PRICE ELASTICITY OF DEMAND FOR PATIENTS WITH SELECT DISEASES USING SPECIALTY MEDICATIONS AND THEIR ASSOCIATION TO TOTAL HEALTHCARE COSTS

by

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ABSTRACT

NIGEL L. ROZARIO. Price Elasticity of Demand for Patients with Select Diseases Using Specialty Medications and Their Association to Total Healthcare Costs. (Under the direction of DR. REUBEN HOWDEN and DR. CHRISTOPHER BLANCHETTE)

Specialty medications are medications that require special manufacturing and distribution processes and usually for the treatment of rare diseases and conditions. As a result of the low volume of use and high overhead associated with manufacturing and distribution, the cost of these drugs are typically in excess of $600 per month and account for 25% of all drug expenditures for patients and payers but less than 1% of privately insured claims. There are plenty of diseases treated with specialty medications, however this study will investigate cystic fibrosis, eosinophilic asthma, alpha-1 antitrypsin deficiency, primary humoral immunodeficiency, and human immunodeficiency virus in order to study a variety of markets. Additionally, we will study the price elasticity of demand for patients using specialty medications for these diseases and further study the payer impact on total healthcare cost after patients miss their specialty drug dose.

The first study investigated the trends in average wholesale price, payer cost-share and patient cost-share for patients using specialty medications. These median costs were assessed directly from the database claims for each drug. Drug assistance in the form of $5000 was found for a drug representing a monopolistic market for cystic fibrosis, while a competitive market of HIV had a estimated drugs assistance of $150 to competitive markets.

The second study investigated the price elasticity of demand for patients using these specialty medications. Proportional changes in subsequent months were used to express the change in demand for patients in the previous month. Segmented regression analysis was used to conduct a time series analysis that assessed price elasticity. Compared to general medicine which has a price elasticity of -20.9%, our study recorded a price elasticity between -3.1% to -0.7% for a

monopolistic market (Cystic Fibrosis) to a competitive market (Primary Humoral Immunodeficiency) respectively, concluding that patients are more price inelastic with specialty drugs in our study.

The third study explored the payer impact of missed specialty medication dose on total healthcare cost. Patients were followed monthly and split into two groups based on whether they had a January specialty drug claim. A random effects model was used to assess a significant difference in the total healthcare cost between these groups for each disease state. PIDD and HIV patients had a significant total healthcare cost increase possibly due to a worsening of their disease after missing a medication dose.

The three studies contribute to an understudied area of patients using specialty medications. Our study showed that competitive markets tend to have lesser patient assistance, but poor drug adherence may lead to significant higher total healthcare cost. The implication of our study findings suggests with the expensive patient cost-share, better finance strategies are required to keep patients to adhering to their medication.

Dedication

To my wife for her support, sacrifice and love.

To my little daughter for motivating me.

To my mother and sister for their support through my journey.

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List of Abbreviations

AATD	Alpha-1 Antitrypsin Deficiency
ALPHA	Alpha-1 Antitrypsin Deficiency
ASP	Average Selling Price
AWP	Average Wholesale Price
CF	Cystic Fibrosis
EA	Eosinophilic Asthma
HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organization
ICD-9 CM	International Classification of Diseases, 9th Revision, Clinical Modification
MS	Multiple Sclerosis
OOP	Out of Pocket Expenses
PIDD	Primary Humoral Immunodeficiency
PPO	Preferred Provider Organization
RA	Rheumatoid Arthritis
WAC	Wholesale Acquisition Cost

Chapter 1 Introduction

Specialty medications are complex molecules derived from biological sources from manufacturing processes, sometimes requiring special handling and redistribution (Kirchhoff, 2015). They are used to treat complex chronic conditions (e.g. multiple sclerosis, rheumatoid arthritis) or diseases with few treatment options (advanced cancers or rare diseases). Specialty drugs are defined by Medicare as any drug which costs more than $600 per month. These specialty drugs are typically placed on the highest patient cost-share, where it was shown that 49% of beneficiaries had a coinsurance of 29%, and 39% of beneficiaries had a copay of $83 (Claxton et al, 2014). For example, KALYDECO® used for the treatment of Cystic Fibrosis costs about $300,000 per year, which includes out of pocket expenses and insurance contributions. Therefore, if a patient is paying 29% coinsurance for KALYDECO®, that patient would be paying $87,000 per year for that medication in addition to the deductible, copays and insurance premiums, which can be burdensome to the patient. With the patient cost-share being excessive, it begs the question whether patients can even afford to pay for these drugs.

The thresholds of patients cost sharing can influence drug compliance. In fact, Doshi et al (2016) found 25% of patients with private insurance abandoned their medication when out-of-pocket cost per claim was greater than $200 for specialty medications treating multiple sclerosis. Prices for drugs are sometimes driven by the competitors in the market. Therefore, if there are multiple drugs treating a disease, and a new drug enters the same market with a similar indication, the manufacturer will not be able to charge a high premium cost, but rather a patient or payer friendly competitive price. On the other hand, when a drug enters the market as the only treatment (commonly known as a monopoly), the manufacturer will tend to keep their premium pricing to attain maximum benefit in order to recoup costs to develop the drug. Therefore, cystic fibrosis and eosinophilic asthma has only one drug treatment which sets them up for monopolistic premium pricing, which will incur high patient cost-share. On the otherhand, primary humoral

immunodeficiency and human immunodeficiency virus have multiple drugs (more than 10) which sets their drug market as a competitive market even though many of the HIV drugs belong different sub classes and not in direct competition with each other. While only three drugs are available to treat alpha-1 antitrypsin deficiency, this market is representing an oligopoly where there are only a few competitors. No previous studies were found that explore market forces within disease areas and impact of pricing, cost and consumer behavior associated with specialty medications.

Price elasticity of demand, which is a change in utilization for every dollar change in the price of a drug, has been assessed for patients using prescription drugs in general as well as patients using specialty drugs for rheumatoid arthritis, multiple sclerosis, kidney diseases and cancers. These diseases are treated by most commonly used specialty medications by volume representing competitive markets. There has been no study which investigated patients using specialty drugs for cystic fibrosis, alpha-1 antitrypsin deficiency, eosinophilic asthma, primary humoral immunodeficiency and human immunodeficiency virus. Further, there are studies which link the burden of cost-sharing to drug adherence, but we were unable to find research which reports the downstream effects on total healthcare costs as a result of non-adherence to specialty drugs.

This study will investigate the trend in average wholesale price, payer cost-share and patient cost-share for specialty drugs for cystic fibrosis, alpha-1 antitrypsin deficiency, eosinophilic asthma, primary humoral immunodeficiency and human immunodeficiency virus. Additionally, this study will investigate the price elasticity of demand for patients with these one of these diseases and using an associated specialty medication. Finally, we will assess the downstream effects on total healthcare costs after non-adherence to specialty drugs when patient the cost-share increases.

Chapter 2: Literature Review

Specialty Medications

Specialty medications are complex molecules derived from biological sources, sometimes requiring special handling and redistribution. They are used to treat complex chronic conditions (e.g. multiple sclerosis, rheumatoid arthritis) or diseases with few treatment options (advanced cancers or rare diseases). Specialty medications accounted for less than 1% of privately insured claims, but for 25% of all drug expenditures for patients and payers (Starner et Al, 2014). In fact, specialty medication represented one third of US prescription drug spending, and some studies project it to be as much as one half by 2018. (Susanne Kirchhoff, Specialty Drugs Background and Policy Concerns 2015). For example, KALYDECO® used for the treatment of Cystic Fibrosis costs about $300,000 per year after paying out of pocket and insurance contributions. If a patient is paying 33% coinsurance, that patient would be paying $100,000 per year for that medication in the form of deductibles, copays and insurance premiums, which can be burdensome to the patient. When looking at patients with rheumatoid arthritis, multiple sclerosis, and cancer aged 65 or older using specialty meds, Trish et al found that these medications represented 6.7% of total drug spending per beneficiary in 2007 as compared to 9.1% to 2011 (Trish, Joyce & Goldman, 2014).

Burden of Specialty Medications

The thresholds of patient's cost sharing can influence their drug compliance. Doshi et al (2016) conducted a systematic review of specialty medications treating multiple sclerosis, cancer and rheumatoid arthritis. They found a strong positive association between high cost sharing and the abandonment of the medications. In fact, 25% of patients with private insurance abandoned their medication when out-of-pocket cost per claim was greater than $200 for specialty

medications treating multiple sclerosis (MS). It was found that a 100% increase in cost sharing led to a 3-4% decrease in patients initiating a MS drug. Additionally, 5-9% of rheumatoid arthritis patients reduced initiating a MS drug after cost sharing increased by 100%. Therefore, it is seen that merely increasing cost sharing can lead to a negative impact on the utilization of specialty medications.

At the same time, specialty medication can have a positive impact on patients. Joyce et al (2008) investigated individuals who had initiated specialty medications for autoimmune disorders of Multiple Sclerosis (MS), rheumatoid arthritis (RA) and non-users of specialty medications, and their behavior 2 years before initiation. They observed that the average out of pocket expenses were $3000 annually for individuals with MS and $4500 for RA during their study period of 1997 to 2005. They also found that MS specialty therapy led to a reduction in both hospitalization and use of expensive procedures two years after initiating specialty medications. Additionally, it was noted that three years before initiating biologic response modifier (BRM) specialty medication, hospitalizations and expensive procedures were constant, but started declining substantially after initiation of BRM. Even patients with RA had a reduction in physician office visits from 10-11 to 8 per year, which was seen within two years of initiation of BRM.

Cost-sharing

Leibowitz et al (1985) studied the human behavior at various forms of cost-sharing thresholds. The RAND Health Insurance Experiment (HIE) showed that a generous health plan coverage meant more coverage with no cost-sharing which led to more utilization of prescription medications (Leibowitz, Maning, & Newhouse,1985). In the HIE, patients were randomly assigned to five health insurance plans. Four groups had varying levels of coinsurance: 0% (free), 25%, 50% and 95%. The fifth group was a non-profit style HMO group where patients received

their care free of charge. The out-of-pocket cost was capped at a percentage of the patient's income or $1000 ($3000 in 2006 dollars). They found that patients with 25% or higher coinsurance had fewer hospitalizations and fewer physician office visits. In fact, health expenditures among the 25% coinsurance group was 20% less for patients with free care, and the 95% coinsurance group spent 30% less than the free care group. The main striking feature was the RAND HIE did not affect the quality of care received by the participants. The experiment also pointed out that poor patients with chronic conditions should have very minimal cost sharing to avoid the risk of forgoing needed healthcare (Brook Et al, 2006). The HIE also showed that the prescription spending on the 95% coinsurance was 57% of the free care plan. (Leibowitz, Maning, & Newhouse, 1985).

Market for drugs

When a pharmaceutical company produces a drug, which enters the market as the only treatment for a disease, there is no substitute for the drug and the company receives patent protection for 5-7 years from generic competition. For a new biologic specialty medication, the patent protection lasts for 12 years. Hence, the company will have the advantage of a monopolistic market which allows for price controls unless external forces such as government or other entities like insurers intervene. When more drugs for the same disease enter the market, it forms an oligopoly (where there are few providers for a single drug) and therefore, it may drive the drug price lower compared to the monopolistic single-drug market. These companies will seek to differentiate their drugs in the market by their product attributes (safety, effectiveness, efficacy, tolerability), manufacturing and distribution processes or marketing and regulatory activities with respect to the first drug.

When a drug obtains generic access, the number of pharmaceutical companies producing these drugs will depend on availability of raw ingredients, company mergers, minimal Research and Development (R&D) costs and attractiveness to the market. Except for the first drug to file for the generic market, thereby receiving a 180-day market exclusivity, other potential generic drugs can enter the market. These drugs will finally provide a competitive market, bottoming out the price of the drug. Therefore, at this stage the pharmaceutical company has the least amount of control on price as competition drives price down (Eichler et al, 2016).

Biosimilars, which are similar to generics but in the biologic drug market, do not have a standard pathway to enter the market because they are not subject to the Hatch-Waxman Act (Drug Price Competition and Patent Term Restoration Act of 1984). To address this fact the Patient Protection and Affordable Care Act (PPACA, 2010) included provisions for approval of biosimilars. The FDA drafted safety and scientific criteria by which biosimilar products are approved. Unlike generic medications, which can cost $1-$5 million to develop, biosimilars cost $100-$200 million to develop due to the cost and complexity of biosimilar development and production. Ultimately these biosimilars will be discounted 20-40% of the biologic price compared to generics being 80-85% of brand name products. This is due to the cost and complexity of biosimilar development and production. (Hirsch, Balu & Schulman, 2014)

When a generic drug serves a small market (few patients with the disease) for a rare disease (e.g., toxoplasmosis), it could lead to less generic manufacturer competition that, in turn, forces a potential monopoly. This scenario occurred when Turing Pharmaceuticals increased the price of pyrimethane (DARAPRIM® used to treat toxoplasmosis) by 50-fold (Kesselheim, Avorn, & Sarpaywari, 2016). However, state and federal policies can have an impact on prices paid for drugs. Thirty states have laws that allow, but do not require, pharmacists to perform a generic drug substitution for drugs; in 26 states pharmacists must secure patient consent before substituting for a generic drug. This latter obligation of securing consent for generic drugs cost

Medicaid $19.8 million in 2006 for a single drug, Simvastatin (ZOCOR®) (Kesselheim, Avorn, & Sarpaywari, 2016). With respect to a brand name drug which serve a small population or a limited population (e.g. Cystic Fibrosis representing a small market) manufacturers have a lesser incentive to produce drugs for about 28,680 cystic fibrosis patients.

Fewer generic drug entrants in the specialty drug market has been concerning. Oral prescription medications are known to have a median of 7 generic entries which would keep a competitive market for these drugs (Gupta et al, 2016). However, Imatinib, a specialty drug for the treatment of leukemia there was only 3 generic manufacturers in the market after 14 years of brand name first entrance, which is about half the generic entrants for prescription drugs. Further, increase in price of generics for specialty drugs are not helping the cost burden on payers or patients (Cole & Dusetzina, 2018).

Drug Pricing

The Biopharmaceutical supply chain is key in understanding prescription drug purchasing and the net price that the patient ultimately pays for a drug. Prescription drug purchasing involves a chain of sellers and buyers, which include manufacturers, wholesalers and pharmacies. The manufacturer sets the price of a drug and then it sells the drug to the wholesaler at an average selling price (ASP). Drugs purchased through Medicare Part D are reimbursed with the following formula: ASP + 6%. The wholesaler, in turn, sells the drug to the pharmacy at the average wholesale price (AWP). When the patient is insured, the Pharmacy Benefit Manager (PBM), negotiates the price that the patient pays the pharmacy. This difference in price (concession) is based on the volume of patients the PBM represents and its power in moving the market share. These concessions or rebates are given to the PBMs by manufacturers and they are passed along the insurers. Unfortunately, these rebates are unknown (Gencarelli, 2005). However, PBMs have

less power to tier drugs with a unique therapeutic profile because patients and doctors are unwilling to accept the formulary controls over clinical choices. As more drugs enter the market, Prescription Drug Plans (PDPs)/PBMs will have a better opportunity to tier placement to negotiate discounts, which can ultimately improve patient access by purchasing drugs on a lower tier. (Danzon & Taylor, 2010). Therefore, with the long supply chain starting from the manufacturer and ending at the patient, there are opportunities for proportional markups and benefit from spread pricing that drive the drug cost higher (Kaltenboeck A, 2012).

Average wholesale Price

Average wholesale Price (AWP), is a benchmark used by government and private payers for pricing and reimbursement of prescription drugs. The AWP is determined by the drug manufacturer, or the publishing company that provides the drug pricing data. The purpose of the AWP is to determine the drug price by which the wholesalers' sell their drugs to providers (e.g. physicians and pharmacies). Databases (e.g. Marketscan Commercial Claims) have the AWP readily available, which will teach us the trend of drug pricing over time. The actual transaction prices paid to the pharmacy by third party payers is the AWP minus a percentage discount. The AWP is known to be 1.2 times the wholesale acquisition cost (WAC) since September 2009 when a lawsuit required Medi-Span and First DataBank (both publishers of AWP) to publish AWP downward to 1.2 times the WAC (Curtiss FR, 2010). Therefore, the AWP is directly related to the actual prices paid the private marketplace and can be used to assess trends too (Sawad et al, 2016).

Patient Cost-Share

Patients obtain drugs through cost-share savings from commercial insurance, Medicare/Medicaid, other sources or OOP expenses. If there are deductibles that need to be met, they then need to pay it before the insurance can contribute to payments on drugs. After yearly deductibles are met, health insurance companies exercise a coinsurance in which the patient pays a percentage of the price of the drug. These copayments and coinsurance provide scenarios where patients pay for drugs placed on various tiers set up by PBMs (private plans). Insurance companies form tiered formularies with patient cost sharing, which are essentially copayments or coinsurance, to the price of the drug. In this tiered formulary setup, generic drugs have the lowest tier and the lowest cost sharing, while some branded drugs have moderate cost sharing with few discounts and specialty drugs have relatively higher cost sharing (Robinson et al, 2017)

Similarly, for patients having Medicare Part D, Prescription Drug Plans (PDPs) decide tiering for drugs. This tier system is setup by PBMs/PDPs; they decide cost-sharing based on previous negotiations with pharmaceutical companies. Tier 1 has generics, which are typically $10-$20 for a 30-day supply. Tier 2 is typically on-patent "preferred" drugs with a $30 per script copay, and Tier 3 includes the "nonpreferred" drugs with a higher copay of $45-$60 per script. Tiers 4 and 5 are typically for specialty medications with 25-33% coinsurance, having the highest OOP burden to the patient. Medicare Part D that covers drug coverage for their beneficiary plans reported a 25% coinsurance patient cost-share for specialty tier drugs (Stern & Resissman 2006). Sometimes, health insurance has an out-of-pocket maximum after which insurance pays most of the prescription costs through the rest of the year until the whole insurance payment system resets at the start of the next year. Patients can have supplemental insurance in the form of Medigap or Medicaid which can aid with patient's OOP commitments. However, when most patients have supplemental insurance the coinsurance provision does little to constrain manufacturer pricing because patients are heavily insured and price insensitive. Senior patients having Medicare Part

D's catastrophic insurance, exceed their plan's OOP cost maximum with expensive specialty medication. They pay their 5% coinsurance margin with the PDPs paying the 15% and taxpayers paying the rest (80%) (Danzon & Taylor, 2010).

