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ASSOCIATION BETWEEN DISPENSING CHANNEL AND CHRONIC OBSTRUCTIVE PULMONARY DISORDER EXACERBATIONS AMONG MEDICARE BENEFICIARIES

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ASSOCIATION BETWEEN DISPENSING CHANNEL AND CHRONIC OBSTRUCTIVE PULMONARY DISORDER EXACERBATIONS AMONG MEDICARE BENEFICIARIES

THESIS

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in the College of Pharmacy at the University of Kentucky

By

April Shenice Prather, Pharm.D.
Lexington, Kentucky

Co-Directors: Dr. Jeffery Talbert, Professor of Pharmacy Practice and Science and Dr. Daniela C. Moga, Professor of Pharmacy Practice and Science
Lexington, Kentucky
2018

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ABSTRACT OF THESIS

ASSOCIATION BETWEEN DISPENSING CHANNEL AND CHRONIC OBSTRUCTIVE PULMONARY DISORDER EXACERBATIONS AMONG MEDICARE BENEFICIARIES

Elderly patients with chronic obstructive pulmonary disorder may be at increased risk of exacerbation due to physical and cognitive deficits that make proper inhaled medication adherence more difficult despite consistent medication access. This retrospective study utilized administrative medical and pharmacy claims data to examine the likelihood of having a COPD exacerbation requiring acute medical care by means of an emergency room visit or hospitalization in elderly patients receiving maintenance COPD medications from mail order and retail pharmacies. It was hypothesized that mail order patients would be more likely to experience exacerbations despite differences in medication access when compared to retail patients. The primary outcome of interest was exacerbation frequency expressed as the incidence density rate, and the secondary outcome was the proportion of days covered (PDC). The incidence rate ratio for acute exacerbations was not significantly different for mail order and retail groups, indicating patients using mail-order pharmacies were not significantly more likely to experience an exacerbation requiring acute medical care. Despite insignificant differences in incidence rates, mail order patients had significantly higher adherence rates.

KEYWORDS: Chronic Obstructive Pulmonary Disorder, Acute Exacerbations, Medicare, Adherence, Dispensing Channel

April Prather

February 07, 2018
ASSOCIATION BETWEEN DISPENSING CHANNEL AND CHRONIC OBSTRUCTIVE PULMONARY DISORDER EXACERBATIONS AMONG MEDICARE BENEFICIARIES

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A special thanks is also extended to Lucy Wells, who has guided and molded my practical application of managed care techniques. The tremendous support and effort from herself and my fellow coalition pharmacists have played an intricate role in my matriculation through the fellowship program.
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Introduction

Chronic obstructive pulmonary disorder (COPD) is an incurable, progressively life threatening disease that is projected to be the third leading cause of death by 2020. [1] Although the exact prevalence is often underestimated, studies have suggested that prevalence of COPD increases in a stepwise manner with age. [1-3] Medication adherence, evidenced by a high proportion of days covered (PDC), has been associated with fewer respiratory related emergency room visits and hospitalizations for COPD patients in general. [4] The complex regimens used to manage COPD patients, however, may be more problematic in older adults as physical and cognitive changes make proper adherence more difficult despite increased PDC rates. [5]. While several studies have linked obtaining maintenance medications through mail order to increased adherence rates for diabetes, hypertension, and hyperlipidemia [6, 7], few have explored the relationship between the dispensing channel and adherence rates or outcomes for individuals with chronic respiratory disorders. [8]

Chronic Obstructive Pulmonary Disorder in Geriatric Populations

Burden of Disease

Chronic Obstructive Pulmonary Disease (COPD) is a life threatening disorder characterized by progressive airflow limitation from chronic inflammation and structural changes in parenchymal tissues. [9] Estimates of the true burden of COPD are often underreported; however, the prevalence is estimated at approximately 14% in patients over 64 years old. [5] As the population ages, the prevalence is believed to increase in a stepwise manner. The natural course of COPD is marked by recurrent exacerbations associated with decreased lung function, lower quality of life, faster disease progression, and increased mortality. [10] These social implications coupled with the financial burden associated with high healthcare utilization have prompted the Centers for Disease Control and Prevention (CDC) to list reducing COPD-related emergency room visits by 30% and COPD-related hospitalizations by 10% by 2020. [11]

Complexities of Medical Management

Adequate medication adherence is a key factor in reducing exacerbation frequency; however, medication adherence among patients with COPD is currently suboptimal. [12] A primary factor associated with poor adherence is complex medication regimens requiring physical coordination for inhaler usage. [13] Some patients are intentionally non-adherent to medications and deliberately discontinue therapy. On the other hand, unintentional non-adherence is often related to cognitive impairment, language barriers, or physical disabilities. [14] Elderly patients with COPD have highlighted difficulties understanding the medication regimen as a major cause in therapy lapses. Additional concerns with regard to elderly patients managing their COPD include visual and dexterity issues preventing the appropriate use of inhaled devices. [15] These challenges may require interventions beyond medication possession to ensure adequate therapy.
Implications of Inadequate Intervention

Currently, COPD interventions follow a reactive pattern in which patient-physician interaction is limited to treatment of acute illness such as exacerbations requiring immediate medical attention. [16] As a multifactorial, progressive disease, rescue care alone is an inadequate approach to improving disease prognosis. [17] While maintenance medications are integral, failure to implement patient care models that address factors beyond medication possession is detrimental to patient outcomes. Appropriate maintenance pharmacotherapy should be coupled with lifestyle modifications such as smoking cessation and increased physical activity to proactively reduce the frequency of acute exacerbations and decrease disease progression. Interdisciplinary care teams which include primary care providers, nurses, and pharmacists are essential in ensuring continuity of care for optimal outcomes. [18]

