
Study report
Study code:D2287R00123
Version 3.0
Date Dec 12 2018

**Association of COPD Maintenance Medication
Adherence with Resource Use and Cost among
COPD Patients**

----Retrospective observational cohort study

Sponsor:

AstraZeneca

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	or	Explanation
special term		
AE		Adverse event
EMR		Electronic Medical Records
ER		Emergency Room
GLM		Generalized Linear Model
GEE		Generalized Estimating Equation
HIS		Health Information System
HRU		Healthcare Resource Use
ICS		Inhaled Corticosteroids
ICS/LABA		Inhaled Corticosteroid/Long-Acting Beta-Agonist
ICU		Intensive Care Unit
IEC		Independent Ethics Committee
IRB		Internal Review Board
ISERP		Independent Safety Epidemiology Review Panel
IVCS		Intravenous Corticosteroid
LOS		Length of Stay
LTRA		Leukotriene Receptor Antagonists
MPR		Medication Possession Ratio
OCS		Oral Corticosteroid
OLM		Other Leukotriene Modifiers
PDC		Percentage of Days' Covered
SABA		Short-Acting Beta-Agonist
LAMA		Long-acting muscarinic antagonist
SAP		Statistical Analysis Plan
SOP		Standard Operating Procedure
UC		Urgent Care
FAS		Full Analysis Set
SABD		Short Acting Bronchodilators

STUDY REPORT SYNOPSIS

This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

This submission/document contains trade secrets and confidential commercial information, disclosure of which was prohibited without providing advance notice to AstraZeneca (AZ) and opportunity to object.

Background/rationale:

Chronic obstructive pulmonary disease (COPD) was a leading cause of morbidity and mortality worldwide and at the same time COPD incurs significant burden in China. Full benefits of a therapy could only be reaped if the patient complies as closely as possible with the physicians' prescription. However, in real world the compliance for COPD patients was worrisome. Poor adherence leads to more healthcare resource consumption.

Maintenance medication for COPD patients improve disease symptoms and avoid exacerbations. Efficacy reported in clinical trials might not reflect effectiveness in real-world settings due to one major reason of non-adherence. Fewer hospitalization and lower health expenditure were reported in COPD patients with higher maintenance medication adherence in US.

No study in China on the clinical and economic consequence of COPD medication nonadherence in real world setting. It was necessary to carry out a well-designed study to understand COPD medication adherence and its association with healthcare resource utilization among COPD patients.

Objectives:

The objective of the study was to identify the association of COPD maintenance medication adherence with resource use and cost among COPD patients.

Primary objective

- To examine the association of COPD maintenance medication (inhaler combination with ICS/LABA) adherence with COPD exacerbation healthcare resource utilization among COPD patients with exacerbation history.

Secondary objective

- To examine the association of COPD maintenance medication (inhaler combination with ICS/LABA) adherence with all-cause hospitalization resource utilization among COPD patients with exacerbation history

Exploratory objective

- To explore whether the association of COPD maintenance medication adherence with healthcare resource utilization was different by medication class among COPD patients with exacerbation history.

- To explore whether the association of COPD maintenance medication adherence with healthcare resource utilization was different by medication class among COPD patients.

Study design:

This study was a retrospective database analysis using 2014-2016 City Medical Insurance Data of a metropolitan city in China.

Data source:

Health insurance database of a metropolitan city in China was used for this study. All outpatient and inpatient visits for one patient during 2014-2016 were available. The date for the first claim of COPD maintenance medication of interest in 2015 constituted the index date.

Study population:

This study included patients with a clinical diagnosis of COPD during 2015.

COPD patient was classified into three medication groups based on their maintenance medication category prescribed on the index date, i.e. inhaled bronchodilator group, inhaled combination with ICS/LABA group and oral therapy group (including methylxanthine and mucolytic) and tracked for their adherence. According to GOLD guideline 2018, inhaled bronchodilators are recommended over oral bronchodilators for treatment of stable COPD. Long-term treatment with ICS might be considered in association with Long-Acting Beta-Agonist (LABA) for patients with a history of exacerbation despite appropriate treatment with long-acting bronchodilators. In our study, patients on inhaled bronchodilator with ICS was paid special attention to for primary and secondary objective purpose.

A total of 11708 patients were included for full analysis set (FAS). Among those, 6011 with exacerbation history were included for primary endpoint analysis and 6011 for the exploratory objective 1 analysis.

Inclusion criteria:

- Patients diagnosed with COPD in 2015
- Patients had continuous eligibility for 1 year prior to and 1 year after the index date through December 31, 2016
- Patients had at least one COPD exacerbation during 1 year prior to the index date (for primary, secondary and the first exploratory objectives)
- Patients had at least 2 COPD maintenance medication claims, as 2 claims are recommended to calculate adherence

Exclusion criteria:

- Inability to determine diagnoses from claims
- Individuals with other chronic respiratory conditions such as respiratory cancer, pulmonary fibrosis, asthma
- Individuals with incomplete records was excluded from the study population

Adherence Calculation:

Treatment adherence was based upon a percentage of days' covered (PDC) calculation. The PDC was calculated as the total days' supply (accounting for overlaps) of prescribed target medications divided by the days within the observation period of interest, expressed as a %. For the purposes of this study, it was measured as the number of days with COPD maintenance medication divided by duration of therapy (DOT) with these agents (365 days). The range of PDC was from 0 to 1. Patients was deemed to be adherent if their PDC was $\geq 80\%$ and not adherent if their PDC was $<80\%$ over the post-index observation period.