Drug Tiers

Depending on the insurance company and the insurer, patients have varying out-of-pocket payments for prescription medications. Insurance companies will have differing deductible and cost sharing plans. Insurance companies also use tiering for pricing drugs; for example, non-preferred drugs placed on the highest tier would have the highest cost sharing for the patient. This tier system is setup by pharmacy benefit managers, who decide the tiering for drugs for any disease based on previous negotiations with pharmaceutical companies. At the same time, pharmaceutical companies offer a lower price for its own drugs to obtain favorable tiering, which can boost sales.

Specialty drug coverage by insurance companies vary across the nation. A study by Chambers et al (2018) observed specialty drugs coverage and decisions across US health insurance plans. They reported that 15.9% of health plans covered drugs with a dual indication (e.g. XOLAIR® for allergic asthma and urticaria in the same manner (health plan decisions) by all health plans. Further, of all the coverage decisions by payers, only 52% of drug pairs were consistent with the drug label, 33% being more restrictive, 10% being restrictive in some form, and the rest 5% not covered (Chambers et al, 2017). These payer coverage decisions have direct implications on patient access due to high cost, which can ultimately lead to abandonment

Patient Assistance

Simultaneously there are patient assistance programs set by pharmaceutical companies to assist patients in combating the soaring prices of specialty medications. Therefore, when the price of a drug is set by a pharmaceutical company, the patient pays for the medication through their insurance, and may use drug coupons to help with out-of-pocket expenses. This leads a patient to choose a drug that is the most cost-effective with the most perceived benefit. In fact, Starner et al, (2014) found that in 2013, drug coupons reduced the out-of-pocket spending on specialty medications treating cystic fibrosis by 28.2%. Additionally, these authors noticed that by reducing the patient's out-of-pocket cost to below $250 a month, it reduced the probability of abandoning their prescriptions. However, if drug coupons were used to pay high out-of-pocket expenses for non-preferred drugs, it will cause loss in formulary management, which can cause a negative effect on insurance premiums (Starner et al, 2014). Further, if patients keep using drug coupons it will ultimately help drug manufacturers' increase their own profit (AIS Health, April 2018). Additionally, assistance programs for cancer drugs, which expanded copay assistance programs were put in place after entrance of the generic versions of the drug, with the intention to attract consumers to brand name drugs. This would keep consumers from buying generics, and hence keeping the higher market share for brand name drugs (Chen & Kesselheim, 2017).

Price elasticity of demand

Patients who are highly responsive to changes to their out-of-pocket expenses of a drug are considered price elastic. However, in cases when they are not price responsive (price inelastic), they obtain medications simply because they need them to survive. However, if drugs are totally covered without any patient payment, it can lead to a moral hazard, where there is over utilization of drugs in the market. To reduce these negative effects of moral hazard, third party

insurers influence drug pricing. The insurers setup cost sharing benefit designs in the form of deductible and coinsurance. The main aim of the insurers is to encourage patients to utilize drugs that are necessary and cost-effective.

Disease States

The price elasticity of demand for specialty drugs will depend on many factors, including treatment options, market for the drugs, multiple drugs options, drug cost, new drugs entering the market, quality of life based on those health conditions and surgical options. There are disease areas where financial burden has been observed but elasticity has not been evaluated in detail. Wu et al (2007) found that Omalizumab used to treat Eosinophilic asthma (EA) was not cost-effective with an estimated $821,000 needed to gain a year of healthy-related quality of life. Gildea et al (2003) concluded for patients treated with augmentation therapy for AATD, therapy costs are incrementally higher than other interventions indicated for use in the AATD population. Patients treated for PIDD and HIV need these specialty medications regularly, to avoid acute exacerbations. The aforementioned studies demonstrate the financial burden on patient populations treated with specialty medications. Therefore, to understand the effects of out-of-pocket expenses, multiple disease states with variation in drug options would be ideal while simultaneously avoiding complex diseases (e.g. cancers). Accordingly, this study will examine three disease states with limited drugs available and two disease states with more than 10 drugs which will provide a good mixture for comparison.

Disease States with <10 drugs available:

- Cystic Fibrosis (CF): 1 drug

- Eosinophilic Asthma (EA): 1 drug

- Alpha-1 Antitrypsin Deficiency (AATD): 3 drugs

Disease States with >10 drugs available:

- Primary Humoral Immunodeficiency (PI): 11 drugs
- Human Immunodeficiency Virus (HIV): 38 drugs

Additionally, these five disease states have little scientific literature compared to diseases which have been extensively studied like MS, RA and cancer.

CF is a genetic disease characterized by the human body producing thick and sticky mucus that ultimately becomes a problem in the lungs and pancreas. It affects 75,000 patients worldwide, and mortality is caused by chronic lung disease. CF is caused by mutations in Cystic Fibrosis Transmembrane conductance regulator (CFTR) gene which could number over 2000 mutations. Currently, there are eight CF drugs: two specialty oral (KALYDECO® and ORKAMBI®) that restore CFTR function, four anti-infective drugs (Azithromycin, Aztreonam, inhaled tobramycin and tobramycin inhaled powder) and one (PULMOZYME®) used for mucus alteration (Cystic Fibrosis 2015 Annual Report). For this research, a monopolistic market for KALYDECO® will be used because the other drug, ORKAMBI®, was approved in July 2015 and it falls outside the range of data (2012-2014) which we will be studying. Patients abandoning KALYDECO® display acute exacerbations, suggesting that patients need to maintain treatment. Patients with severe lung disease sometimes need a lung transplant. Other surgical options include removal of nasal polyps, repair of bowel intestines, removal of a bowel obstruction and chest tube drainage. Other supportive therapies include bronchodilators (e.g. Albuterol), taken to open airways and anticholinergics (e.g. atrovent) that help in opening large airways. The barriers for patients with CF are Medicaid clearance which differ by state, and step therapy, which is used when first-line therapy falls.

Eosinophilic Asthma is treated by three drugs - XOLAIR®, NUCALA® and CINQAIR® - that treat elevated eosinophilic levels (eosinophilic phenotype). Since NUCALA® and CINQAIR® were approved in November 2015, only XOLAIR® will be studied in a monopolistic market. Patients with eosinophilic asthma need XOLAIR® as maintenance treatment with inhaled corticosteroids to avoid acute exacerbations. XOLAIR® cessation causes the return of IgE levels (which is suppressed by the XOLAIR®) (Wu et al, 2007). XOLAIR® is used in the form of long-term treatment to control moderate to severe asthma. NUCALA® and CINQAIR® are used for patients with severe eosinophilic phenotype asthma.

Alpha-1 Antitrypsin Deficiency (commonly known as Alpha-1 or AATD) is a disease where the human body does not produce the Alpha-1 antitrypsin protein that prevents breakdown of air sacs in the lungs. It is a genetic condition passed from parents to children causing, serious lung disease in adults and/or liver disease at any age. Patients with AAT may also undergo COPD treatment for respiratory infections. Currently, AATD can be treated by three drugs delivered intravenously. These drugs are used for augmentation treatment. PROLASTIN® was the first of the three drugs to enter the market. Two other drugs, ZEMAIRA® and ARALAST®, entered the market after proving that they were non-inferior to the primary drug. A potential oligopolistic market will be assessed with these three drug treatments. None of the drugs has a superior formulation. AAT augmentation reduces emphysema, but this treatment lacks compelling evidence of its benefit. AAT augmentation treatment can cost both insurers and patients between $60,000 and $150,000 annually, depending on pricing, body weight and nursing care (Silverman & Sandhaus, 2009). Mullins et al (2001) showed that patients weighing 100kg using IV augmentation infusion therapy can have a weekly total cost of $1,296, which amounted to $67,430 yearly. Unfortunately, patients on AAT, require lifelong treatment. Patients who have AAT deficiency also have a chance of contracting liver disease due to protein deficiency; therefore, patients are given vaccines for Hepatitis A and B. Bronchodilators are used to help

breathing; additionally, patients may need oxygen or pulmonary rehabilitation. Patients with both AAT and liver disease require endoscopic and medical treatment for esophageal varices. Surgical options include portosystem shunting and liver transplants in end-stage liver failure.

Primary Humoral Immunodeficiency (PI) has 12 treatment drugs available (six intravenous (IVIG), three subcutaneous (SCIG), and three either IV/SC). For this research, a competitive market of 11 drugs approved to treat PI before January 2015 will be used for the analyses. PI belongs to a group of chronic disorders, where the body's immune system is missing or does not function correctly. Usually, it is an inherited defect of the immune system. Treatment is primarily immunoglobulin replacement (replacing the antibodies needed to fight infections). Therefore, patients with this deficiency simultaneously take antibiotics to fight infections because they are missing white blood cells that normally fight infections. For serious infections, intravenous antibiotics usage is considered. Most people with PI can lead productive lives. A survey conducted in London showed that patient preferring self-administered SCIG treatment more than IVIG treatment. Another study by Espanol et al (2014) stated that some patients receiving IVIG experienced side effects, but there were even patients with SCIG experiencing side effects Coverage, cost, side effects and product safety seem to be the reason patients are discontinuing otherwise effective immunoglobulin replacement (Espanol et al, 2014). Higher patient cost sharing can defer patients away from treatment and poor coverage access to drugs in location where patients reside can explain reasons why patients discontinue these drugs.

Human Immunodeficiency Virus (HIV) weakens the immune system, making the individual easily susceptible to common germs, viruses, fungi and infections. This virus ultimately causes acquired immune deficiency syndrome (AIDS). HIV requires lifelong drug treatment, and the market for these drugs is fully competitive with 42 drugs available. Today, 41 oral drugs and one IV infusion drug (FUZEON®) are available for the treatment of HIV. Treatment can be a combination of these drugs, whichever is the most beneficial to the patient. In

fact, there are at least five combination drugs available in a single pill, and patients may have a high quality of life with the treatments now available. For this research 38 drugs will be used approved prior to January 2015. Today, triple drug combinations, most commonly called highly active antiretroviral therapy (HAART) treatments are used to avoid drug resistance and long-term side effects of HIV treatment. For example, ATRIPLA® is a combination of three drugs in a single pill. Therefore, treatment has become convenient, and individuals with HIV/AIDS are known to maintain their employment, take fewer sick days, have better quality of life and lead productive lives (Hirsch et al, 2011).

After reviewing the five disease states discussed above, the patient's OOP spending trend on specialty medications will teach the patient's burden and cost sharing amounts set by their health insurance. To understand the price elasticity of demand for a patient, the utilization trend of specialty medications and the OOP will need to be measured, which will be calculated by measuring the change in quantity of drugs demanded (utilization) divided by the change in the OOP. Additionally, to understand the impact of the health insurance (payer) after patients miss their medication, total healthcare cost will be compared for patients who were adherent versus patients who are non-adherent. Simultaneously, the relationship of this ratio with the patient's total healthcare costs (inpatient +outpatient + other care) will show the downstream impact of the health insurance onto the future patient care.

Research Aims

Aim 1: To describe the trend in payer cost-share, patient cost-share and average wholesale price for patients using specialty medications by each disease state

Aim 2: To measure the price elasticity of demand for patients using specialty medications by disease state

Aim 3: To measure the impact on total health cost (Inpatient + Outpatient + Other Care Sought) for patients missing their January monthly dose versus patients who do not miss their January dose

Chapter 3: Trend of out-of-pocket costs, payer cost share and AWP for patients treated with specialty medications for select disease states

Introduction and Background

Specialty medications are complex molecules derived from biological sources, sometimes requiring special handling and redistribution. They are used to treat complex chronic conditions (e.g. multiple sclerosis or rheumatoid arthritis) or diseases with few treatment options (e.g. advanced cancers or rare diseases). Specialty medications accounted for less than 1% of privately insured claims but 25% of all drug expenditures for patients and payers (Starner et Al, 2014). In fact, specialty medications represented one third of US prescription drug spending, and some studies project it to be as much as one half by 2018 (Susanne Kirchhoff, Specialty Drugs Background and Policy Concerns 2015). However, in 2017 specialty drugs accounted for 46.5% of total drug spending, which was 24.7% in 2008(IQVIA Institute for Human Data Science, 2017). When considering prescription drugs only, specialty drug prescriptions accounted for 3% of total number prescriptions, but specialty drug spending accounted for 34% of all prescription drug spending in 2017 (Prescription drug costs trend update, Blue Cross Blue Shield, November 2018)

In order to understand these high cost medications, it is important to factor in the market in which these specialty medications serve. Traditionally, in a well-functioning market product are priced to balance the value to consumers and the cost to producers to give maximum benefit to both entities. However, healthcare markets work differently where patients, physicians, drug manufacturers and payers do not align value with prices. Drug manufacturers can charge brand name pricing for newly patented products while they have a monopoly with no competitors. Slowly the market may have additional manufacturers that form a potential oligopoly, with multiple manufacturers, which may reduce the pricing. Finally, when the patents expire in 5-7

years and generic drugs enter the market, the manufacturers bottom-out the price. (Danzon & Taylor 2010). However, specialty drugs exhibit different patent laws, which include 12 years of exclusivity and can extend for 20 years due to the novel nature of the invented drug (Kesselheim, Avorn and Sarpatwari, 2016)

Pharmacies sell drugs and patients share the cost with insurance companies, depending on the health insurance plan. Insurance companies form tiered formularies with patient cost sharing, which are essentially copayments or coinsurance, to the price of the drug. In this tiered formulary setup, generic drugs have the lowest tier and the lowest cost sharing, while some branded drugs have moderate cost sharing with few discounts and specialty drugs have relatively higher cost sharing (Robinson et al, 2017). If insurance pays a smaller proportion of the total drug cost, then patients share a higher proportion of the cost concluding in a higher patient cost-sharing. For example, patients who were newly diagnosed with rheumatoid arthritis (RA) and continuing medication had an average biologic out-of-pocket (OOP) cost of $1456 (Karaca-andic, P., Joyce, G. F., Goldman, D. P., & Laouri, M. (2010)). Additionally, a study investigating cancer drugs from 1997-2005 found that the average annual OOP cost ranged from $809 (Erlotinib-pancreatic cancer) to $4294 (RITUXIMAB®- autoimmune disease) (Goldman, D. P., Jena, A. B., Lakdawalla, D. N., Malin, J. L., Malkin, J. D., & Sun, E. (2010))

Therefore, a change in drug prices can occur due to drug shortages, loss of drug patent, new entrants in the market, high cost of generics, no new entrants in the market even after the patents for brand name drugs expire and other potential reasons. However, there are few disease states treated with specialty medications, which are relatively understudied with respect to patient cost-sharing or OOP expenses, payer cost-sharing, and Average wholesale price (AWP). These diseases include cystic fibrosis (CF), eosinophilic asthma (EA), primary humoral immunodeficiency (PIDD), human immunodeficiency virus (HIV) and alpha-1 antitrypsin deficiency (AATD). Starner et al, (2014) found that in 2013, drug coupons reduced the OOP on

specialty medications treating CF by 28.2% but did not quantify the monthly OOP costs for patients. Monk et al (2013) reported that in a survey for the Alpha-1 Foundation Research Society, 49% of the study's AATD patients paid less than $50 monthly, but 13% paid more than $500 monthly. Another study by Sieluk et al (2017) investigated the OptumLabs Data Warehouse AATD claims prior to December 31, 2015 and found the patient's yearly share of payment amounted to $1,875. Average annual OOP expenditures were $1159 for HIV patients who were treated with complementary and alternative medicine. However, patients living with HIV have access to additional finiancial resources, e.g. Ryan White foundation, which supports therapeutic medication costs and make medications easily accessible to patients. There is limited research in PIDD, with respect to OOP, but a study looking at expenditures found that PIDD patients with at least one infection incurred an inpatient hospitalization cost of $38,574 (Menzin et al, 2014). Omalizumab, used to treat EA, had a copay of $60.26 under pharmacy benefit; while under the medical benefit, the coinsurance amounted to 19.2%, capped at a $1000 annual maximum (Campbell, Spackman and Sullivan, 2010). In summary, HIV and EA did not study monthly OOP or the payer cost-share.

The purpose of this study is to quantify the trends in OOP expenses, AWP and payer costs for CF, AATD, EA, PIDD and HIV patients each month in years of 2012, 2013 and 2014. This paper also investigated the relationship between the AWP and the payer cost-share. Policymakers and health services researchers will have a better understanding of the economic burden patients' experience regarding OOP expenses for these five diseases. Policymakers could use these metrics to make key state and federal policy decisions, to better serve these patient populations and to reduce patient cost burden.

Methods:

Data Sources:

The analysis was conducted using the 2012 - 2014 IBM Marketscan Commercial claims and encounters research database which include over 40 million patients who have employer-sponsored insurance from a sample of US private health plans (Feng, L. B., Grosse, S. D., Green, R. F., Fink, A. K., & Sawicki, G. S. (2018)) This database comprised outpatient services, outpatient pharmaceutical services and inpatient services. The Outpatient Pharmaceutical services claims was used to quantify the pharmacy benefit costs while the Outpatient services claims were used to assess physician/clinician office visits costs, which included drug infusions. Appropriate approval for institutional review board (IRB) was sought and the data was de-identified conforming to the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Compared to other claim level databases, the Marketscan claims database was selected because it could capture a larger sample of patients with the diseases of interest.