Dispensing Channel and Chronic Disorders

Several studies have linked the use of mail order pharmacies to improved health outcomes across several chronic disease states such as diabetes, hypertension, and hyperlipidemia due to higher medication adherence rates. [7, 15] These increased adherence rates have been attributable to the availability of 90 day supply prescriptions when using mail order. In recent years, many prescription drug plans have allowed patients to fill 90-day supply prescription regardless of the dispensing channel. [19] A systematic review of recent studies shows mixed results with regards to whether the use of a mail order pharmacy improves adherence rates with regards to chronic disease. [7] Even though some patients are financially incentivized to use mail order, the ability to obtain the same quantity at a local pharmacy may reduce the perceived benefit of mail order use. Adherence, however, can be measured in various ways, and is difficult to capture through current acceptable methods.

Medication adherence has been evaluated repeatedly by applying measures such as medication possession ratio (MPR) and proportion of days covered (PDC) to administrative claims data. [20] While MPR directly calculates the sum of days’ supply dispensed over a period, PDC considers the medication supply available throughout the period. [21] Both measures reflect a ratio that compares a proxy for days of medication compliance in the numerator to an observed period in the denominator. [22] Unfortunately, these methods are limited because they do not account for personal attributes that lead to non-adherence. More personalized approaches such as direct observation and patient surveys are often limited by increased costs. [23] Healthcare providers not only have the ability to encouraging patients to be more adherent to medications, but also ensure adherence burdens such as regimen comprehension or administration technique are overcome.
Section Two: Specific Aims

Specific Aim and Hypothesis

Because the medication regimens for elderly COPD patients are highly susceptible to adherence problems beyond medication possession, it is critical to assess whether the use of a mail order or retail pharmacy influences health outcomes of this patient population. This study aimed to evaluate the frequency of respiratory-related hospitalizations and emergency room visits in patients filling their COPD maintenance medications at mail order pharmacies compared to patients filling these medications at retail pharmacies.

The specific aims are as follows:

1. Evaluate the likelihood of having a COPD exacerbation requiring acute medical care by means of an emergency room visit or hospitalization in elderly patients receiving maintenance COPD medications from mail order and retail pharmacies

   It was hypothesized that Medicare beneficiaries using mail order pharmacies will be more likely to experience COPD exacerbations requiring hospital care.

2. Measure the adherence rates of elderly patients utilizing mail order and retail pharmacies.

   It was hypothesized that there would not be significant difference between adherence rates among Medicare beneficiaries using different dispensing channels.

The rationale supporting the expressed hypotheses is based upon evidence that medication possession alone is not indicative of appropriate administration techniques or adequate compliance, especially with regard to inhaled medications. Furthermore, the hypotheses account for the value of potential physical interactions with local pharmacy staff in the management of complex regimens.

Significance

As the population of geriatric COPD patients continues to rise, this study will provide additional information for developing health system interventions that improve health outcomes in the presence of adequate medication access. By improving health outcomes and proper medication adherence, we not only reduce the morbidity and mortality associated with COPD, but also reduce overall healthcare spending and utilization linked to preventable events.

Approach

A randomized trial to evaluate the effect of dispensing channel on health outcomes would need to mimic plan benefit designs with mandatory home delivery or retail services. Mandatory mail order has been shown to negatively influence adherence rates and thusly therapy effectiveness.
A design in which the action of randomization can potentially influence the outcome due to human preference would yield inherently biased results; therefore, an observational study controlling for known confounders while allowing patient preference would be more desirable. Previous studies have investigated the association between medication adherence and dispensing channel across several chronic disease states and medication classes. Few of these studies have focused on Medicare eligible populations and even fewer have examined the impact on COPD. Because the results of these studies have generally concluded there is little difference in adherence rates when using mail order over retail pharmacies, it is important to evaluate any variations in health outcomes and quality of care for each dispensing channel. Pharmacists are uniquely trained to assist ambulatory patients in the management of chronic disorders, including COPD. With frequent physical pharmacist interaction, patients can be assessed for regimen comprehension as well as administration technique. This is a benefit not available through mail order pharmacies.

Section Three: Methodology

Research Design

Data Source and Overall Approach

This retrospective, observational study focused on retired beneficiaries enrolled between January 1, 2007 and January 1, 2012 in a Medicare Advantage plan. De-identified and internally linked paid claims with respect to prescriptions, inpatient services, outpatient services, and person-level enrollment information was obtained directly from one of the nation’s largest claims databases, the Humana Comprehensive Health Insights Outcomes Data. Data extraction was completed through consultation with a trained data analyst. Due to the de-identified nature of the data, informed consent was not required from study participants.

A new-user design approach with an active comparator was applied in order to capture the impact of the dispensing channel on the outcomes. While utilizing new-users may limit the observation of study participants with more advanced disease, this approach reducing the challenge of confounding by indication. The active comparator was necessary for the purposes of this study because of the nature of the specified exposure criteria.

