtriphylline Theophylline	
Rescue Medications	
Short-Acting, Inhaled Beta-2 Agonist (SABA) 1) Albuterol 2) Bitolterol 3) Isoetharine 4) Isoproterenol 5) Levalbuterol 6) Metaproterenol 7) Pirbuterol 8) Terbutaline	**Anticholinergics** 1) Nebulized Ipratropium or Ipratropium/Albuterol combination
Oral Corticosteroids (OCS) 1) Betamethasone 2) Cortisone 3) Dexamethasone 4) Hydrocortisone 5) Methylprednisolone 6) Prednisolone 7) Prednisone **8)** Triamcinolone	**Antibiotics** 1. Macrolides (azithromycin, clarithromycin, dirithromycin, erythromycin) 2. Fluoroquinolones (ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin) 3. Cephalosporin (cephalexin, cefaclor, cefadroxil, cefdinir, cefditoren, cefepime, cefixime, cefotaxime, cefpodoxime, cefprozil, ceftazidime, ceftibuten, ceftriaxone, cefuroxime) 4. Trimethoprim-Sulfamethoxazole 5. Tetracycline derivatives (doxycycline) 6. Penicillins (amoxcillin, ampicillin)

Overall Conclusion and Policy Implications

Medications are most often considered the most cost-effective intervention for disease management in patients with chronic conditions. The study shows that maintenance medications are often under-utilized in a group of newly diagnosed individuals and among those with pre-existing disease. The study found that among a cohort of newly diagnosed individuals only 1 in 4 individuals with COPD remained adherent to their maintenance medications over a two year period. Among a cohort of individuals who had pre-existing disease, adherence was again poor and only 50% of the patients were adherent to medications in the first year of follow-up.

This study also demonstrated that adherence to medications can be beneficial in reducing subsequent costs and reducing adverse outcomes such as exacerbations which are linked to disease progression. Non-adherence individuals were associated with a 55% higher risk of exacerbations and $784.06 higher healthcare expenditure per patient as compared to an adherent individual.

From a policy perspective, this study demonstrated that prior medication adherence was the best predictor of future medication adherence which shows the importance of patient level behavioral aspects that need to be further understood to help improve medication use behavior. Newly diagnosed individuals are best positioned to obtain treatment benefits until a progressive disorder such as COPD worsens in disease severity. Non-adherent individuals also used other short acting medications to manage their symptoms temporarily, rather than using maintenance medications which could improve their long-term outcomes. Within a group of newly diagnosed COPD patients, educational opportunities exist in explaining long-term disease progression of COPD

and describing the importance of adherence to maintenance medications to manage this progressive disorder.