Study Population Selection

Patients were selected based on any single claim for a specialty drug listed in Table 2 using their corresponding National Drug Code (NDC), which corresponds to each disease state (CF, EA, Alpha, PIDD and HIV) for the years 2012 to 2014. The NDC code were used to select the study population as it captured patients using specialty drugs. Then after selecting with the NDC code, at least one disease ICD-9 diagnosis code was confirmed from those patients to remove off-label drug use by beneficiaries. Since, we are selecting patients using drugs within the five disease states, severe combined immune deficiency (SCID) patients, who are highly susceptible to cancer, are commonly prescribed PIDD drugs, were excluded from our population. Therefore, patients for PIDD were cross checked to ensure that they did not include patients who

had malignant cancer, which was achieved by removing patients using PIDD specialty drugs who had their Major Diagnostic Code (MDC) as myeloproliferative diseases and poorly differentiated neoplasms (MDC=17). The NDC for the specialty drugs were obtained from the Redbook supplied by the 2013 Marketscan database. For example, patients with at least one Omalizumab were selected under the EA cohort using NDC codes. Additionally, patients were also selected if they had at least one claim for an infused specialty drug administered in an outpatient setting. These claims for the specialty drugs were selected using the Healthcare Common Procedure Coding System (HCPCS). These HCPCS codes for each specialty drug were selected using the corresponding codes. Ivacaftor used for Cystic Fibrosis does not include any HCPCS code as it is only administered orally, therefore it was only obtained from Outpatient Pharmaceutical claims data. Enfuvirtide (FUZEON®) was the only infused drug selected from the HIV cohort. The rest of the HIV drugs were administered orally.

These medications were chosen because they represented variable markets. CF and EA belonged to a monopolistic market, AATD had an oligopolistic market with three drugs, and PIDD/HIV had a competitive market with more than 10 drugs each. For this study, only eight drugs were selected for HIV and five drugs for PIDD. Additionally, these disease states were selected as there is no literature on AWP, payer cost share and patient cost share after keeping in mind that patients pay high out of pocket costs for these drugs. Moreover, there is an increasing trend in producing specialty drugs, and therefore, studying more varied classes (diseases) which are poorly represented in the literature would be beneficial to patients, payers and researchers.

Study Design, Data Setup and Measures

A retrospective cohort study design was used to study the trends of OOP costs, average Wholesale Price (AWP), payers' cost-share for specialty medications per month. Patient claims

were selected based on the study population selection discussed above to study these drug price trends with the corresponding reimbursed payer-share and patient out of pocket expense. The reason for using the claim level is that patients took varied amount of drugs due to dosing determined by the prescriber and prescribed doses by patient weight. Therefore, by using a claim level dataset, we could assume an equal representation of all weight classes and doses.

Patient characteristics included age, sex, health plan indicator and insurance provider. Health plan indicator was used to describe whether patients belonged to a large employer health plan or had individual health plans. Further, plan type indicator was categorized based on the health plan incentives that the patient used when selecting providers. For example, patients using a health plan with preferred provider organization (PPO) had a financial incentive with lower cost-sharing for a select group of providers, whereas comprehensive plans entailed that the patient had no incentive to go to a select provider. Patients using Health Maintenance Organization (HMO) plans can only a select from specific group of providers for health services. Age was described under age ranges of 0-17, 18-34, 35-44, 45-54, and 55-64.

Patient cost-share burden was quantified with direct costs paid out-of-pocket (OOP) by patients for specialty medication. OOP costs were calculated as a summation of the deductible, copay and coinsurance. Payer cost-share and AWP were extracted directly used from the claim level database. Table 2 shows the drugs which were studied in each cohort. Drug classes: CF, ALPHA and EA had one to three drugs which were selected for analysis. Five drugs were selected from the PIDD cohort, which was commonly used in the Outpatient setting. HIV cohort had more than 40 drugs in the database, therefore our study selected the six drugs which represented the different classes of HIV drug treatments. Two drugs namely REYATAZ® and VIREAD® were selected as they had generic available during the near course of the study, and their cost trend were important to study with the other HIV drugs.

Statistical Methods

Descriptive statistics in the form of means and standard deviations were calculated for continuous variables and frequencies and percentages were calculated for categorical variables for each of the disease states. Graphs were produced with median cost-share, AWP by the month from 1st January 2012 to 31st December 2014 were produced.

Table 3.1: Demographics						
	ALPHA	**CF**	**EA**	**HIV**	**PI**	**Overall**
Number of Patients	1125	281	14591	95723	24885	136605
Age Group						
00-17	0%	38.07%	7.20%	0.73%	13.39%	3.80%
18-34	2.75%	44.83%	15.39%	22.27%	14.32%	19.97%
35-44	10.57%	8.89%	19.19%	25.61%	14.41%	22.72%
45-54	34.66%	5.69%	27.53%	33.84%	23.14%	31.17%
55-64	52%	2.49%	30.66%	17.53%	34.71%	22.32%
Gender						
Male	51.20%	51.60%	34.94%	81.08%	40.67%	68.49%
Female	48.80%	48.39%	65.05%	18.91%	59.32%	31.50%
Health Plan Indicator						
Employer	39.55%	57.29%	52.76%	54.62%	41.30%	51.88%
Health Plan	60.44%	42.70%	47.23%	45.37%	58.69%	48.11%
Plan Indicator						
Comprehensive	2.22%	1.06%	1.74%	0.93%	2.28%	1.27%
EPO	2.13%	1.42%	1.68%	1.89%	1.87%	1.87%
HMO	7.02%	12.45%	9.95%	16.93%	8.53%	14.56%
POS	6.57%	6.40%	6.95%	7.40%	6.48%	7.18%
PPO	60.71%	63.70%	62.58%	59.69%	63.49%	60.71%
POS with capitation	0.53%	0.71%	0.56%	0.58%	0.57%	0.58%
CDHP	4.53%	4.62%	5.07%	4.74%	5.01%	4.82%
HDHP	4.17%	3.91%	3.94%	3.10%	3.74%	3.32%

Table 3.2: Specialty Drugs (Brand Names) Used for this study
Cohort: ALPHA
ARALAST, PROLASTIN, ZEMAIRA
Cohort:CF
KALYDECO
Cohort: EA
XOLAIR
Cohort: PIDD
GAMMAGARD LIQUID, GAMMAKED, GAMUNEX, GAMUNEX-C, HIZENTRA, OCTAGAM, PRIVIGEN
Cohort: HIV
ATRIPLA, ISENTRESS, NORVIR, PREZISTA, REYATAZ, SUSTIVA, TRUVADA, VIREAD

Results

Demographics

From January 2012 to December 2014 we observed a total of 136,605 patients from five drug classes. Over 30% of the patients in this study sample had age of 45-54. Though, some variability was seen where more than half of the beneficiaries using ALPHA specialty drugs were aged 55-64 while 45% of patients in the CF cohort belonged to the 18-34 age group. About 68% of the patients were male in the total sample, which included the HIV cohort dominated by 81% males. However, EA had patients had over 65% female beneficiaries. The total number of

beneficiaries were closely split with 52% employer sponsored health insurance though HIV and ALPHA had mostly health plans. Preferred provider organization (PPO) comprised 60.7% of the health plans for the patients. Of note, the high deductible health plans increased from 2.39% in 2012 to 4.32% in 2014. There were 68% males and more than 53% of the patients were more than 45 years of age. Fifty-eight percent of the patients listed in a self-insured employer health plan.

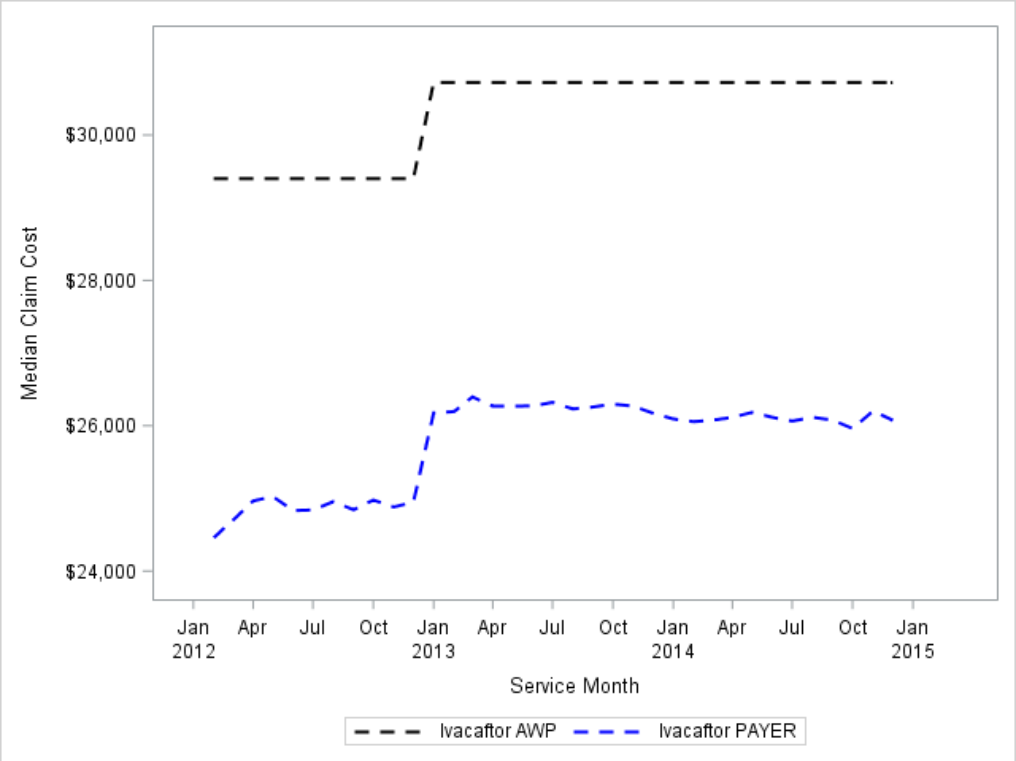

Figure 3.1 - Ivacaftor Median Monthly Expenditures: AWP, Payer Cost-Share

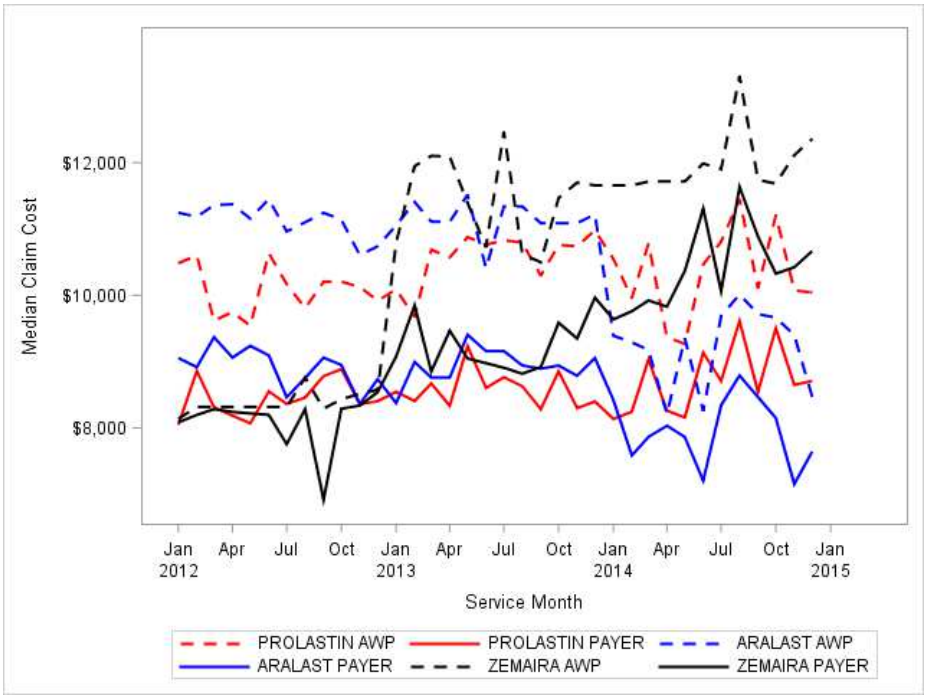

Figure 3.2 - ALPHA drugs Median Monthly Expenditures: AWP, Payer Cost-Share

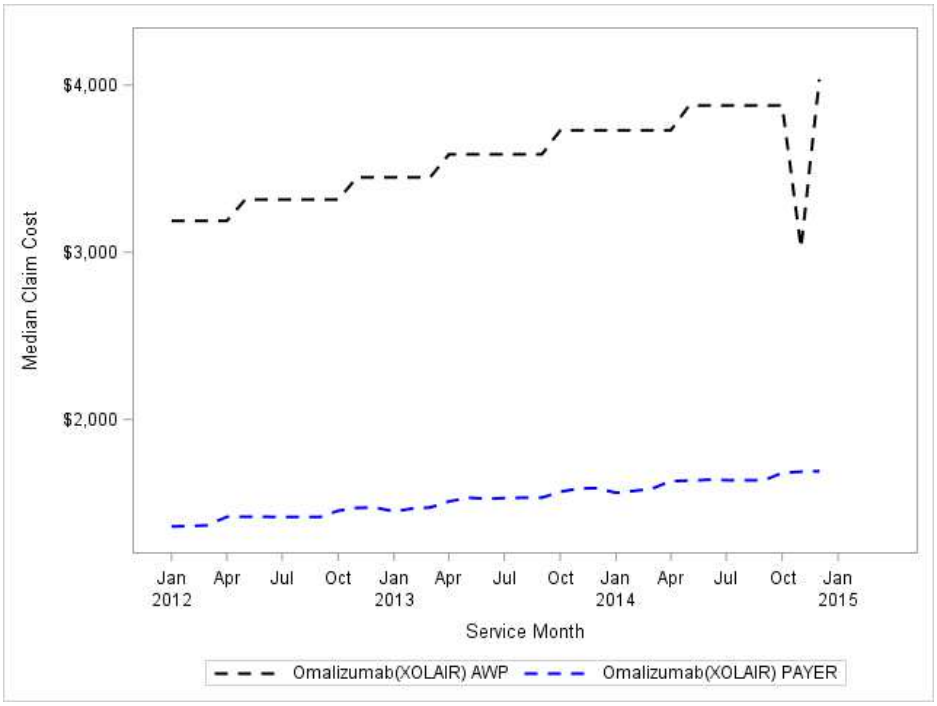

Figure 3.3 - Omalizumab Median Monthly Expenditures: AWP, Payer Cost-Share,

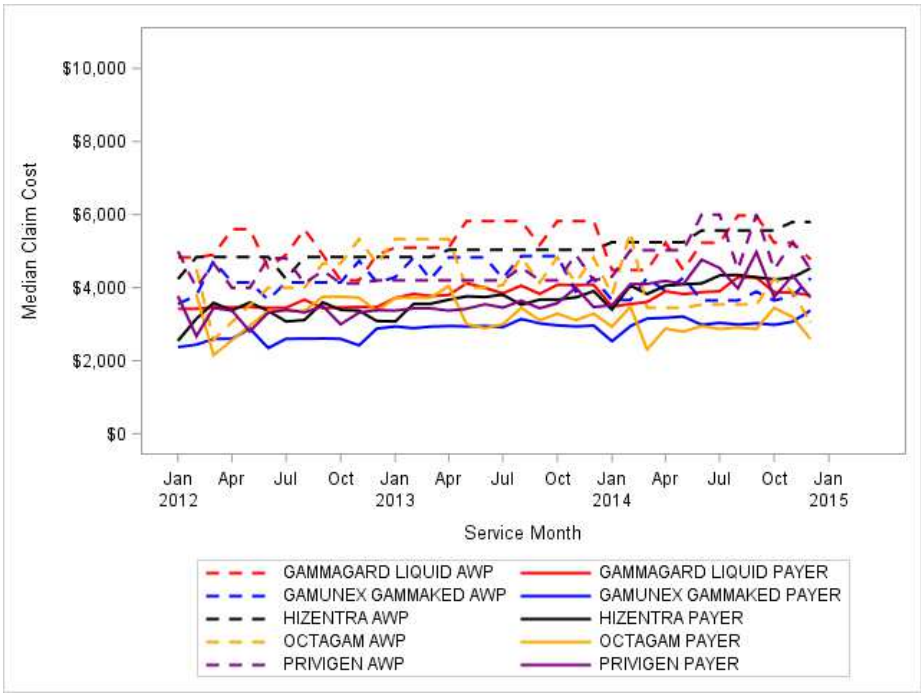

Figure 3.4 - PIDD drugs Median Monthly Expenditures: AWP, Payer Cost-Share

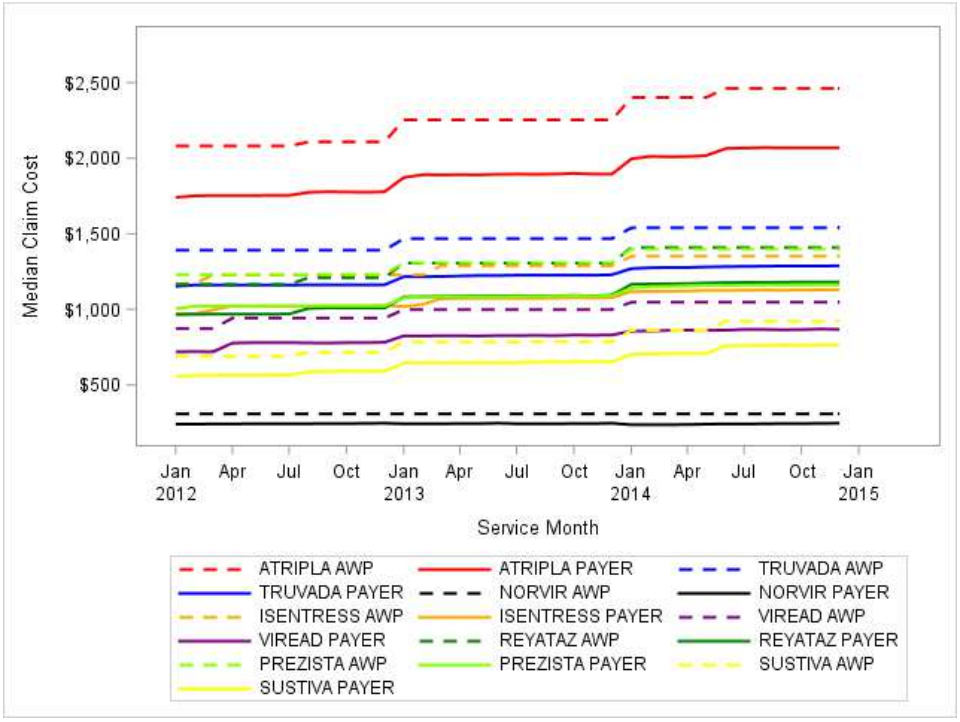

Figure 3.5- HIV drugs Median Monthly Expenditures: AWP, Payer Cost-Share

Drugs distribution for each cohort

GAMMAGARD LIQUID™ was the most commonly used drug for PIDD from 2012 to 2014. Also, over 85% of the PIDD drugs were attributed to beneficiaries' claims from a physician office setting. Two cohorts had single drugs, which were Ivacaftor and Omalizumab belonging to the CF and EA cohort respectively. The ALPHA cohort showed more than 80% claims coming from the Physician Office. Since all the drugs in the ALPHA shared the same procedure J code, differentiating the drug on the physician office claims would not be possible. But, the rest 20% ALPHA claims could be drug differentiated by NDC codes. Over 18% of the claims for HIV belonged to the triple combination drug, ATRIPLA®, while the twin combination drug, TRUVADA®, captured 16% of the HIV drug claims.