Inclusion/Exclusion Criteria

The sample was restricted to patients aged 65 years and older who were diagnosed with COPD as defined by the following: chronic bronchitis (ICD-9 codes 490-491), emphysema (ICD-9 code 492), bronchiectasis (ICD-9 code 494), or chronic airway obstruction (ICD-9 code 496). Inclusion was limited to patients who were continuously enrolled in a Medicare plan with both medical and pharmacy benefits for at least eight months between January 1, 2007 and January 1, 2012. A minimum eight month enrollment period was required in order to observe both a six month preliminary period prior to diagnosis and the subsequent filling of two qualifying inhaled prescriptions. Federally approved inhaled prescription medication for the chronic management of COPD include long-acting beta agonists (LABA), inhaled corticosteroids (ICS), inhaled anti-muscarinics, or a combination product containing these medication classes throughout the study period (see Appendix A for a complete list of qualifying inhaled medications).
Prevalent users, defined as patients with prescription claims for any of the previously specified inhaled therapies within the 6 months preceding the first coded COPD diagnosis during the study period, were excluded. Patients who did not obtain a medication refill within 90 days of expected medication depletion from the initial fill were excluded from the study. Additionally, patients without available diagnostic data were excluded from the study. A total of 28,657 Medicare patients were identified as having COPD. Of this cohort, 4,316 patients met the inclusion criteria. (Figure 3.1) The control population for this study consisted of 3,802 retail pharmacy patients while the intervention arm consisted of 514 mail order patients. There were 512 patients in each treatment arm following propensity score matching.

Figure 3.1 Flow Chart of Sample Selection

Medicare beneficiaries aged 65 using inhaled medications (N=28,657)

Excluded patient with less than 2 prescription fills (N=11,302)

Patients with at least 2 COPD related prescription fills (N=17,355)

Greater than 90 days gap in therapy (N=7,822)

Patients assessed for outcomes data (N=9,533)

Missing diagnostic data (N=5,217)

Cohort before matching (N=4,316)

Mail Order (N=514)  Retail (N=3,802)

1:1 Propensity Matched Cohort (N=1028)

Unable to identify a match (N=2)

Mail order (N=512)  Retail (N=512)
Study Period

The study period consisted of three unique time-frames or points: a pre-index period, index date, and follow-up. (Figure 3.2) The COPD index date was defined as the first prescription claim for a maintenance COPD inhaler following an initial study inclusion diagnosis. A 6-month pre-index lookback was performed to ensure only new-users proceeded to follow-up as well as gather prior medical history. Baseline characteristics such as age, race, and geographical region were assessed as of the COPD index date. The dispensing channel of the first refill or dispensing of the second prescription for a maintenance medication determined participant classification as a mail order or retail users and study follow-up began from that point. Follow-up continued from assignment through the earliest of 15 months, discontinuation of all maintenance COPD medications, or termination of either medical or prescription benefits. (Figure 2) Because the primary aim did not focus on comparing efficacy between drug classes, individuals utilizing multiple inhalers concurrently were evaluated as a single observation. Furthermore, changes between therapeutic classes of medications within this period did not constitute discontinuation of therapy.

Figure 3.2 Flow Chart of Study Design

Exposures

The primary exposure was the dispensing channel, mail order or retail pharmacy, for which the patient filled his or her maintenance COPD medications. Pharmacy type was identifiable through a binary mail order indicator featured in the claims database. Because it is common for patients to start new medications at their local pharmacies and switch to mail order once tolerated, dispensing channel use was defined at the second prescription for a COPD maintenance medication. A sensitivity analysis (Appendix B) to assess the appropriateness of this exposure definition was performed by classifying dispensing channel based on initial maintenance COPD medication. The analysis did not show statistically significant differences in classification and supported the decision to capture dispensing channel at the first refill.
Outcomes
The primary outcome of interest was COPD-related exacerbations requiring acute medical care by means of an emergency room (ER) visit, non-routine outpatient visit, or hospitalization. Medical visits and hospitalizations were deemed COPD-related through medical claims reflecting COPD exacerbation diagnosis (ICD-9 CM code 491.21, 491.22, 492.0, 494.10) in the primary diagnostic position. A list of COPD related ICD-9 codes presented in Table 3.1. Exacerbation dates and medical setting were also obtained for each event. Medical treatments were only considered events if they occurred after the follow-up began in order to reduce the impact of immortal time bias. Patients with an exacerbation coded in multiple medical locations were observed as having a single exacerbation for analysis purposes.

Secondary outcomes included frequency of exacerbation by medical setting and COPD medication adherence during the study. The measure of adherence chosen was proportion of days covered (PDC).

Table 3.1 COPD related ICD-9 diagnostic codes

<table>
<thead>
<tr>
<th>Diagnostic Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>490.00</td>
<td>Bronchitis, not specified as acute or chronic</td>
</tr>
<tr>
<td>491.00</td>
<td>Simple chronic bronchitis</td>
</tr>
<tr>
<td>491.10</td>
<td>Mucopurulent chronic bronchitis</td>
</tr>
<tr>
<td>491.20</td>
<td>Obstructive chronic bronchitis without exacerbation</td>
</tr>
<tr>
<td>491.21</td>
<td>Obstructive chronic bronchitis with (acute) exacerbation</td>
</tr>
<tr>
<td>491.22</td>
<td>Obstructive chronic bronchitis with acute bronchitis</td>
</tr>
<tr>
<td>492.00</td>
<td>Emphysematous bleb</td>
</tr>
<tr>
<td>492.80</td>
<td>Other emphysema</td>
</tr>
<tr>
<td>494.00</td>
<td>Bronchiectasis without acute exacerbation</td>
</tr>
<tr>
<td>494.10</td>
<td>Bronchiectasis with acute exacerbation</td>
</tr>
<tr>
<td>496.00</td>
<td>Chronic airway obstruction, not elsewhere classified</td>
</tr>
</tbody>
</table>