Statistical methods:**General Aspects**

Descriptive statistics was used for all variables, as appropriate. Continuous variables was summarized by the number of observations, mean, standard deviation, median, minimum, maximum, first quartile and third quartile. Categorical variables was summarized by frequency counts and percentages at each category. Number of patients and number of missing for each variable was summarized. We chose different subset for the study population to do the analysis based on the analysis needs.

As to multivariate analysis, in order to reduce selection bias, based on prior knowledge, all unbalanced baseline characteristics, that was age, sex, comorbidity, baseline COPD severity indicators (exacerbation times, COPD related inpatient visit times, COPD treatment cost), COPD medication prescription and explanatory variables that was adherence, medication class (inhalation with/without ICS, inhalation/oral) was put into the model to control potential confounding.

Logistic regression was used to estimate the risk of any hospitalization. Negative binomial regression model tracking exacerbation events was conducted with the cohort (low vs high adherence) as the factor and with other applicable covariates or factors. Generalized Linear Models (GLMs) with a gamma distribution and log link was used to approximate the highly right-skewed distribution of medical expenditure.

For exploratory objectives, the interaction of medication class * adherence or subgroup analysis (by medication class) was considered when conducting the regression model.

Sample Size and Power Calculations

Based on a query of the number of candidates for this study using the inclusion criteria in the database, 1261 high adherence and 10447 low adherence COPD patients were identified as eligible for this study, suggesting that there were more than adequate numbers of patients to conduct this study and that under-powering was not a risk.

Results:**1. Patient Selection and Baseline Characteristics:**

A total of 567 (31.9%) and 1210 (68.1%) patients were identified as high adherence and low adherence groups for inhale combination with ICS/LABA user category among COPD patients with exacerbation history, with mean (SD) age 71.0 (8.9) and 71.6 (9.9) ($P=0.83$)

and male 83.8%. Male accounted for 83.8% and 76.1% for the two cohorts, respectively (P=0.07). During baseline period (the one year period prior to the index date), 33.3% patients in the high adherence group and 42.2% in the low adherence group had at least one inpatient COPD visit (P= 0.002), the average baseline COPD related cost were 13575.2 and 13593.2 Chinese Yuan (CNY) for high adherence group and low adherence group respectively (P<0.001). Besides, high adherence group had more maintenance medication prescriptions during baseline (all P<0.001).

2. Major Followup Results: high adherence correlated to reduced inpatient AECOPD risk, occurrence rate and cost comparing with low adherence cohort among COPD population with exacerbation history

During the follow-up one year after index date, for patients using inhale combination with ICS/LABA among COPD population with exacerbation history, high adherence (PDC \geq 0.80) was significantly associated with reduced inpatient AECOPD risk (adjusted odds ratio (OR)= 0.555; 95% CI: 0.43, 0.71), lower rate of inpatient AECOPD (adjusted rate ratio (RR)=0.76; 95% CI: 0.64, 0.91) and lower inpatient AECOPD treatment cost (11923.7 vs 19138.7 (CNY), mean difference (MD)[95% CI]: -7215.0[-12893.8,-1536.3]), compared with low adherence group with PDC<0.80.

3. Interaction and subgroup analysis: in oral therapy user category, high adherence was significantly correlated with higher inpatient AECOPD risk , more inpatient AECOPD event rate and higher one-year inpatient AECOPD treatment cost; while in inhale bronchodilator user category, no significant correlation was observed among COPD population with exacerbation history.

Test for interaction between drug category and adherence indicates that there was a significant interactive effect of drug category and adherence on inpatient AECOPD risk (P \leq 0.001), rate of inpatient AECOPD (P<0.001) and one-year inpatient AECOPD treatment cost (P=0.012) among both COPD population with exacerbation history as well as COPD population (N=11708). Only in inhale combination with ICS/LABA user category, high adherence demonstrated protective effect in terms of both clinical and economic endpoints; while in inhale bronchodilator user category, no significant association was observed; and in oral therapy user category, high adherence was significantly correlated with higher inpatient AECOPD risk , more inpatient AECOPD event rate and higher one-year inpatient AECOPD treatment cost.

Conclusion:

Results from this study indicated that

1. High adherence to inhale combination with ICS/LABA therapy over an extended period was correlated with better clinical outcomes in terms of reduced inpatient AECOPD risk and inpatient AECOPD frequency
2. Improving adherence to inhale combination with ICS/LABA therapy could provide significant cost saving for inpatient AECOPD treatment

3. Among user of oral or inhale bronchodilator group, high adherence did not demonstrate protective clinical effectiveness and cost saving in terms of inpatient AECOPD treatment
4. The results highlighted the need to improve the adherence to inhale combination with ICS/LABA among COPD patients to reduce inpatient exacerbations and associated expenditure