AWP, Payer Cost-Share and Patient Cost-Share

The median monthly claims for the cohorts by each drug with the listing prices are displayed in Figures 1-10, with the first half having the AWP and payer cost-share and the rest quantifying the patient cost-share by each drug for each cohort. For the CF cohort, the AWP and payer-share were the biggest. The margins between the AWP and payer cost-share separated by a margin of $5,000. It must be noted that the AWP of Ivacaftor (60 tablet count, taken 2 times daily), showed little variation and stayed in the range of $29,000 to $31,000 for a month supply. The median patient cost-share stayed in the range of $30-$60 per month.

For the ALPHA cohort, the AWP was listed at a higher price than the payer cost-share, with the monthly difference between the AWP and payer cost-share being at $2000 for the three drugs, but this difference bottomed at $0 for ZEMAIRA® in December 2012 and went as high as $3000 for ZEMAIRA® July 2013. The median reimbursed amount for ARALAST®, PROLASTIN® and ZEMAIRA® started approximately $8000 to $8500 and then ultimately

ZEMAIRA® settled at $10,500, which was higher than PROLASTIN® at $8,750, with ARALAST® being third at $7,500. PROLASTIN® dominated the market with 85% of the patient claims.

The EA cohort showed an increasing pattern in the monthly median cost for the listed AWP and the payer cost-share. The difference between the payer cost share and AWP stayed at about $5,000. The Median cost share for patient cost-share stayed at estimated $50 with a peak reached at $60 in January 2014. Omalizumab is administered at the dose of 150mg through 375 mg and administered every 2-4 weeks.

The PIDD cohort showed the five drugs to be more variable with respect to the patient cost-share in 2012 and 2013, but in 2014 the five drugs were within the the range of $30-$50. The difference between the AWP and payer cost-share stayed at $1000. GAMMAGARD LIQUID™ was the highest listed AWP at $5,000 for most of the study period, while HIZENTRA® was the next highest listed priced drug at $4,750.

The HIV cohort showed only yearly increase bumps in the median payer cost-share and AWP. ATRIPLA® had the highest listed AWP throughout the study with median AWP of $2,100 in January 2012 and increasing to $2,500 in December 2014. TRUVADA® was the second highest listed AWP, starting at $1400 in 2012 and settling at $1500 in 2014, while the payer cost-share showed a constant difference of $200 below AWP. The difference between the AWP and the payer cost-share was the highest for ATRIPLA® at about $500 but the other HIV drugs saw a difference of $100 to $250.

Discussion

Our study investigated the behavior of AWP, payer cost-share and patient cost-share from 2012 to 2014 with respect to the markets they represented. We found that when a drug (CF

and EA) was in a monopolistic market the difference in AWP and payer cost-share was the highest ($5,000). As multiple drugs entered a drug class e.g. ALPHA, we found this difference decreased to $2000. Finally, with a fully competitive market of HIV, the difference was only $150. Therefore, as more drugs with the same indication enter the market, the prices naturally drop, but it is also possible that the drug discount or the coupon value reduce. The difference can represent a combination of factors, namely the patient cost-share, drug discount coupons, coordination of benefits, and the negotiated discount between payers and manufacturers. From this combination of factors, the drug discount or coupons make up the bulk of this difference, which we will be discussing for the five disease states.

CF, which is a monopolistic market with a single drug has shown to have variable compliance rate of 61% when authors investigated the electronic medical record and monitored the adherence rate for patients using Ivacaftor (Siracusa et al, 2017). Ivacaftor is known to have a very good patient assistance program that helps with patient out of pocket costs. CF foundation is one such organization that helps with finding assistance for patients. It provides support by connecting patients to programs with a myriad of support services, which include insurance awareness, copay assistance, and financial assistance with all forms of out of pocket expenses (Cystic Fibrosis Foundation CFF.org). KALYDECO® is useful in only 6% of the 30,000 patients with CF, but in November 2015 ORKAMBI® was introduced into the market and was efficacious in nearly half of the US population with CF (Boeck & Davies, 2017). It must be noted that both these drugs are manufactured by Vertex Pharmaceuticals, suggesting sustained high prices as there is really only one firm in the market.

The ALPHA cohort observed variation in the difference between the AWP and payer cost-share. Previously, it has been suggested that drugs could be reimbursed at 17.1% to 72% of the AWP (Gencarelli, 2005). In this study, the ALPHA cohort received a 76% to 99% in payer reimbursement of the AWP. PROLASTIN®, which represented 85% of the ALPHA cohort,

showed a relatively constant reimbursement between $8000 to $9000. It must be noted that PROLASTIN® was the fifth most prescribed specialty drug (2.2% market share) for respiratory conditions in 2012 and moved to sixth in 2013 (3.4% market share) (Express Scripts Drug Reports 2012, 2013). Therefore, based on market share, PROLASTIN® may have stayed the same in volume sales, but other drugs with the same indication held a larger market share compared to PROLASTIN®., This change would mean the utilization of respiratory specialty drugs increased from 2012 to 2013. In a clinical trial ZEMAIRA® was associated with a reduction in lung tissue loss in severe ALPHA patients, which may explain the increase in median payer cost-share compared to PROLASTIN®. (Chapman et al, 2015).

The EA cohort showed an increase in the average wholesale price from January 2012 to December 2014. The steady increase in payer reimbursement from approximately $1200 to $1700 may have been influenced by the impending release of NUCALA®, which was eventually approved in November 2015, competing with XOLAIR®. We assumed that the drop in AWP in November 2014 signifies a reduction in the patient assistance for that timeframe. However, we were unable to measure was the Average Selling Price (ASP) for the physician offices or outpatient settings. Our study aggregated the payer reimbursements for outpatient pharmacy claims as well as outpatient office claims. However, the AWP was only available for the outpatient pharmacy claims. Therefore, the drop in November may represent a change in price on the Pharmacy level. Pharmacy and physician office level claims are known to have different reimbursements. For example, a study by Motheral B and Belken C (2014) showed that Omalizumab (XOLAIR®) was reimbursed 4% higher by pharmacies compared to physician offices. The authors observed that a specific health insurance plan reimbursed XOLAIR® for 165% of the ASP, which was higher than the average reimbursement of 107%-109% of the ASP seen throughout this study. This study also observed overall higher cost per unit charged for specialty drugs in the outpatient pharmacy claim system.

We observed in the PIDD cohort five drugs that were essentially the same ingredient, but GAMMAGARD LIQUID™ and GAMUNEX® dominated over 50% of the claims of this cohort. Our study showed that GAMMAGARD LIQUID™ was reimbursed at $3800 per month, a higher price compared to GAMUNEX® at $3000. Similar results with respect to payer reimbursement for GAMMAGARD LIQUID™ were reported by Bagwell et al (2018) and a drug report by Magellan Medical Pharmacy Report 2014. Although the Magellan report consistently found a higher median cost-share for GAMUNEX® and GAMMAKED™ for an estimated $4426 in 2013, the higher cost-share may be due to the inclusion of oncology patients. With PIDD having multiple drugs, it seems to behave closer to a competitive market, where the prices for the five drugs are relatively close to each other. It must be noted that PIDD drugs are increasing in expenditures, with a 13% rise from 2012 to 2013 and a 32.55% surge from 2013 to 2014. (Schumock et al, 2015). In our study, we look at only five drugs, and the increase in payer reimbursements show an increase in reimbursement comparable to the previous years Compared to our study, Schumock showed even higher increases during the same years. One must note that the authors examined data until September 2014 and compared only the first 9 months of 2014 to the first 9 months of 2013 to compute the percentage increase. Schumock noted that PIDD was the 14th highest class in drug expenditures for US clinics in 2013 and rose to 10th by September 2014. Our study did not differentiate whether PIDD drugs were administered via the subcutaneous (SCIG) or the intravenous route (IVIG), but the literature suggested home-based SCIG was significantly less expensive than IVIG administered in the clinic. Therefore, the location of the treatment would affect the reimbursed amount (Jolles et al, 2015).

The HIV cohort showed a perfectly competitive market where reimbursed amounts for each drug were close to the cost of other drugs. ATRIPLA®, which was the first triple combination drug and was the highest reimbursed drug was essentially a drug added to the double combination of TRUVADA®. Since ATRIPLA® is the only triple combination drug in this study,

it would be expected to have the highest in expenditures. When looking at marketshare for these drugs, these combinations seem to represent equal proportions of the population, based on commonly prescribed combinations: ATRIPLA® represented 20% of the market, TRUVADA® (16.8%) + SUSTIVA® (2.5%) , PREZISTA® (6.8%) + NORVIR® (13%) and REYATAZ® (6.5%) + NORVIR® (13%). Of the eight drugs studied, REYATAZ® and VIREAD® had generics available had generics available in April 2014 and March 2015, respectively. [The REYATAZ® generic was rolled outside of our timeline.] In 2014, REYATAZ® did not see a decrease in listed AWP with the release of its generic in April or a semiannual increase in July 2014, as seen in ATRIPLA® and SUSTIVA®. The drug trend report for Express Scripts 2014 found the same top four drugs (ATRIPLA®, TRUVADA®, NORVIR® and ISENTRESS®) in marketshare similar to our study. The same drug report showed a 14.8% increase in per member per year cost from 2013 to 2014. To help with out-of-pocket the Ryan White Foundation provides assistance for eligible patients to receive HIV treatment.

CF and ALPHA are designated as rare diseases by the FDA, which means that they have a preferential seven years of added patent exclusivity after accounting for the 20 years from filing for the new drug. Manufacturers may be able to keep prices high because of limited competitors entering the market, or sometimes manufacturers pay other manufacturers, to delay the entrants of their competitors. In the case of XOLAIR® (EA) manufacturers may try to keep the prices till their competitors enter the market. During our study the drugs treating the PIDD have HIV cohorts are competitive, and hence listing prices for these drugs could stay the same or drop with newer drugs entering the market. The older HIV drugs are known to have many side-effects but the newer drugs e.g. ATRIPLA® have patients with least side-effects and reduced virulence. Therefore, newer combination treatments with less side effects available for HIV treatment, will lead to increased drug prices.

Specialty drugs continue to represent a larger part of prescription drug expenditures. Manufacturers ultimately have the right to control the prices in the distribution channels (McCain, 2012). Payers and pharmacy benefit managers will always be critical in negotiating with payers and employers in helping patients access these critical lifesaving medications. Finally, patient utilization and compliance will be important in advancing therapy and obtaining better treatment through research.

Limitations

Population for the HIV cohort might be misrepresented in the age group of 18-35 as majority of these patients tend to be uninsured (Yehia et al, 2015). The Marketscan claims database comprises employer sponsored commercial insurance, which is a convenient sample, which is not representative of the US population. Although the Marketscan database has been shown to represent more than 90% of US patients with private insurance (Grosse et al, 2018).

Another important limitation is the expenditure information is incomplete. The reason for this limitation is that after drugs are purchased from manufacturers, and eventually used, there are funds given back to the pharmacy benefit managers as incentives. Therefore, the net revenue to the manufacturers, which is the pharmacy statement can be overstated in the data. In fact, net revenue to manufacturers was reported at 28.2% less than the gross revenue in 2016. (Augustine et al, 2017)

Also, the data showed seasonality with respect to OOP costs as patients pay higher costs at the start of the year relative to the end of the year

Conclusions

. There was a decrease in discounts (AWP - Payer cost share) in disease states with more available treatments. The patient cost-share trend seems to be in line with payer cost share reimbursements for specialty drugs. Researchers will always have a limitation of the true costs' payers are paying due to negotiated discounts and rebates not available for research. The FDA have recently increased approvals for cancer drugs, orphan drugs (drugs treating a population of less than 200,000 e.g. CF), and it will be important to investigate the market and the related disease to determine the price competition