Statistical Analysis

Baseline Comparisons of Treatment Groups
Summary statistics were used to describe each cohort. Continuous measures were described using means and standard deviations while categorical variables were described using percentages. Continuous and categorical variables were also compared between each dispensing channel using standard t-tests and chi-square test, respectively with standardized differences to assess similarities of each dispensing arm.
**Estimating the Propensity Score**

In efforts to reduce selection bias, a propensity score was estimated using nine variables: age, gender, geographical region, race, history of diabetes mellitus, history of heart failure, smoking status, quantity of pre-index prescription claims, pre-index medical expenses [25-27]. A directed acyclic graph was compiled to determine the minimum sufficient variable set for analyzing the association between the specified exposure and primary outcome. (Figure 3.3) These variables were chosen due to their likelihood of influencing the outcomes of interest or a patient’s decision to choose mail or retail pharmacy to fill maintenance medications. A logistic regression model, which regressed dispensing channel (mail order vs retail pharmacy) on the aforementioned baseline characteristics to estimate the propensity score [28-30].

**Figure 3.3 Directed Acyclic Graph**

![Directed Acyclic Graph](image)

**Matching on the Propensity Score**

Mail order and retail patients were matched 1:1 on the propensity score using a radius method optimized for the closeness of the propensity scores. [28] There were significantly more control (retail) patients than were intervention (mail order) patients. The matching process generated matches with absolute differences between propensity scores no greater than 0.02. Baseline characteristics were then compared between the matched and unmatched patients using means and standard deviations for continuous variables and counts and percentages for categorical variables. In order to check the balance of the propensity score estimation, standardized differences and p-values were used to quantify the difference between dispensing channels.

**Estimating Effect**

An intention-to-treat analysis as of the second prescription fill was used. Each study participant was followed from dispensing arm classification to the study end or medication discontinuation regardless of whether he or she continued to refill medications at the original pharmacy type.

All outcomes were analyzed in both the overall and propensity score matched cohorts. The primary outcome of interest was the frequency of acute COPD exacerbations during the observed study period, expressed as incidence rates. Incidence rates were estimated with the dependent variable, count of events, and an offset variable of total time the patients were exposed to an inhaled maintenance medication filled through one of the dispensing channels. An incidence rate ratio (IRR) and 95% confidence interval (CI) was then estimated by Poisson regression. As a secondary
outcome, incidence rates by each of three exacerbation settings; outpatient, emergency room, and hospital admittance, were compared in the same manner as the primary outcome of interest. Additionally, adherence rates, reported as PDC, were calculated for all patients with at least two consecutive fills following dispensing channel assignment. The PDC algorithm truncated fill dates occurring outside the observation window and adjusted fill dates to reflect early refills during the study period. The PDC means were compared using a two-sample t-test and paired t-test for the unmatched and propensity score matched cohorts, respectively. The percentage of patients meeting adequate adherence, defined as a PDC greater than or equal to 0.8, were also reported. These measures were compared using chi-square tests. All analysis were performed using SAS software version 9.4.

Section Four: Results

Overall Sample Description

The study sample consisted of 4,316 participants, of whom 514 used a mail order pharmacy and 3,802 used a retail pharmacy. The baseline characteristics of retail and mail order patients are described in Table 4.1. Prior to propensity score matching, patients using mail order pharmacies tended to have fewer unique prescription claims and lower medical spend during the pre-index period (p < 0.001). Retail patients were more likely to reside in the southern region (p<0.001) while mail order patients were more likely to reside in western and mid-western regions (p =0.003 and p = 0.02, respectively). All other measured covariates were similar between dispensing channels.

Table 4.1 Baseline Characteristics of Study Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Retail (N=3802)</th>
<th>Mail Order (N= 514)</th>
<th>Overall Sample (N= 4,316)</th>
<th>SD of the Mean/Median (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>73.92 ± 7.64</td>
<td>73.28 ± 7.45</td>
<td>73.84 ± 7.62</td>
<td>-8.43</td>
<td>0.08</td>
</tr>
<tr>
<td>Male</td>
<td>1823 (47.95)</td>
<td>235 (45.72)</td>
<td>2058 (47.68)</td>
<td>-4.46</td>
<td>0.34</td>
</tr>
<tr>
<td>White</td>
<td>3381 (88.93)</td>
<td>460 (89.49)</td>
<td>3841 (88.99)</td>
<td>1.83</td>
<td>0.70</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>1047 (27.54)</td>
<td>166 (32.30)</td>
<td>1213 (28.10)</td>
<td>10.40</td>
<td>0.02</td>
</tr>
<tr>
<td>Northeast</td>
<td>141 (3.71)</td>
<td>17 (3.31)</td>
<td>158 (3.66)</td>
<td>-2.18</td>
<td>0.65</td>
</tr>
<tr>
<td>South</td>
<td>2210 (58.13)</td>
<td>251 (48.83)</td>
<td>2461 (57.02)</td>
<td>-18.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>West</td>
<td>404 (10.63)</td>
<td>80 (15.56)</td>
<td>484 (11.21)</td>
<td>14.67</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Contributing Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1026 (26.99)</td>
<td>138 (26.85)</td>
<td>1164 (26.97)</td>
<td>0.31</td>
<td>0.95</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>814 (21.41)</td>
<td>102 (19.84)</td>
<td>916 (21.22)</td>
<td>-3.87</td>
<td>0.42</td>
</tr>
<tr>
<td>Smoker</td>
<td>372 (9.78)</td>
<td>42 (8.17)</td>
<td>414 (9.59)</td>
<td>-5.64</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Indicators of Prior Health Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Monthly Medical Expenses ($)</td>
<td>3,503.52 (10,721)</td>
<td>1,751.88 (4,430)</td>
<td>3,211.30 (9,848)</td>
<td>6.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior Monthly Prescription Claims median(IQR)</td>
<td>8.67 (13.6)</td>
<td>5.92 (7.52)</td>
<td>8.16 (12.93)</td>
<td>1.35</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: Continuous variables are presented as means ±standard deviation; dichotomous variables are presented as N (%)
Indicators of Prior Health expressed as medians and IQR
Abbreviation: SD, Standardized Differences; IQR, interquartile range
Propensity score matching

The 1:1 radius matching technique, which was maximized on closeness of the propensity score, generated matches for 513 mail order patients to retail patients within an absolute difference of less than or equal to 0.02 of the propensity score. Only one mail order patient was unable to be successfully matched to a retail patient with a similar propensity score. The baseline characteristics of each dispensing arm in the matched cohort are described in Table 4.2. Post-matching, all standardized differences were less than 10%. The only covariates that differed by more than 5% were related to geographic region (West and Midwest) and monthly medical expenses during the pre-index period, exceeded differences of 5 percent.

### Table 4.2 Baseline Characteristics of Mail Order and Retail Participants in the Propensity Score Matched Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Retail (N=512)</th>
<th>Mail order (N=512)</th>
<th>SD of the Mean/median (%)</th>
<th>Variance Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic Characteristics</strong></td>
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<td></td>
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<td>73.28 ± 7.45</td>
<td>-2.98</td>
<td>1.12</td>
<td>0.63</td>
</tr>
<tr>
<td>Male</td>
<td>234 (45.70)</td>
<td>235 (45.72)</td>
<td>0.03</td>
<td>1.00</td>
<td>0.99</td>
</tr>
<tr>
<td>White</td>
<td>456 (89.06)</td>
<td>460 (89.49)</td>
<td>1.39</td>
<td>1.04</td>
<td>0.82</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>178 (34.77)</td>
<td>166 (32.30)</td>
<td>-5.23</td>
<td>1.04</td>
<td>0.40</td>
</tr>
<tr>
<td>Northeast</td>
<td>24 (4.69)</td>
<td>17 (3.31)</td>
<td>-7.04</td>
<td>1.40</td>
<td>0.26</td>
</tr>
<tr>
<td>South</td>
<td>240 (46.88)</td>
<td>251 (48.83)</td>
<td>3.92</td>
<td>1.00</td>
<td>0.53</td>
</tr>
<tr>
<td>West</td>
<td>70 (13.67)</td>
<td>80 (15.56)</td>
<td>5.35</td>
<td>1.11</td>
<td>0.39</td>
</tr>
<tr>
<td>Diabetes</td>
<td>130 (25.39)</td>
<td>138 (26.85)</td>
<td>3.32</td>
<td>1.04</td>
<td>0.60</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>107 (20.90)</td>
<td>102 (19.84)</td>
<td>-2.61</td>
<td>1.04</td>
<td>0.68</td>
</tr>
<tr>
<td>Smoker</td>
<td>36 (7.03)</td>
<td>42 (8.17)</td>
<td>4.30</td>
<td>1.15</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Indicators of Prior Health Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Monthly Medical Spend ($)</td>
<td>2,091.92 (6,737)</td>
<td>1,751.88 (4,430)</td>
<td>7.09</td>
<td>1.19</td>
<td>0.17</td>
</tr>
<tr>
<td>Prior Monthly Prescription Claims median(IQR)</td>
<td>5.60 (7.20)</td>
<td>5.92 (7.52)</td>
<td>1.47</td>
<td>1.04</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Note. Continuous variables are presented as means ±standard deviation; dichotomous variables are presented as N (%)
Indicators of Prior Health expressed as medians and IQR
Abbreviation: SD, Standardized Differences; IQR, interquartile range
Effect on acute exacerbations

Prior to matching, retail pharmacy patients had a higher incidence rate of an acute exacerbation when compared to patients using mail order pharmacies (2.41 per 10 person years vs. 2.07 per 10 person years). The difference in rates, however, was not found to be statistically significant (IRR 0.86; 95% CI, 0.63 - 1.17; Table 4.3). Retail patients also had higher incidence rates for exacerbations treated in an emergency room setting; however, this difference was not found to be significant. The rates were the same for both outpatient and hospital settings prior to matching.

Table 4.3 Event rates of acute exacerbation in a cohort of COPD patients using retail and mail order pharmacies

<table>
<thead>
<tr>
<th>Before Propensity Score Matching</th>
<th>Retail (N=3802)</th>
<th>Mail Order (N=514)</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Exacerbation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event, (n)</td>
<td>732</td>
<td>84</td>
<td>0.86 (0.63-1.17)</td>
</tr>
<tr>
<td>Person-years</td>
<td>3,035.19</td>
<td>404.28</td>
<td></td>
</tr>
<tr>
<td>IR/ 10 PY</td>
<td>2.41</td>
<td>2.07</td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event, (n)</td>
<td>441</td>
<td>52</td>
<td>0.88 (0.64-1.23)</td>
</tr>
<tr>
<td>Person-years</td>
<td>3,035.19</td>
<td>404.28</td>
<td></td>
</tr>
<tr>
<td>IR/ 10 PY</td>
<td>1.45</td>
<td>1.45</td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event, (n)</td>
<td>118</td>
<td>9</td>
<td>0.57 (0.27-1.20)</td>
</tr>
<tr>
<td>Person-years</td>
<td>3,035.19</td>
<td>404.28</td>
<td></td>
</tr>
<tr>
<td>IR/ 10 PY</td>
<td>0.39</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Office Visit, Unspecified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event, (n)</td>
<td>3783</td>
<td>450</td>
<td>0.89 (0.80-0.99)</td>
</tr>
<tr>
<td>Person-years</td>
<td>3,035.19</td>
<td>404.28</td>
<td></td>
</tr>
<tr>
<td>IR/ 10 PY</td>
<td>12.46</td>
<td>11.13</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PY, person-years; IR, incidence rate; IRR, Incidence Rate Ratio; CI, confidence interval