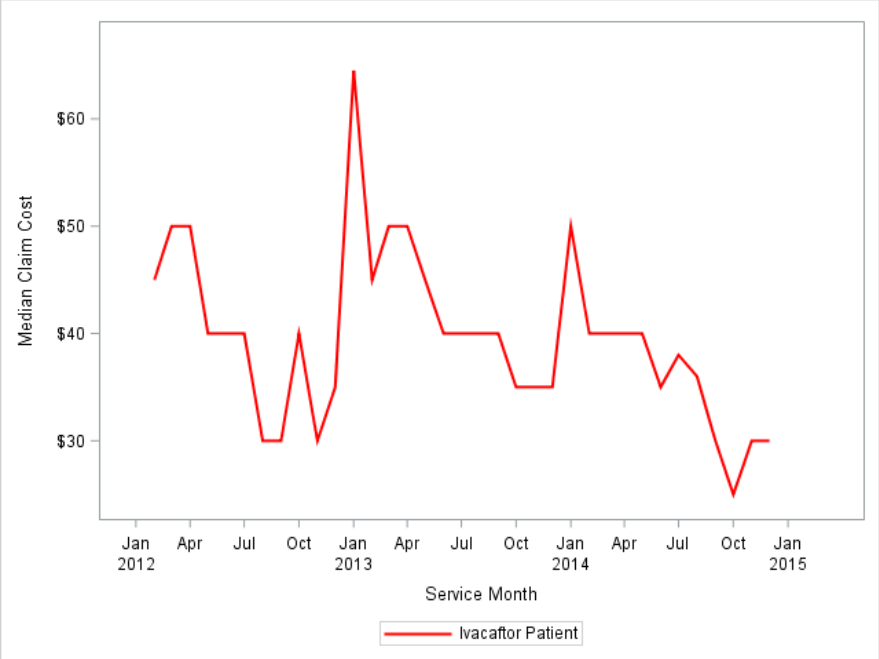

Figure 3.6 - Ivacaftor Median Monthly Expenditures: Patient Cost-Share

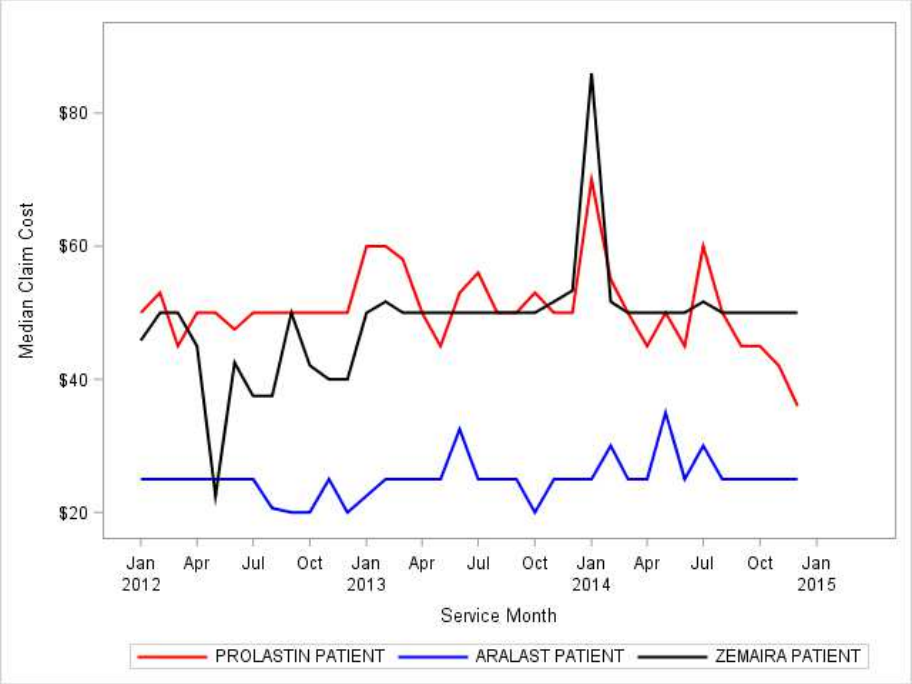

Figure 3.7 : ALPHA drugs Median Monthly Expenditures: Patient Cost-Share

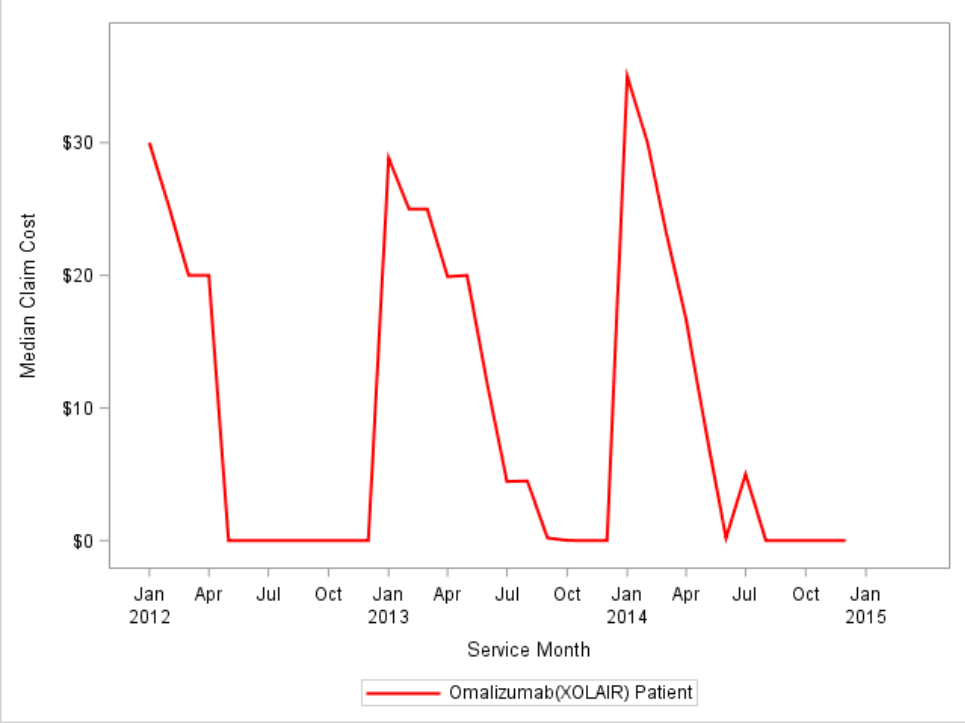

Figure 3.8 – Omalizumab Median Monthly Expenditures: Patient Cost-Share

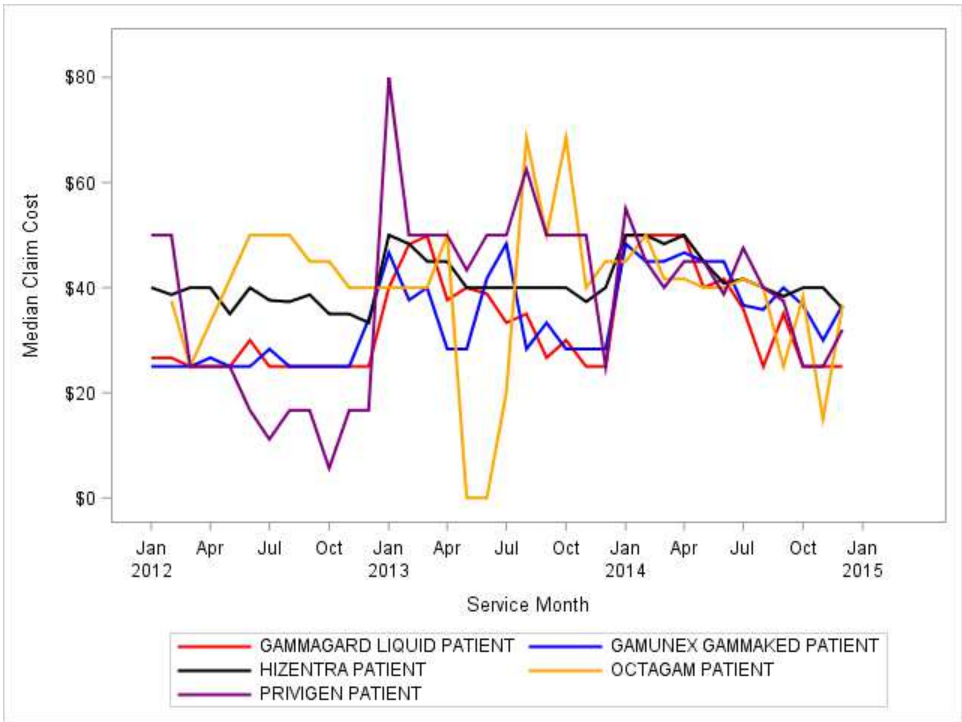

Figure 3.9 - PIDD drugs Median Monthly Expenditures: Patient Cost-Share

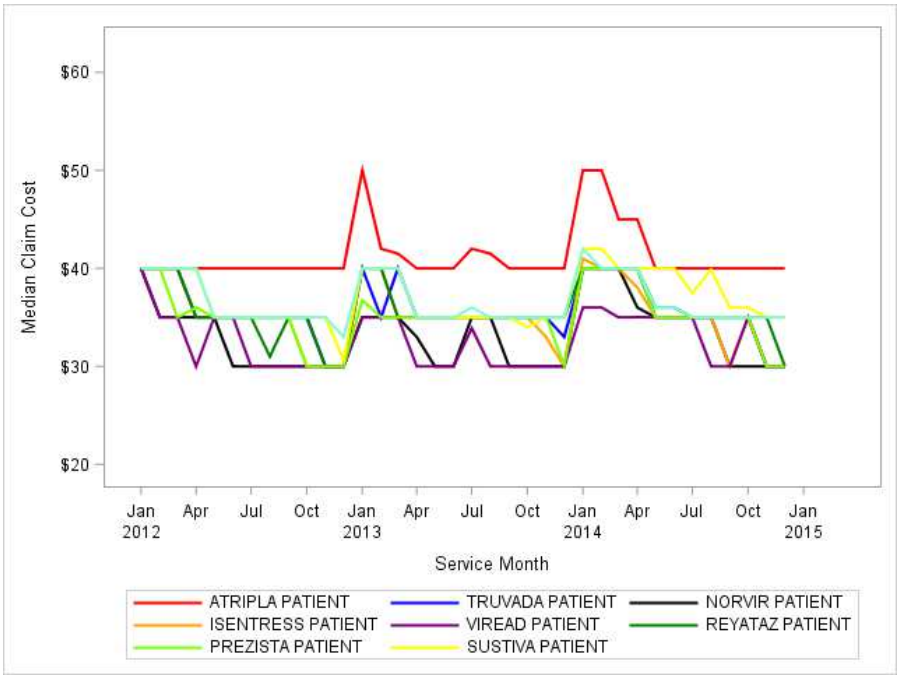

Figure 3.10 - HIV drugs Median Monthly Expenditures: Patient Cost-Share

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Chapter 4: Price Elasticity of Demand for patients using specialty medications. for select diseases

Introduction

Specialty medications are costly, and the cost-sharing placed on patients has been steadily increasing in the US. Use of specialty medications are rising because of the ability of the drugs to improve patients' life-expectancy and quality of life. This is an important incentive for pharmaceutical companies to set the cost of specialty medication much higher than other routine standards of care and places them in a higher tier with greater out-of-pocket (OOP) costs to the patient. For example, a patient may have 20% coinsurance on a $30,000 drug per month, costing the patient $6,000 out-of-pocket monthly. Patients living with eosinophilic asthma (EA), cystic fibrosis (CF), alpha-1 antitrypsin deficiency (AATD), primary humoral immunodeficiency (PIDD) and human immunodeficiency virus (HIV) are commonly prescribed such specialty medications that have an allowable cost of more than $600 per month for each patient. These high costs are important as some diseases may only have one drug available for treatment, which leave patients and payers with very little options. In such cases, with a single drug, the manufacturer tends to set high prices due to lack of competitors. Hence, eosinophilic asthma and cystic fibrosis have a single drug each in the market, setting them up for monopolistic pricing. However, competitive markets reflect the presence of multiple drugs with indicated use and treatment for a single disease, which is an advantage to patients as the price of these medications are competitive due to multiple drugs treating the same indication. AATD has limited options with only 3 indicated medications, while HIV and PIDD have more than 10 drugs respectively treating the same disease in a competitive market.

Price Elasticity of demand is a proportional change in the quantity demanded or number of prescriptions with respect to a unit increase in price. For example, the price elasticity of demand for prescription medications is -21%, which means that if the price of a prescription medication increased by a single dollar it causes 21 in every 100 individuals to not purchase these prescription medications. (Merrill, Costa-font, McGuire 2006). There are disease areas where financial burden has been observed but elasticity has not been evaluated in detail. Wu et al (2007) found that Omalizumab used to treat Eosinophilic asthma (EA) was not cost-effective with an estimated $821,000 needed to gain a year of healthy-related quality of life. Gildea et al (2003) concluded for patients treated with augmentation therapy for AATD, therapy costs are incrementally higher than other interventions indicated for use in the AATD population. Patients treated for PIDD and HIV need these specialty medications regularly, to avoid acute exacerbations. The aforementioned studies demonstrate the financial burden on patient populations treated with specialty medications. In general, patient assistance and quantifying the price elasticity of demand for patients with rheumatoid arthritis, kidney disease, cancer and multiple sclerosis has been studied in the past. But previous studies fail to quantify the price elasticity for these five disease states: eosinophilic asthma (EA), cystic fibrosis (CF), AATD, PIDD, and HIV.

After quantifying the price elasticity, policymakers and health services researchers will have a better understanding of the economic burden patients' experience regarding OOP expenses for these five diseases. Policymakers could use these metrics to make key state and federal policy decisions, to better serve these patient populations and avoid patient cost burden. Health plan designers will use the elasticity metrics to design better health insurance plans with cost-sharing thresholds, enabling more patient access to these specialty medications. Pharmacy benefit managers who work for insurers and negotiate with manufacturers, help design pharmaceutical health plans and are involved in decisions on the amount of cost-share paid by patients. Their

cost-sharing agreement will be critical to employer sponsored insurance where they have a single health plan option. This essentially means that when these specialty medications are made affordable to the population which needs it the most, it may lead better access and better overall outcomes.

Based on the literature above, this study will attempt to analyze the burden of OOP costs to the consumers by calculating the price elasticity of demand for specialty medications treating eosinophilic asthma, cystic fibrosis, AATD, PIDD and HIV. Again, these medications were chosen because they represented variable markets (i.e. Monopoly, oligopoly and competitive) and the paucity of literature with respect to these diseases was noticed. Price Elasticity of demand has been studied with Rheumatoid arthritis, kidney diseases, cancer and multiple sclerosis only because they were the most common diseases treated with specialty drugs in 2003 and 2004 (Goldman et al, 2006). With data from years 2012-2014, having many more diseases treated with specialty drugs, we will study the price elasticity of demand in different markets. This study hypothesizes patients taking specialty medications are more price inelastic as compared to patients taking prescription medications (-21%). Therefore, this study will attempt to show that with an increase of OOP expense to patients, there will only be a negligible change in utilization (i.e. more than -21% and less than 0%) among the number of patients receiving prescription for specialty medications as compared to patients taking other prescription medications.

Methods

Study Design

An ecological study design was used to quantify the price elasticity of demand for these patients. An ecological design entails analyzing the utilization of the population in aggregate on a monthly basis. This means that subjects utilizing specialty medications for these five

corresponding disease states will be selected from the claims database. An advantage of using the ecologic design is that the summary data will be able to include both (a) patients coming in and leaving in all years with (b) patients moving from different health plans. The insurance health plan will provide the group level database where patient utilization of specialty medications will be assessed.

With these criteria in mind, the Marketscan healthcare claims database was used to assess whether claims data is a reliable data source in observing patient utilization behavior across consecutive months from 2012 through 2014. There were no exclusions of patients based on age. The Marketscan healthcare database, with patient cost details and utilization behavior provided an essential foundation for quantifying the price elasticity of patients receiving prescriptions for specialty medications.

Data Sources

The analysis was conducted using the 2012 - 2014 IBM Marketscan Commercial claims and encounters research database which includes millions of patients who have employer-sponsored insurance from a sample of US private health plans (Feng, L. B., Grosse, S. D., Green, R. F., Fink, A. K., & Sawicki, G. S. (2018)). This study will use selected tables from the Marketscan database, which were outpatient services, outpatient pharmaceutical services and inpatient services. The Outpatient Pharmaceutical services claims was used to quantify the pharmacy benefit costs while the Outpatient services claims were used to assess physician/clinician office visits costs, which included drug infusions. Appropriate approval for institutional review board (IRB) was sought and the data was de-identified conforming to the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Compared to other claim

level databases, the Marketscan claims database was selected because it could capture a larger sample of patients with the diseases of interest.

Table 4.1: Specialty Drugs Used for Analysis
Cohort: ALPHA (Alpha-1 proteinase inhibitor)
ARALAST, PROLASTIN, ZEMAIRA
Cohort: CF
Ivacaftor (KALYDECO)
Cohort: EA
Omalizumab (XOLAIR)
Cohort: PIDD (Immune Globulin Infusion)
BIVIGAM, CARIMUNE NF, FLEBOGAMMA 10% DIF, FLEBOGAMMA 5%, FLEBOGAMMA 5% DIF, GAMASTAN S/D, GAMMAGARD LIQUID, GAMMAGARD S/D, GAMMAGARD S/D (IGA<1UG/ML), GAMMAKED, GAMMAPLEX, GAMUNEX, GAMUNEX-C, HIZENTRA, OCTAGAM, OCTAGAM 10%, PRIVIGEN, VIVAGLOBIN
Cohort: HIV (therapeutic name not listed)
APTIVUS, ATRIPLA, COMBIVIR, COMPLERA, CRIXIVAN, EDURANT, EMTRIVA, EPIVIR, EPIVIR HBV, EPZICOM, FUZEON, INTELENCE, INVIRASE, ISENTRESS, KALETRA, LEXIVA, NORVIR, PREZISTA, RESCRIPTOR, RETROVIR, REYATAZ, SELZENTRY, STRIBILD, SUSTIVA, TIVICAY, TRIUMEQ, TRIZIVIR, TRUVADA, VIDEX, VIDEX EC, VIDEX PEDIATRIC, VIRACEPT, VIRAMUNE, VIRAMUNE XR, VIREAD, VITEKTA, ZERIT, ZIAGEN, TYBOST,

Study Population Selection

Patients were selected based on any single claim for a specialty drug listed in Table 1 using their corresponding National Drug Code (NDC), which aligns with each disease state (CF,

EA, Alpha, PIDD and HIV) for the years 2012 to 2014. CF and EA belonged to a monopolistic market, AATD had an oligopolistic market with three drugs, and PIDD/HIV had a competitive market with more than 10 drugs each. The NDC code were used to select the study population as it captured patients using specialty drugs as compared to patients selected based on ICD-9 diagnosis code but may or may not have used specialty medications. Then, after acquiring claims using NDC codes for medications, at least an ICD-9 code for the corresponding disease state was confirmed for each patient to ensure exclusion of off-label drug use. Additionally, patients for PIDD were cross checked to ensure that they did not include patients who had malignant tumors (cancer) as cancer patients use IVIG for their treatment. The other specialty drugs (all except PIDD) were solely indicated for their corresponding disease states. This was achieved by removing patients using PIDD specialty drugs who had their Major Diagnostic Code (MDC) described as myeloproliferative diseases and poorly differentiated neoplasms (MDC=17). The NDC for the specialty drugs were obtained from the Redbook supplied by the 2013 Marketscan Redbook table. For example, patients with at least one Omalizumab were selected under the EA cohort using NDC codes. Additionally, patients were also selected if they had at least one claim for an infused specialty drug administered in an outpatient setting. These claims for the specialty drugs were selected using their corresponding Healthcare Common Procedure Coding System (HCPCS). Ivacaftor used for Cystic Fibrosis does not include any HCPCS code as it is only administered orally, therefore it was only obtained from Outpatient Pharmaceutical claims data. Enfuvirtide (FUZEON®) was the only infused drug selected from the HIV cohort. The rest of the HIV drugs were administered orally.

Data Setup and Measures

Patient claims that correspond to the specialty drug of interest were aggregated by each patient per calendar month. Proportional utilization changes in subsequent months were used to

express the change in demand for patients in the previous month. Therefore, only future measures were recorded for patients whose utilization was recorded relative to the previous month. These future measures include the OOP expenses, AWP and payer cost-share for the specialty drugs.

Patient cost-share burden, in the form of OOP, was quantified with direct costs paid for specialty medication. OOP costs were calculated as a summation of the deductible, copay and coinsurance. To study the balance between the payer and patient cost-share, the payer cost share was summed up for each patient per month. Total Healthcare costs were expressed as the healthcare costs incurred that did not include the specialty drug spending in pharmacy or physician office claims and inpatient services. Payer portion of the total healthcare cost was calculated to study payer cost-sharing and trends.

Demographic variables were studied in a table to understand the distribution of various characteristics in the population for the disease states. Patient characteristics included demographic variables of age group, sex, health plan indicator and insurance provider were quantified for the five disease states. Age was described as the average, and also under age ranges of: 0-17, 18-34, 35-44, 45-54, and 55-64. Health plan indicator was used to describe whether the patients belonged to a large employer health plan or had individual health plans. Further, plan type indicator was categorized based on the health plan incentives that the patient used when selecting providers. For example, patients enrolling in a health plan with preferred provider organization (PPO) had a financial incentive with lower cost-sharing for a select group of providers, whereas comprehensive plans do not give the patient an incentive to select a specific provider. Health Maintenance Organization (HMO) plans require patients to select from group of providers for non-emergent care.

Statistical Methods

Descriptive statistics in the form of means and standard deviations were calculated for continuous variables and frequencies and percentages were calculated for categorical variables for each of the disease states. Segmented regression analysis was used to analyze trends of the measures over time for each disease state. Trend analysis was used to study the cost burden to patients using specialty medications. Therefore, the unit of analysis was patient months. Since the deductible and the OOP maximum resets at the beginning of the year, the outcome variables of OOP costs, proportional utilization, and payers' total costs were seasonally adjusted in a time series model with the help of seasonal decomposition. Stationarity testing for this autoregressive time series was completed using the KPSS test, where a p-value of over 0.05 was considered stationary. SAS Enterprise Guide 7.11 was used to analyze the data. A two-sided alpha of 0.05 was used for all the analyses.

The data was assessed from January 2012 to December 2014 and summary monthly data will be analyzed forming a time series data structure. Therefore, the trend in OOP expenses with respect to time was assessed for differences in utilization of specialty medications using a segmented regression analysis. Essentially, the change in utilization habits (increase or decrease) was measured based on the change in OOP costs to the consumers. The price elasticity of demand was analyzed by OOP expenses as the independent variable, while the utilization was the dependent variable in a time series segmented regression. The parameter estimate for the average OOP cost, which is the slope, quantified the price elasticity of demand because it will quantify the change in utilization with respect to the average change in out of pocket cost. The price elasticity of demand for patients using cigarettes and smoking deterrents was abstracted from literature in order to put the price elasticity estimates into context.

Results

Demographics

Over 30% of the patients in this study sample had age of 45-54. Though, some variability was seen where more than half of the beneficiaries using ALPHA specialty drugs were aged 55-64 while 45% of patients in the CF cohort belonged to the 18-34 age group. About 68% of the patients were male in the total sample, which included the HIV cohort dominated by 81% male. However, EA had patients had over 65% female beneficiaries. The total number of beneficiaries were closely split with 52% employer sponsored health insurance though HIV and ALPHA had mostly health plans.

Table 4.2: Demographics						
	ALPHA	**CF**	**EA**	**HIV**	**PI**	**Overall**
Number of Patients	1125	281	14591	95723	24885	136605
Age Group						
00-17	0%	38.07%	7.20%	0.73%	13.39%	3.80%
18-34	2.75%	44.83%	15.39%	22.27%	14.32%	19.97%
35-44	10.57%	8.89%	19.19%	25.61%	14.41%	22.72%
45-54	34.66%	5.69%	27.53%	33.84%	23.14%	31.17%
55-64	52%	2.49%	30.66%	17.53%	34.71%	22.32%
Gender						
Male	51.20%	51.60%	34.94%	81.08%	40.67%	68.49%
Female	48.80%	48.39%	65.05%	18.91%	59.32%	31.50%
Plan Indicator						
Comprehensive	2.22%	1.06%	1.74%	0.93%	2.28%	1.27%
EPO	2.13%	1.42%	1.68%	1.89%	1.87%	1.87%
HMO	7.02%	12.45%	9.95%	16.93%	8.53%	14.56%
POS	6.57%	6.40%	6.95%	7.40%	6.48%	7.18%
PPO	60.71%	63.70%	62.58%	59.69%	63.49%	60.71%
POS with capitation	0.53%	0.71%	0.56%	0.58%	0.57%	0.58%
CDHP	4.53%	4.62%	5.07%	4.74%	5.01%	4.82%
HDHP	4.17%	3.91%	3.94%	3.10%	3.74%	3.32%

Specialty Drug OOP costs and Utilization

The average monthly OOP cost for the study sample was $125. ALPHA had the highest average monthly OOP of $172 with the lowest belonging to EA at $94.50. The AWP for 30-day supply of Ivacaftor (CF) was the highest at $30,306. Figure 2 through Figure 6 shows the utilization and the average out of pocket expenses for patients in the five disease states. Most of them show the seasonal pattern of OOP costs being the highest at the start of the year and then reducing as time reaches the end of the year. The utilization shows the highest drop in January because of these increased OOP expenses at the start of the year. There are sometimes drops in utilization and increased OOP expenses in July due to some health insurance plans being issued every 6 months. Figure 2 shows CF utilization and OOP expenses starting from February 2012 as Ivacaftor was released in the market in January 2012 and there were claims starting in February 2012.

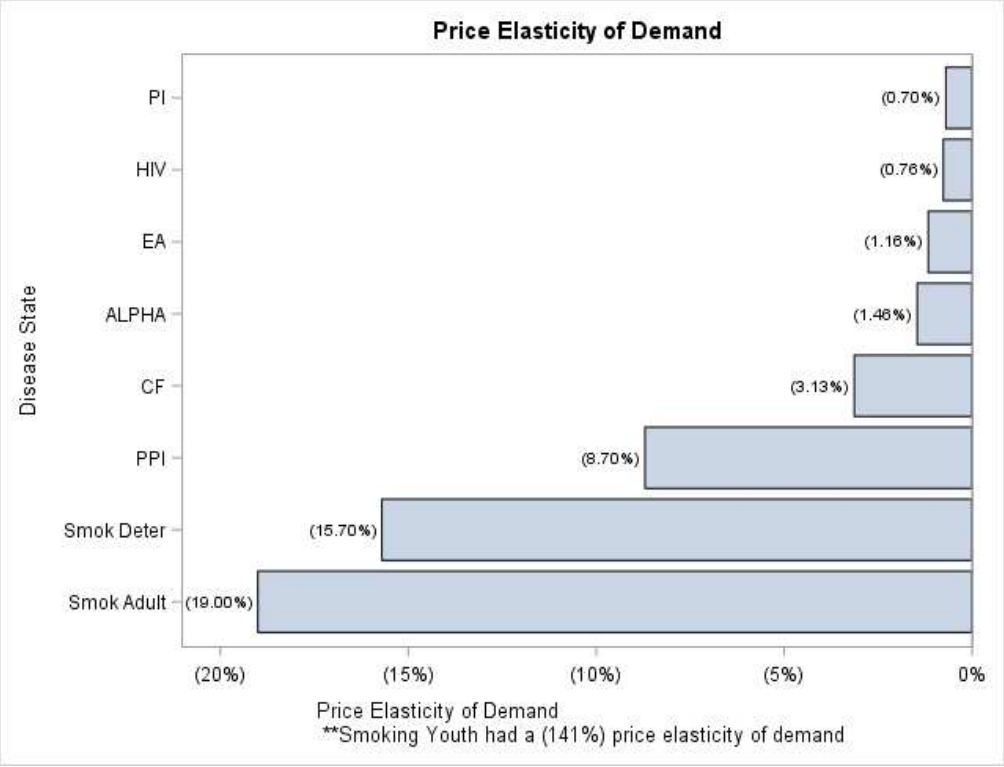

Figure 4.1: Price Elasticity of Demand for Specialty drugs versus other drugs/agents

Price Elasticity of Demand

The price elasticity of demand of patients using CF specialty drugs was the most responsive to OOP expenses as compared to the other 4 drug classes. Price elasticity of demand was 3.1% and therefore a 3.1% decrease in the utilization of Ivacaftor after a $1 increase in average monthly OOP expense. The price elasticity of demand for PIDD was the least OOP expense responsive at (0.7%) which meant that there was a reduction in utilization for 7 of every 1000 individuals using PIDD specialty drugs after a unit increase in average monthly OOP. The rest of the price elasticity of demand for the diseases can be seen in Figure 1.

Discussion:

In this study, we attempted to examine the price elasticity of demand for five disease states belonging to varying types of market, which range from monopolistic to competitive. Despite specialty medications being very expensive, we realized that patients are less price responsive, compared to all other patients using prescription medications not including specialty medications. Looking at the five disease states, three of them: cystic fibrosis, alpha-1 antitrypsin deficiency and eosinopilic asthma had elasticity estimates of less than (1%). While patients using drugs for PIDD and HIV, who have more than ten drug options were less price responsiveness at (1%) to 0. When these metrics are compared to smoking deterrents or proton pump inhibitors, patients in the five disease states included in this study are more price insensitive. In Figure 1, a price elasticity estimate of (15.7%) would mean a dollar increase in the price of smoking deterrents would lead to 157 individuals (in every 1000) would discontinue using smoking deterrents. Therefore, the price inelastic nature of the study patients is confirmed as compared to the elastic nature of patients who use smoking deterrants.

The results from this study suggest that patients using specialty medications are more price inelastic compared to patients using prescription medications at (20.9%) (Gemmill, Costa-

Front et al McGuire, 2007). In their study, a meta regression approach was used in an attempt to eliminate publication bias by reviewing literature from various sources not limited to journals. They finally settled with an unbiased estimator for price elasticity at (20.9). In our study the price elasticity ranged from (3.1%) for CF to (0.6%) for PIDD. Therefore, our study does show that patients are less price responsive compared to all patients utilizing prescription medications.

Goldman et al (2006) investigated price elasticity of demand for specialty drugs but looked at a different disease population, which comprised of Multiple Sclerosis, rheumatoid Arthritis, kidney diseases and cancer between 2003 to 2004. The authors found that the overall elasticity ranged from (21%) to (1%). This study looked at patients with pharmacy and medical plan benefits between 2003 to 2004. As compared to Goldman's study which used a two-part model, a segmented regression approach using proportional utilization as the outcome and out of pocket expenses as the only explanatory variable, which is a different yet simple approach to calculating elasticity. The market for drugs was less variable as the authors noted that patients with the four diseases had less drug options and the number of patients needing specialty drugs were only 1-5% compared to all other patients taking prescription medications. In our study the market for patients with five disease states ranged from competitive to monopolistic markets. But our results were less variable suggesting that the patients were even less price responsive compared to the Goldman et al (2006) study. The similarity our study and Goldman et (2006) was that the patients were less price responsive to high cost medications.

Gatwood et al (2014) investigated the effects of cost sharing and the usage of prescription drugs by measuring the price elasticity of demand for patients using medications belonging to eight drug classes. Compared to our study, the authors also used Marketscan data but did not look at specialty medications, but at eight classes of prescription medications. This study Gatwoods's study did have a similar population with respect to the majority of patients had Preferred Provider Organization (PPO) as their health plan type. The authors found that the price elasticity of

demand ranged from (15%) for smoking deterrents to (1.57%) for NSAID/opiods, which had an overlap with some diseases in our study. Since Gatwood's study did not include specialty drugs the patients cost sharing was not as high as compared to our study but nevertheless showed a similar inelastic response with Thyroid hormone (3.2%), Anticonvulsants (5.1%) and Proton Pump Inhibitors (8.7%). These drug classes studied by Gatwood et al (2014) represent drugs which can be replaced by other drugs and even still show an inelastic response, similar to the specialty drugs in our study, hence showing how cost-sharing is not affecting utilization, due to various factors, including, the need of the medications.

Specialty drugs are used abundantly in the field of oncology too. A study by Goldman et al (2010) investigated the patients' price elasticity of demand for five relevant oncology drugs treatments from the administrative claims database for the span of 1997 to 2005. They found that the price elasticity for RITUXIMAB® used to treat non-Hodgkin's Lymphoma was (1.2%) while the other four cancer treatment drugs collectively had an elasticity of (21%). Reduced utilization by 20% was close to the elasticity numbers by Gemmill et al for-prescription drugs but RITUXIMAB® did fall in the range of elasticity found in our study. The authors used a similar approach to our methods where out of pocket expenses for drugs were used as the dependent variable. Therefore, even a specialty drug, namely RITUXIMAB®, treating cancer show that patients are price inelastic to this oncology treatment.

The price elasticity of demand is also dependant on the health plan designs, with respect to the tiers system formulated by pharmacy benefit managers. A study by Landsman et al (2005) investigated the influence of three-tier system on drug utilization. They found that patients changed to generics more when changing from a 2-tier system to a 3-tier system compared to patients with no drug tier change. The authors also found that the medication adherence ratio reduced mainly for the patients changing to 3 tiers system, where patients were looking for more inexpensive alternates. Compared to our study where CF and EA have a monopoly for the

indications they treat, patients would not have access to an alternate and cheaper drug. This can cause the drug prices in monopolistic markets to increase. The authors also took an interesting approach, where they categorized the nine drug classes studied under symptomatic conditions and asymptomatic conditions. They found that the elasticity was low, that is (16%) to (10%) for asymptomatic conditions treated with ACE inhibitors, ARBs and CCBs, but was moderate that is (60%) to (24%) for symptomatic conditions treated with COX-2 inhibitors, NSAIDs, triptans and SSRIs. Compared to our study the authors used a similar approach of calculating the denominator of elasticity as the average change in the copayment which is a part of the patient's cost-share. But the coinsurance and deductible were not included, which is understandable because these classes of drugs do not share a large patient-share compared to specialty medications.

With the patient cost-share being expensive, it begs the question whether patients can even afford these drugs. An article in Economic Policy for the Washington Post pointed out that the average retail price for 115 specialty drugs were $53,384 which was more than the median household salary in United States in 2013. Obviously, these are retail prices of which the bulk is paid by the payers. On a patient's perspective, the Express Reports 2014 mentioned that patients paid $2,782 annually on average for drugs costing more than $100,000 retail per year. Though, it might seem less than 2%, these out of pocket costs increase yearly, and these high costs are eventually passed on patients in the form of higher premiums per year. Therefore, regulation might be required to ensure patients are treated fairly when assessing the sum of the health plan premiums and the out-of-pocket expenses for the year as compared to an affordable income for these patients.

Conclusions

Compared to general medicine, which has a price elasticity of -20.9%, this study has an elasticity of (3.1%) to (0.7%) showing that patients are more price inelastic with specialty drugs treating cystic fibrosis, eosinophilic asthma, alpha-1 antitrypsin deficiency, primary humoral immunodeficiency and human immunodefiency virus. Drug Adherence, out of pocket expenses, affordability, drug assistance programs and other socio-economic factors can possibly influence decision whether patients will take their drugs. In our study patients were more price inelastic when they had more drug options as compared to the single drug, leading us to suggest that patients are more likely to be compliant to high patient cost-sharing drugs when they have more drug options. Policy makers will have more insight into the options patients have and how a competitive market with multiple drugs treating diseases will help drive costs down. They will also need to review health plans in order to ensure fairness in cost-sharing for patients paying for expensive specialty medications.

Limitations

Patients often have assistance paying for expensive medications. For example, the Cystic Fibrosis Family foundation connects patients, who cannot afford expensive treatment to foundations, which provide financial assistance. With these resources the true financial burden of the patients might be underestimated. Additionally, drug companies give discounts to patients, pharmacy benefit managers and providers after purchase of medications, which is not recorded in administrative claims databases. Personal financial resources for patients coming through donations (e.g. gofundme.com) will be very difficult to assess for such patients. Further these claims belonged to large employers, and the income of these patients is unknown. Therefore, some patients may easily afford these medications while others may find it difficult paying for these medications. Specialty drug coverage has shown to vary across commercial health plans. In fact, Chambers et al (2018) showed that only 15.9% of the specialty drug indication pairs (e.g.

omalizumab - urticaria and allergic asthma) were covered the same way, which meant that the rest of the 84.1% pairs varied by different health plans with respect to coverage. The variations included these reasons for restricted overage: step edits, prescriber restrictions, combination therapy, patient subgroup restrictions and multiple restrictions.