Overall, results following matching continued to show slightly lower incidence rates for mail order patients, regardless of treatment setting. Acute exacerbation incidence rates were 2.44 per 10 person years and 2.07 per 10 person years for retail and mail order patients, respectively. The difference in these rates, however, remained statistically insignificant (IRR 0.85; 95% CI, 0.59-1.23; Table 4.4).

Table 4.4 Event rates of acute exacerbation and office visits in a matched cohort of COPD patients using retail and mail order pharmacies

<table>
<thead>
<tr>
<th>After Propensity Score Matching</th>
<th>Retail (N=512)</th>
<th>Mail Order (N=512)</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Exacerbation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event, (n)</td>
<td>84</td>
<td>84</td>
<td>0.85 (0.59-1.23)</td>
</tr>
<tr>
<td>Person-years</td>
<td>343.62</td>
<td>404.28</td>
<td></td>
</tr>
<tr>
<td>IR/ 10 PY</td>
<td>2.44</td>
<td>2.07</td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event, (n)</td>
<td>53</td>
<td>52</td>
<td>0.83 (0.54-1.27)</td>
</tr>
<tr>
<td>Person-years</td>
<td>343.62</td>
<td>404.28</td>
<td></td>
</tr>
<tr>
<td>IR/ 10 PY</td>
<td>1.54</td>
<td>1.45</td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event, (n)</td>
<td>10</td>
<td>9</td>
<td>0.77 (0.31-1.91)</td>
</tr>
<tr>
<td>Person-years</td>
<td>343.62</td>
<td>404.28</td>
<td></td>
</tr>
<tr>
<td>IR/ 10 PY</td>
<td>0.29</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event, (n)</td>
<td>21</td>
<td>23</td>
<td>0.93 (0.49-1.75)</td>
</tr>
<tr>
<td>Person-years</td>
<td>343.62</td>
<td>404.28</td>
<td></td>
</tr>
<tr>
<td>IR/ 10 PY</td>
<td>0.61</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Office Visit, Unspecified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event, (n)</td>
<td>430</td>
<td>450</td>
<td>0.89 (0.78-1.02)</td>
</tr>
<tr>
<td>Person-years</td>
<td>343.62</td>
<td>404.28</td>
<td></td>
</tr>
<tr>
<td>IR/ 10 PY</td>
<td>12.51</td>
<td>11.13</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PY, person-years; IR, incidence rate; IRR, Incidence Rate Ratio; CI, confidence interval
Effect on adherence rates

The adherence rates, defined as proportion of days covered (PDC), were significantly lower for retail patients (0.66 ± 0.24; 95% CI 0.65-0.67) when compared to mail order patients (0.79 ± 0.20; 95% CI, 0.77-0.81) in the overall sample population (p < 0.001, Table 5). While the average PDC in mail order patient was identical in the matched cohort, the average retail PDC was slightly lower at 0.63. The difference in mean adherence rates continued to be significantly different in the matched cohort (p < 0.001, Table 6). Neither mail order or retail pharmacy patients had an overall adherence rate indicative of adequate adherence (pdc ≥ 0.8), but there were nearly twice as many mail order patients that were adequately adherent (54.81%) when compared to retail patients in the overall sample and matched cohort (29.77% and 54.81%, respectively).

Table 4.5 Inhaled maintenance medication adherence rates in COPD patients using mail order and retail pharmacies

<table>
<thead>
<tr>
<th></th>
<th>Retail</th>
<th>Mail Order</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before Propensity Score Matching</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDC</td>
<td>0.66 ± 0.24</td>
<td>0.78 ± 0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adherent† (%)</td>
<td>1132 (29.77)</td>
<td>228 (54.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>After Propensity Score Matching</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDC</td>
<td>0.63 ± 0.24</td>
<td>0.78 ± 0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adherent† (%)</td>
<td>117 (28.54)</td>
<td>228 (54.81)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: PDC, proportion of days covered
†Adherence, PDC greater than or equal to 0.80

Section Five: Discussion and Conclusions

Discussion

This population based study examining the association between dispensing channel and acute COPD exacerbations among Medicare patients did not yield statistically significant findings; however, there are notable trends within this population that should be examined with further studies. Pharmacy benefit managers have promoted mail order use as a means to increase medication access and therefore improve adherence. Medication adherence may be defined as a PDC greater than or equal to 0.80. By this definition, neither retail nor mail order elderly COPD patients achieved adequate adherence. Patients using mail order pharmacies not only yielded higher PDC rates, but also had a significantly greater percentage of patients achieve adequate adherence per the definition.