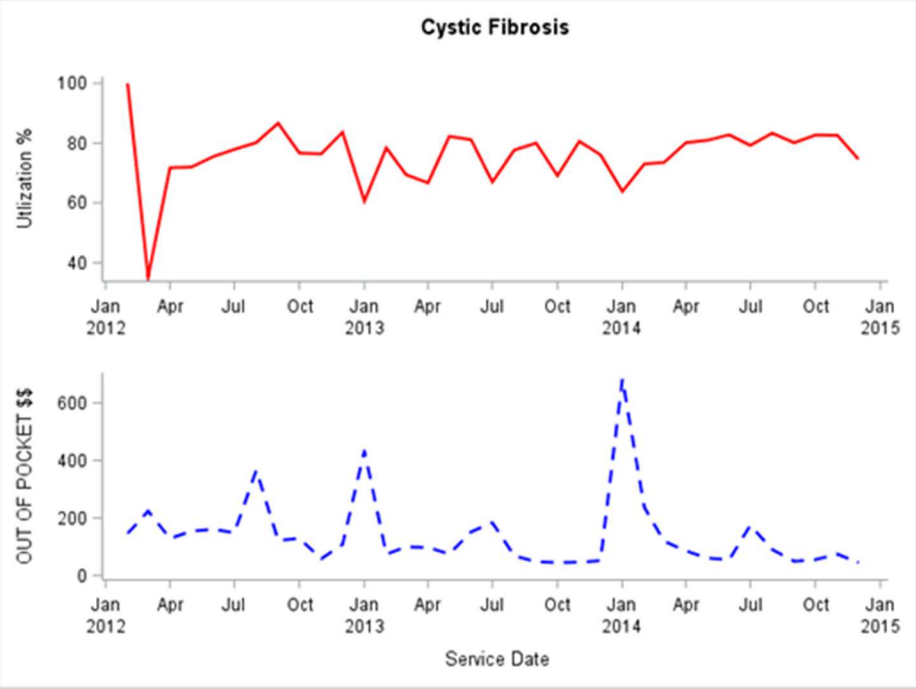

Figure 4.2: Utilization Percentage and Out of Pocket Expenses for CF Patients

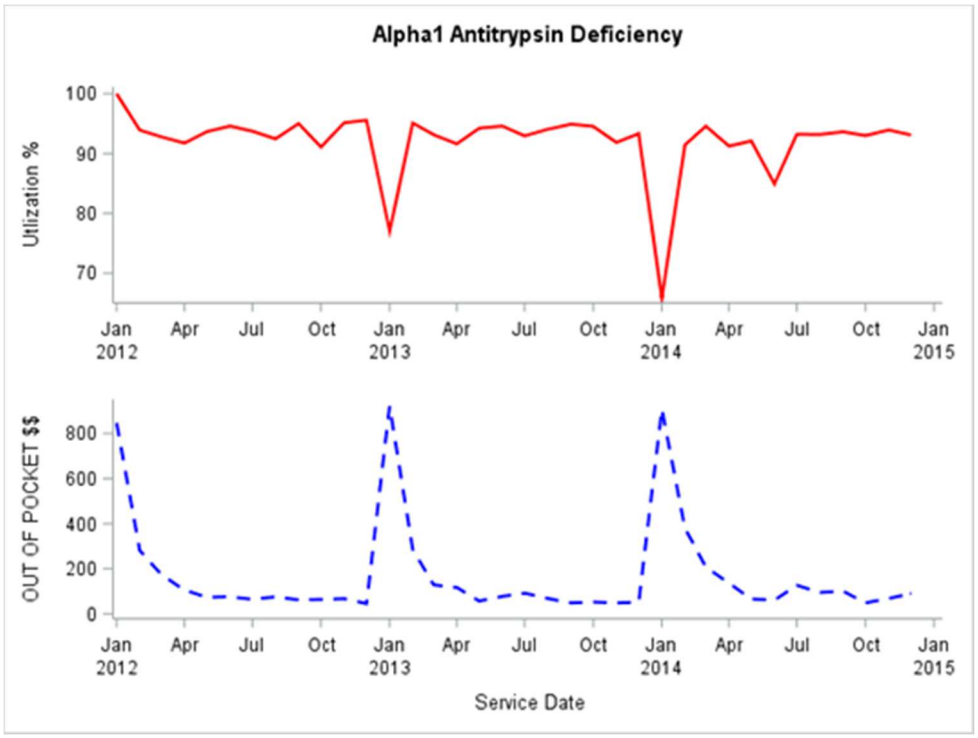

Figure 4.3: Utilization Percentage and Out of Pocket Expenses for AATD Patients

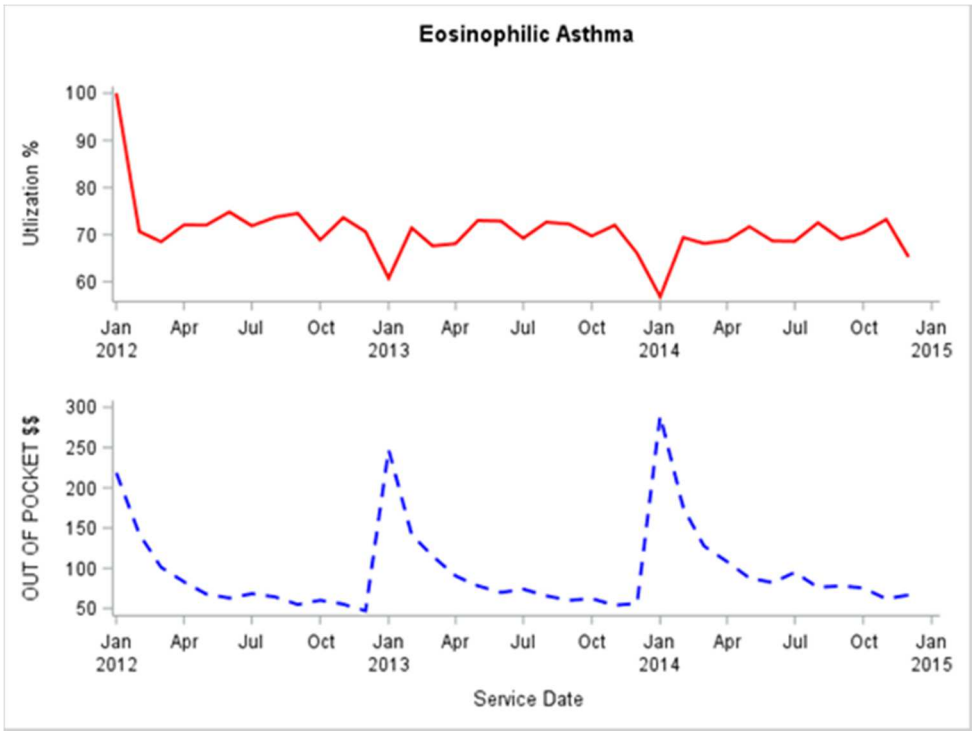

Figure 4.4: Utilization Percentage and Out of Pocket Expenses for EA Patients

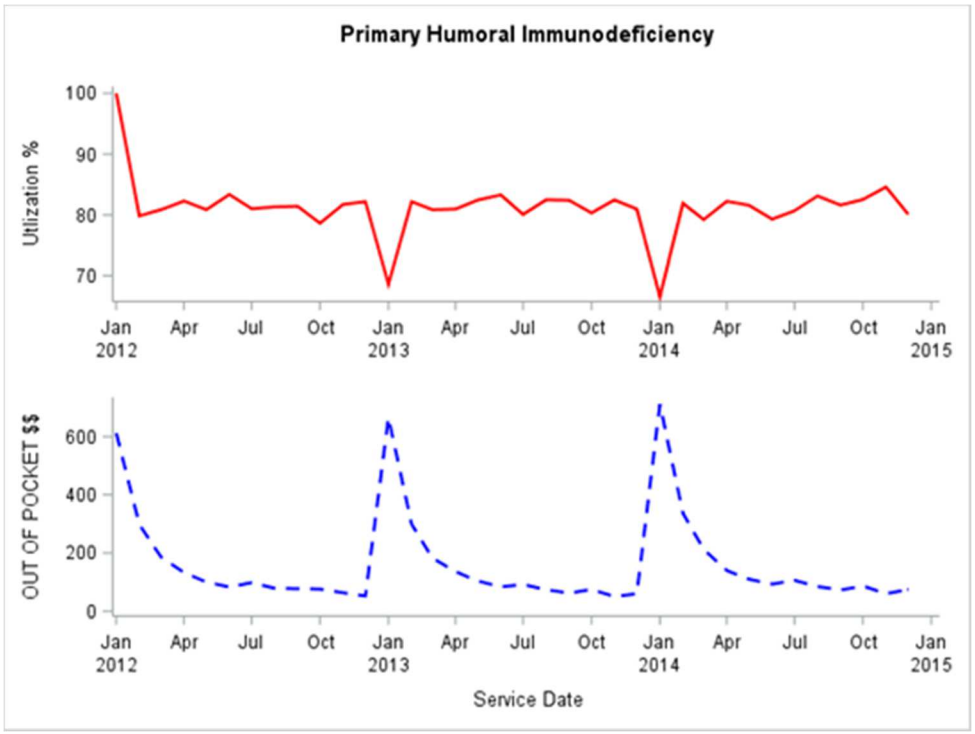

Figure 4.5: Utilization Percentage and Out of Pocket Expenses for PIDD Patients

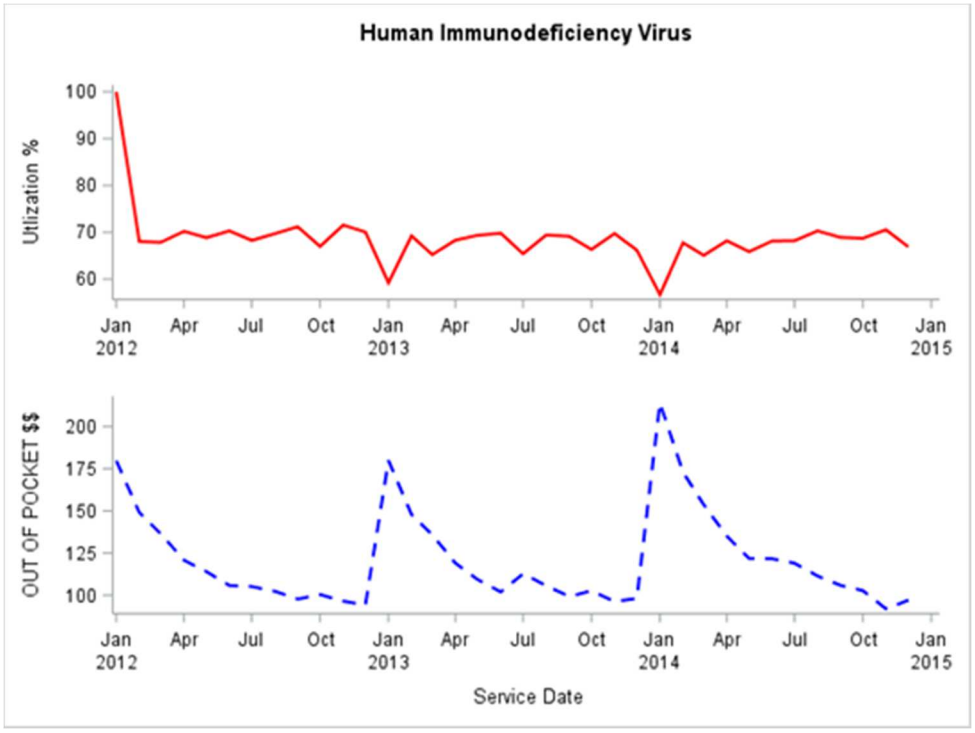

Figure 4.6: Utilization Percentage and Out of Pocket Expenses for HIV Patients

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The 2014 Drug Trend Report - The Express Scripts La4. (2015, March). Retrieved from http://lab.express-scripts.com/lab/drug-trend-report/previous-reportsEconomic Policy – Washington Post - Carolyn Johnson - Specialty drugs now cost more than the median household income

Chapter 5: The effect of missing a specialty medication dose on total healthcare cost burden

Introduction

Patients using specialty medications face high cost sharing burden due to the high cost share borne on patients in the form of copays and coinsurance. The RAND experiment concluded that cost-sharing helped with containing overall healthcare costs and thereby reduce waste of health services while keeping health and quality of care (Keeler, 1992). But, higher prescription cost sharing on patients has resulted in undesired effects in treatments disruptions, which can be defined as treatment initiation, continuation or adherence (GIbson, Ozminkowski et Goetzel, 2005). In fact, patients treated with specialty drugs for Multiple Sclerosis, Hepatitis C and TNF blockers have a 14% to 19% higher risk of nonadherence when they have an Out of pocket (OOP) expense greater than $150 as compared to patients with an OOP of $20. (Express Scripts 2009). Additionally, when looking at patients 90 days after initiating a specialty drug, they abandoned their medications 13.4% of the time when the OOP was over $250 and doubled to 26.4% when the OOP was over $500 when comparing to the patients having an OOP below $101 (Gleason et al, 2009).

Drug coupons are often rolled out by manufacturers to patients to defray these high OOP expenses in the hopes of increasing adherence. In a study, authors noticed that by reducing the patient's out-of-pocket cost to below $250 a month, it reduced the probability of abandoning their prescriptions (Starner et al, 2014). However, it was pointed out that if drug coupons were used to pay high out-of-pocket expenses for non-preferred drugs, it will cause loss in formulary management, which can cause a negative effect on insurance premiums (Starner et al, 2014). This would further compound the problem of high cost share for patients.

Poor adherence to medication can have downstream effects on worsening of conditions, which can ultimately lead to systemic level high costs (Bestvina et al, 2014). In fact, patients with HIV on highly active retroviral treatment (HAART) face adherence challenges in the form of complex dosing, food interactions and poor tolerability. Drugs for condition, which have no symptomatic relief e.g. hypertension have a risk of non-adherence too (Osterberg et Blaschke, 2005). In sum, as Goldman et al (2006) stated "… patients using specialty drugs can face extreme financial burden not just for their biologic products but across the entire constellation of health care services". There is limited literature in the disease areas of cystic fibrosis (CF), alpha-1 antitrypsin deficiency (ALPHA), eosinophilic asthma (EA), primary humoral immunodeficiency (PIDD) and human immunodeficiency virus (HIV) with respect to observed downstream effects on total healthcare cost (THC) due to poor adherence. Therefore, this paper explores the payer impact of missed specialty medication dose on total healthcare cost (THC) for CF, ALPHA, PIDD, EA, and HIV. Additionally, the reason for looking at these five disease states is that they represent different markets in the form of monopoly (EA, CF) to competitive (PIDD and HIV). With this information payers can be mindful of the efficacy, safety and value for these specialty drugs and the need to assess the financial implications bases on patients' cost burden at the start of the year. The start of the year was selected because patients are typically faced with multiple financial challenges that are paying off high deductible, social expenses in the form of holiday expense credits in addition to the routine monthly expenses.

Methods:

Data Sources:

The analysis was conducted using the 2012 - 2014 IBM Marketscan Commercial claims and encounters research database which includes millions of patients who have employer-

sponsored insurance from a sample of US private health plans (Feng, L. B., Grosse, S. D., Green, R. F., Fink, A. K., & Sawicki, G. S., 2018). This database comprises outpatient services, outpatient pharmaceutical services and inpatient services. The Outpatient Pharmaceutical services claims was used to quantify the pharmacy benefit costs while the Outpatient services claims were used to assess physician/clinician office visits costs, which included drug infusions. Appropriate approval for institutional review board (IRB) was sought and the data was de-identified conforming to the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Compared to other claim level databases, the Marketscan claims database was selected because it could capture a larger sample of patients with the diseases of interest.

Study Population Selection

Patients were selected based on any single claim for a specialty drug listed in Table 2 using their corresponding National Drug Code (NDC), which corresponds to each disease state (CF, EA, Alpha, PIDD and HIV) for 2014. The NDC code were used to select the study population as it captured patients using specialty drugs as compared to using the disease ICD-9 diagnosis codes. However, patients for PIDD were cross checked to ensure that they did not include patients who had malignant cancer. It was achieved by removing patients using PIDD specialty drugs who had their Major Diagnostic Code (MDC) as myeloproliferative diseases and poorly differentiated neoplasms (MDC=17). The NDC for the specialty drugs were obtained from the Redbook supplied by the 2013 Marketscan database. For example, patients with at least one Omalizumab were selected under the EA cohort using NDC codes. Additionally, patients in the EA, PIDD, and ALPHA were also selected if they had at least one claim for an infused specialty drug administered in an outpatient setting. These claims for the specialty drugs were selected using the Healthcare Common Procedure Coding System (HCPCS). These HCPCS codes for each specialty drug were selected using the corresponding codes. Ivacaftor used for Cystic

Fibrosis does not include any HCPCS code as it is only administered orally, therefore it was only obtained from the Outpatient Pharmaceutical claims data. Enfuvirtide (FUZEON®) was the only infused drug selected from the HIV cohort. The rest of the HIV drugs were administered orally. Additionally, patients were selected who were enrolled for 365 days in 2014 using the annual enrollment summary table in the Marketscan databases to study effect of patients who were enrolled for the whole year.

These medications were chosen because they represented variable markets. CF and EA belonged to a monopolistic market, AATD had an oligopolistic market with three drugs, and PIDD/HIV had a competitive market with more than 10 drugs each. Additionally, these disease states were selected as there is no literature out there to show total healthcare cost for them, and patients pay high out of pocket costs for these drugs. Additionally, it was seen that specialty drug utilization reduced due to the high patient cost-sharing which is commonly seen with these drugs (Doshi et al, 2016), which lends the argument that lower utilization may trigger other healthcare costs.

Study Design, Data Setup and Measures

A retrospective longitudinal study design was used to study the total healthcare cost impact on payers when comparing patients missing their January dose compared to patients who did not miss their January dose. Total healthcare cost was measured as any payer cost which belonged to the patient, which did not belong to the specialty drug, for example an inpatient hospitalization for asthmatic exacerbation would count toward a total healthcare cost. But the infusion of Omalizumab (XOLAIR®) would not count toward the total healthcare cost, because it was a specialty drug cost.

Patient characteristics included demographic variables of age group, gender, health plan indicator and insurance provider were quantified for the five disease states. Health plan indicator was used to describe whether the patients belonged to a large employer health plan or had individual health plans. Further, plan type indicator was categorized based on the health plan incentives that the patient used when selecting providers. For example, patients having health plan with preferred provider organization (PPO) had a financial incentive with lower cost-sharing for a select group of providers, whereas comprehensive plans entailed that the patient had no incentive to go to a select provider. Plan types of Health Maintenance Organization (HMO) entailed that they patients had only a selected group of providers to select health services. Age will be described as the average and will also be described under age ranges of: 0-17, 18-34, 35-44, 45-54, 55-64.

Patient cost-share burden was quantified with direct costs paid for specialty medication. OOP costs were calculated as a summation of the deductible, copay and coinsurance for specialty medications. To study the balance between the payer and patient cost-share, the payer cost share was summed up for each patient per month for the specialty drug. The Coordination of Benefits was also quantified to understand any additional sources of payment.

Total Healthcare costs (THC) were expressed as the healthcare costs incurred that did not include the corresponding specialty drug spending in pharmacy, physician office claims (J codes) and inpatient services. Payer portion of the total healthcare cost was calculated to study payer cost-sharing and trends. Patient cost-share was calculated similarly by adding the deductible, copay and coinsurance amounts. Coordination of Benefits was also included as part of the total healthcare cost. Additionally, median cost share was plotted for payer cost share for THC for the two groups, as well as patient median cost share for specialty drugs. The median was selected as it isn't influenced by outliers, as well as the median estimates would be stable and plausible over time

Statistical Methods

Descriptive statistics in the form of means and standard deviations were calculated for continuous variables and frequencies and percentages were calculated for categorical variables for each of the disease states. Line graphs were made to assess the payer portion of the total healthcare cost for the patients who were missing and not missing their January doses for the year of 2014. Mixed models with random effects was used to assess the differences in the total healthcare cost in both the groups. The unique patients were considered random effects, with data aggregated by each month. Patients were followed from January through December in the year 2014 and investigated on this longitudinal scale. SAS Enterprise Guide 7.15 was used to analyze the data. A two-sided alpha of 0.05 was used for all the analyses.