As adherence to medication increases, outcomes should improve as long as the medication is an efficacious treatment option. Despite superior adherence rates in mail order patients, there were insignificant differences in incidence rates of exacerbation between the two groups. The findings suggest that apparent medication access alone is not indicative of appropriate medication adherence, especially when administration techniques are critical to therapy efficacy. Because COPD is such a complex chronic condition, there may be an increased need to implement disease management programs focusing on factors beyond medication access that contribute to decreased exacerbation frequency and improved outcomes. These results could lead one to believe that a large portion of medication dispensed to mail order recipients is wasted to either voluntary non-adherence or inappropriate medication administration.
A major strength of this study was national representation of a large number of Medicare beneficiaries of varying ages. The sample is not only representative of an understudied population in which COPD is a highly prevalent disease, but also accounts for demographic traits that are applicable to disease progression. Furthermore, propensity score matching helped reduce the effects of confounding variables. There is limited data available that highlights which factors make a patient more or less likely to fill medications at a retail or mail order pharmacy. The low predictive value of the propensity score can be explained by the fact that patient preference, a key driver in pharmacy choice, is not measureable through administrative claims data.

It was hypothesized that mail order patients would be more likely to experience acute exacerbations. The primary rationale behind the hypothesis took into account the potential for direct interaction with pharmacy personnel for retail patients. Unfortunately, this was not a measurable attribute utilizing claims data. As prescription volume increases, retail pharmacists and support staff have less time to actively counsel and assess appropriate medication use. Taking advantage of opportunities available through retail pharmacies to encourage medication regimen compliance could help reduce exacerbations, especially in geriatric populations requiring additional assistance. Currently, the lack of difference in exacerbation rates coupled with increased adherence rates among mail order patients contradicts the general notion that medication adherence improves patient outcomes.

One possible explanation of the failure of this study to identify a significant difference in exacerbation rates is related to potentially observing patients with less severe disease through a new-user design. While some patients may only begin treatment after the disease has significantly progressed, it is possible that the participants in this study were identified the earlier stages of disease. Balcells et al. demonstrated that one-third of newly diagnosed COPD were identified as a result of a COPD exacerbation requiring acute care. [31] These same patients also had a decreased risk of re-hospitalization when compared to patients with an established COPD diagnosis. A relatively healthy population is supported by the low incidence rate ratio of exacerbations compared to reported averages ranging from low as 0.09 to 2.4 per patient per year. [32] Additional studies that identify patients of varying COPD stages may show more difference between the two dispensing channels. Additionally, neither mail order nor retail patients in this population achieved adequate adherence overall. While the difference in adherence may be statistically significant, this difference could potentially not translate to clinical significance if the additional access is not sufficient to prevent additional exacerbations.

It was also hypothesized that there would be no significant difference in the adherence rates between mail order and retail patients. The most prominent explanation for this difference is the financial incentives associated with mail order use.[33] While 90-days supply prescriptions can be filled at both retail and mail order pharmacies, medication affordability makes filling medications through mail order more economically feasible. The majority of the inhaled maintenance medications are still branded medications and could cost significantly more at a retail pharmacy, thusly reducing the ability of Medicare patients using this dispensing channel to refill their medications.

There were several limitations to this study. Firstly, there was potential opportunity for misclassification of dispensing arm due to the intention to treat analysis. It is common for patients starting a new medication to begin the initial prescription at the local pharmacy, especially when the timing of therapy initial is critical. While most patients tended to fill their maintenance medications through a single dispensing channel (mail order or retail pharmacy), there was a possibility that patients could alternate between the two as frequently as desired throughout the study period. A dispensing sequence sensitivity analysis showed that there was little difference in
classification for patients when assigned at the second prescription when compared with the initial prescription (Appendix B).

Secondly, several outpatient events were nonspecific as acute or chronic in nature as defined by the ICD-9 code selected from the provider. Issues related to ambiguous coding could be reduced by including prescription data that also captured antibiotics and/or steroid prescriptions filled on the same day as the medical treatment date of COPD related event. Outpatient visits with non-specific codes were deemed as routine visits for the purpose of this study. Although not an official outcome of this study, post-hoc analysis showed no significant difference in the rates of office visits (unspecified as acute or an exacerbation) between groups in the matched cohort. Without additional data, it is unclear whether the specificity of the outcome definition significantly influenced the study results.

Lastly, current adherence measures through administrative claims are a proxy for actual adherence and cannot take into account a patient’s true actions. This study was unable to distinguish patients who requested medication refills from patients taking advantage of automatic refill programs. It is plausible to consider mail order patients increased adherence rates were attributable to automatic refill programs rather than actual medication adherence. While automatic refill programs and patient reminder systems are also prevalent at local pharmacies, a primary difference in the application of these types of programs is the need for retail patients to visit a brick-and-mortar pharmacy to receive medications that may have been automatically refilled. The PDC algorithm used to estimate adherence reduces the impact of automatic refill programs in either arm by adjusting fill dates when overlap occurs.

Conclusion

There is no significant difference in exacerbation frequency among Medicare beneficiaries using mail order pharmacies when compared to retail pharmacies. Increased medication adherence rates have been repeatedly associated with both mail order pharmacies and fewer exacerbations in patients with COPD; however, limitations of current adherence measures, unfortunately, make examining this association difficult. Further studies are needed to examine the impact of direct patient interaction in a retail environment as compared to self-management with a mail order pharmacy.
## Appendices

### Appendix A

Table A1 Federal Drug Administration Approved Inhaled Maintenance COPD Medication between 2007-2011

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>Inhaler Type</th>
<th>Usual Adult Dosage</th>
<th>Product NDC (USA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alvesco®</td>
<td>ciclesonide</td>
<td>MDI</td>
<td>80-320 mcg inhaled BID</td>
<td>63402-0711, 63402-0712, 54868-5989, 54868-5990</td>
</tr>
<tr>
<td>Asmanex® Twixthaler</td>
<td>mometasone furoate</td>
<td>DPI</td>
<td>220-440 mcg inhaled QD or BID</td>
<td>00085-1341, 00085-1461</td>
</tr>
<tr>
<td>Flovent® Diskus</td>
<td>fluticasone propionate</td>
<td>DPI</td>
<td>100-500 mcg inhaled BID</td>
<td>00173-0600, 00173-0601, 00173-0602</td>
</tr>
<tr>
<td>Flovent® HFA</td>
<td>fluticasone propionate</td>
<td>MDI</td>
<td>88-440 mcg inhaled BID</td>
<td>00173-0718, 00173-0719</td>
</tr>
<tr>
<td>Pulmicort Flexhaler®</td>
<td>budesonide inhalation</td>
<td>DPI</td>
<td>360-720 mcg inhaled BID</td>
<td>00186-0916, 00186-0917, 21695-0291, 54868-5844</td>
</tr>
<tr>
<td>QVAR</td>
<td>beclomethasone dipropionate</td>
<td>MDI</td>
<td>40-320 mcg inhaled BID</td>
<td>59310-0202, 59310-0204, 16590-0860, 50090-1342, 54868-5857, 54868-5858</td>
</tr>
<tr>
<td><strong>Long Acting Beta Agonists (LABA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serevent® Diskus</td>
<td>salmeterol xinofate</td>
<td>DPI</td>
<td>50 mcg inhaled BID</td>
<td>00173-0520, 00173-0521</td>
</tr>
<tr>
<td>Foradil® Aerolizer</td>
<td>formoterol fumurate</td>
<td>DPI</td>
<td>12 mcg inhaled BID</td>
<td>00085-1401, 00085-1402</td>
</tr>
<tr>
<td><strong>Corticosteroid/ LABA combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advair® Diskus</td>
<td>fluticasone propionate/ salmeterol</td>
<td>DPI</td>
<td>1 inhalation BID</td>
<td>00173-0695, 00173-0696, 00173-0697</td>
</tr>
<tr>
<td>Advair® HFA</td>
<td>fluticasone propionate/ salmeterol</td>
<td>MDI</td>
<td>2 inhalations BID</td>
<td>00173-0715, 00173-0716, 00173-0717</td>
</tr>
<tr>
<td>Dulera®</td>
<td>mometasone furoate/ formoterol fumarate dihydrate</td>
<td>MDI</td>
<td>2 inhalations BID</td>
<td>08546-1001, 08572-0601</td>
</tr>
<tr>
<td>Symbicort®</td>
<td>Budesonide/ formoterol fumarate Dihydrate</td>
<td>MDI</td>
<td>2 inhalations BID</td>
<td>18603-7020, 18603-7220</td>
</tr>
<tr>
<td><strong>Muscarinics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spiriva Handihaler®</td>
<td>tiotropium bromide</td>
<td>DPI</td>
<td>18 mcg inhaled QD</td>
<td>59700-7541</td>
</tr>
</tbody>
</table>

*Abbreviations: NDC, national drug code; HFA, hydrofluoroalkane; DPI, dry powder inhaler; MDI, metered-dose inhaler; QD, once daily; BID, twice daily References[34]*
Appendix B

Because the exposure, dispensing channel, was highly dependent upon patient preference, it was important to identify the best method of classifying the exposure arm. An intention-to-treat analysis as of the second prescription was utilized in the study. The robustness of this classification strategy was assessed with a sensitivity analysis. Table B1 compares the dispensing sequence of all patients with qualifying COPD prescriptions when analysis was performed from either the initial prescription or the second prescription. The intention-to-treat analysis yielded accurate classification for approximately 90 percent of all participants through the study observation period regardless of whether the dispensing channel was established at the initial prescription or the second prescription. Figure B1 demonstrates the percentage of patients who remained in the determined dispensing channel throughout the study in both the overall and matched cohorts.

Table B1 Fill Sequence Comparison in All COPD Patients

<table>
<thead>
<tr>
<th>Fill Sequence of Dispensing Channel Switch</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Switch</td>
<td>25,314</td>
<td>90.17</td>
<td>15,494</td>
<td>89.28</td>
</tr>
<tr>
<td>At 2nd Observation</td>
<td>1155</td>
<td>4.11</td>
<td>738</td>
<td>4.25</td>
</tr>
<tr>
<td>After 2nd Observation</td>
<td>1606</td>
<td>5.72</td>
<td>1123</td>
<td>6.47</td>
</tr>
</tbody>
</table>

Figure B1: Intention-to-treat Classification Accuracy in Study Population

Abbreviations: Rx, prescription; PS, propensity score

There are two reasons why it was desirable to classify patients as of the second prescription fill. The first reason is that it is common for patients beginning a new prescription to begin at the local pharmacy and transition to a mail order pharmacy once they are stabilized on the medication. Secondly, classifying exposure as of the second fill reduces the impact of immortal time bias on treatment outcomes. The primary outcome of interest, exacerbations, is closely related to
medication adherence. There is a portion of time between the first and second fill where we can neither attribute an exacerbation to the exposure of filling a medication at a particular dispensing channel nor estimate medication adherence. Had analysis began at the initial prescription, the exacerbation rate may have been overestimated. The sensitivity analysis demonstrates there was minimal difference between classifying patients as of the second prescription and the initial prescription.
References:

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Dean’s List

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Excellence in Clinical Communication Scholarship

May 2014
Ambitious Collegiate Graduate Scholarship

September 2013
College of Pharmacy Scholarship

September 2012
Best Poster Award, FAMU Minority Biomedical Research Support Student Forum

August 2009
Life Gets Better Scholarship Recipient

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