Table 5.1: Demographics						
	ALPHA	**CF**	**EA**	**HIV**	**PIDD**	**Overall (N)**
Number of Patients	505	142	6,630	41,426	9,925	58628
Age Group						
00-17	0%	35.91%	7.57%	0.63%	14.27%	2232
18-34	3.56%	45.77%	12.76%	19.49%	13.77%	10370
35-44	10.49%	9.15%	18.79%	25.35%	14.59%	13264
45-54	38.61%	7.04%	30.25%	36.53%	24.77%	19806
55-64	47.32%	2.11%	30.61%	17.98%	32.57%	12956
Gender						
Male	50.69%	52.11%	34.34%	81.21%	39.42%	40165
Female	49.30%	47.88%	65.65%	18.78%	60.57%	18463
Health Plan						
Employer	47.92%	68.30%	58.20%	67.36%	47.54%	36825
Health Plan	52.07%	31.69%	41.79%	32.63%	52.45%	21803
Plan Indicator						
Comprehensive	2.77%	1.40%	1.62%	1.23%	2.15%	849
EPO	1.98%	0%	1.50%	1.62%	1.68%	952
HMO	6.93%	14.78%	9.57%	17.99%	8.42%	8982
POS	7.32%	7.74%	7.39%	8.80%	7.21%	4902
PPO	57.02%	60.56%	61.08%	56.33%	60.13%	33729
POS with capitation	0.19%	1.40%	0.75%	0.55%	0.65%	347
CDHP	6.13%	5.63%	6.01%	6.08%	6.86%	3639
HDHP	5.34%	4.22%	4.23%	3.40%	4.26%	2146

Table 5.2: Specialty Drugs Used for Analysis
Cohort: ALPHA
ARALAST, ARALAST NP,PROLASTIN,PROLASTIN-C,ZEMAIRA
Cohort:CF
KALYDECO
Cohort: EA
XOLAIR
Cohort: PIDD
BIVIGAM, CARIMUNE NF, FLEBOGAMMA 10% DIF,FLEBOGAMMA 5%,FLEBOGAMMA 5% DIF,GAMASTAN S/D,GAMMAGARD LIQUID,GAMMAGARD S/D,GAMMAGARD S/D (IGA<1UG/ML),GAMMAKED,GAMMAPLEX,GAMUNEX,GAMUNEX-C,HIZENTRA,OCTAGAM,OCTAGAM 10%,PRIVIGEN,VIVAGLOBIN
Cohort: HIV
APTIVUS,ATRIPLA,COMBIVIR,COMPLERA,CRIXIVAN,EDURANT,EMTRIVA,EPIVIR,EPIVIR HBV,EPZICOM,FUZEON,INTELENCE,INVIRASE,ISENTRESS,KALETRA,LEXIVA,NORVIR,PREZISTA,RESCRIPTOR,RETROVIR,REYATAZ,SELZENTRY,STRIBILD,SUSTIVA,TIVICAY,TRIUMEQ,TRIZIVIR,TRUVADA,VIDEX,VIDEX EC,VIDEX PEDIATRIC,VIRACEPT,VIRAMUNE,VIRAMUNE XR,VIREAD,VITEKTA,ZERIT,ZIAGEN,TYBOST

Results

Demographics (Table 1)

Males represented 51% in the ALPHA cohort, 52% in CF, 34% in EA, 81% in HIV, and 39% in PIDD. Though, some variability was seen, where nearly half of the beneficiaries using ALPHA specialty drugs were aged 55-64 while 46% of patients in the CF cohort belonged to the

18-34 age group. Most of the beneficiaries had health insurance plans which belonged to the preferred provider organization (PPO).

Table 4 shows the average total cost share monthly broken down by payer and patient for specialty drugs and THC, regardless of whether the patients were compliant in January. CF and HIV patients had a monthly OOP of over $500 for total healthcare costs. The monthly OOP for specialty drugs ranged between $100 to $200 with ALPHA having the highest. The monthly payer cost share for THC ranged from $1327 (HIV) to $3204 (PIDD)

Specialty Drug OOP costs (Table 3)

Patients who had a January claim, had a first month OOP at an average $285 for EA, $960 for ALPHA, $710 for PIDD. $226 for HIV and $654 for CF. Since, they were compliant in January, they paid lesser monthly amount for the full year because the spread their specialty drug cost payment for the full year. Although, all disease state (except for CF patients) who missed their January dose still paid more in total specialty drugs cost annually compared to patients who did not miss their dose in January.

Effect of missing January dose on the Total Healthcare Cost (table 3)

The average monthly payer cost share for patients missing their January medication for CF were $834 lower ($5063 vs $5897, $p=0.57$), $238 higher for ALPHA ($2100 vs $1862, $p=0.80$), $51 higher for EA ($1588 vs $1537, $p=0.66$), $1,669 higher for PIDD ($4504 vs $2835, $p<0.01$), and $319 higher for HIV ($1600 vs $1281, $p<0.01$). Therefore, PIDD and HIV cohorts showed significant effects on THC after missing the January specialty drug in 2014.

Table 5.3: Average Total Healthcare Cost and Average Specialty Drug Cost					
	CF	ALPHA	EA	HIV	PIDD
Specialty Drug OOP January Average					
Missed January	0	0	0	0	0
Compliant	654.96	960.77	285.37	226.42	710.14
Specialty Drug OOP Monthly Average					
Missed January	117	264	117	162	202
Compliant	110	161	85	115	143
THC Payer - Monthly Average					
Missed January	5063	2100	1588	1600	4504
Compliant	5897	1862	1537	1281	2835

** THC = Total healthcare Cost excluding Specialty Drug

Table 5.4: Average Monthly Expenses by cost-share (All Patients)					
	ALPHA	**CF**	**EA**	**HIV**	**PIDD**
Specialty Drug					
Payer Cost-Share	10103.22	31089.59	3124.42	2817.41	6868.28
Patient Cost-Share (OOP)	180.6	127.26	103.05	126.54	167.6
COB	74.42	0	36.53	1.77	162.27
Total healthcare Cost					
Payer Cost-Share	1877.9	5635.56	1539.2	1327.87	3204.27
Patient Cost-Share	68.91	575.29	96.16	874.26	114.98
COB	83.12	34.78	22.61	58.18	129.66
*COB=Coordination of Benefits					

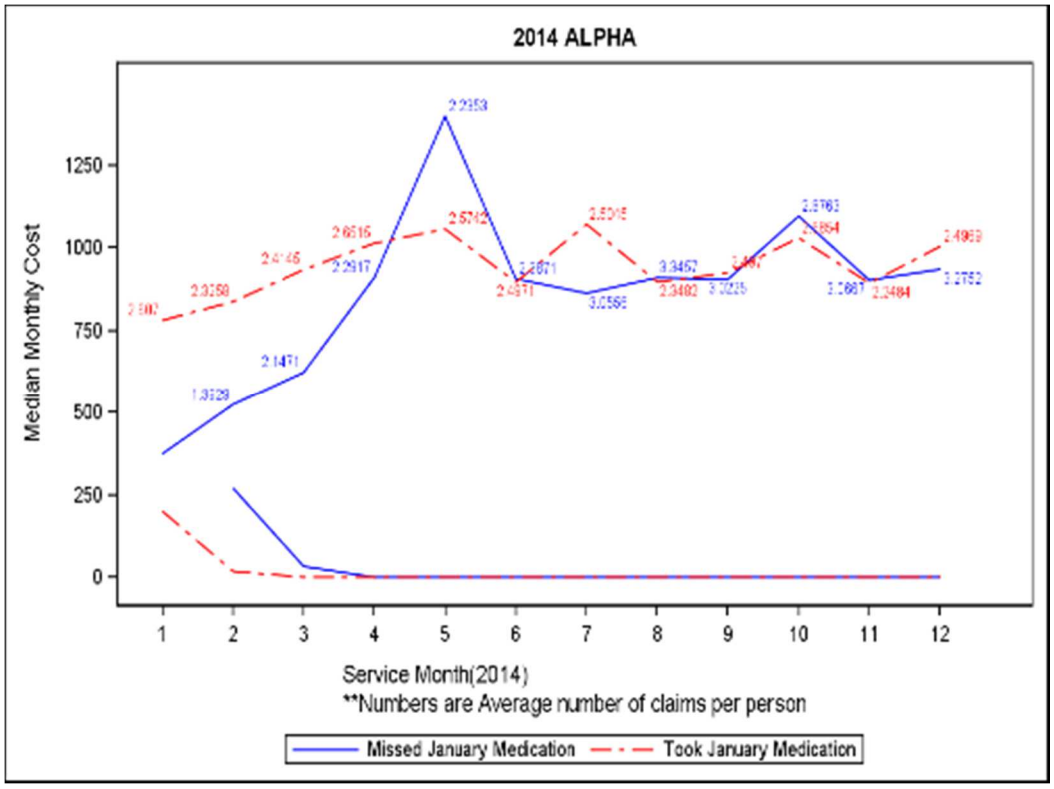

Figure 5.1: – Total Healthcare Cost (Payer) and Specialty Drug (Patient) for ALPHA Patients for the two group in 2014

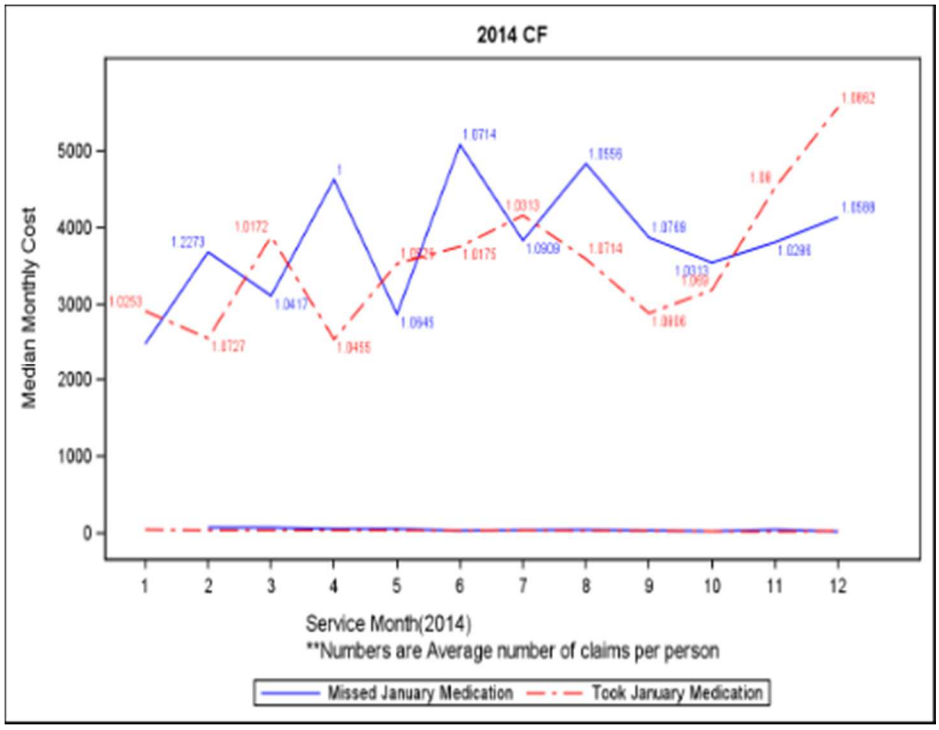

Figure 5.2: – Total Healthcare Cost (Payer) and Specialty Drug (Patient) for CF Patients for the two group in 2014

The median payer cost share on total healthcare for the ALPHA cohort showed that the patients missing their January medication did not see higher THC in the first four months compared to the patients who were January compliant. But, in May the median cost share was about $250 higher with the patients who missed their medication. Finally, the THC cost in both the groups did stay relatively the same till the end of the year.

In the CF group the median THC in both groups seem to fluctuate, with one group being higher in one month and the other group being higher in the following month. Therefore, there was no difference between the groups statistically and this can be confirmed in the graph, which shows no distinct difference between the groups

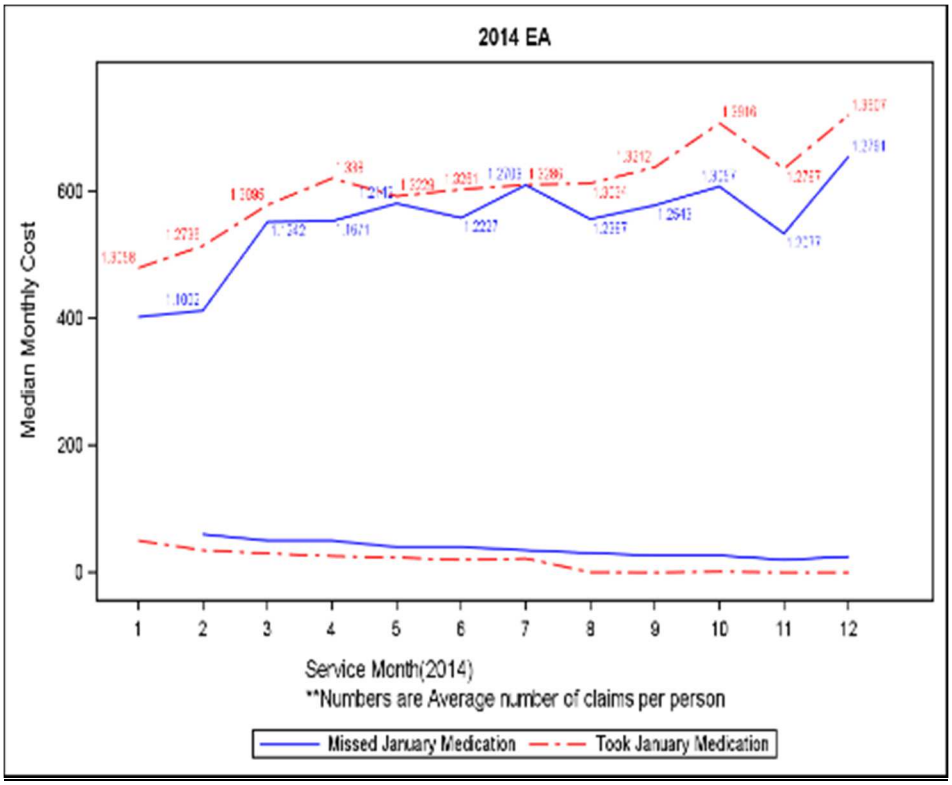

Figure 5.3: Total Healthcare Cost (Payer) and Specialty Drug (Patient) for EA Patients for the two group in 2014

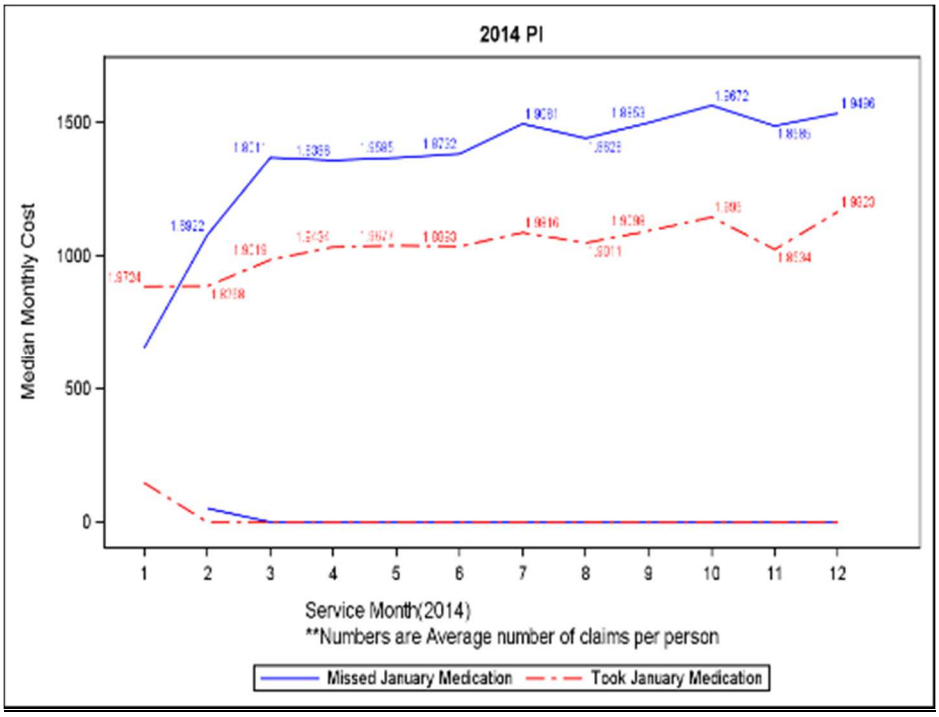

Figure 5.4: Total Healthcare Cost (Payer) and Specialty Drug (Patient) for PIDD Patients for the two group in 2014

Interestingly, the EA group showed an increased median monthly THC in the complaint patients through the year compared to patients who did not take their January medication. The difference seems to be $75 higher in the patients who had January claim. Conversely, the mean monthly THC stated that the patients missing their January medication were $51 higher.

The PIDD showed a significant difference in the payer THC between the groups with the patients missing their January being about $600 higher. January was the only month where the patients who did take medication had a higher THC compared to the patients who did not take their january medication.

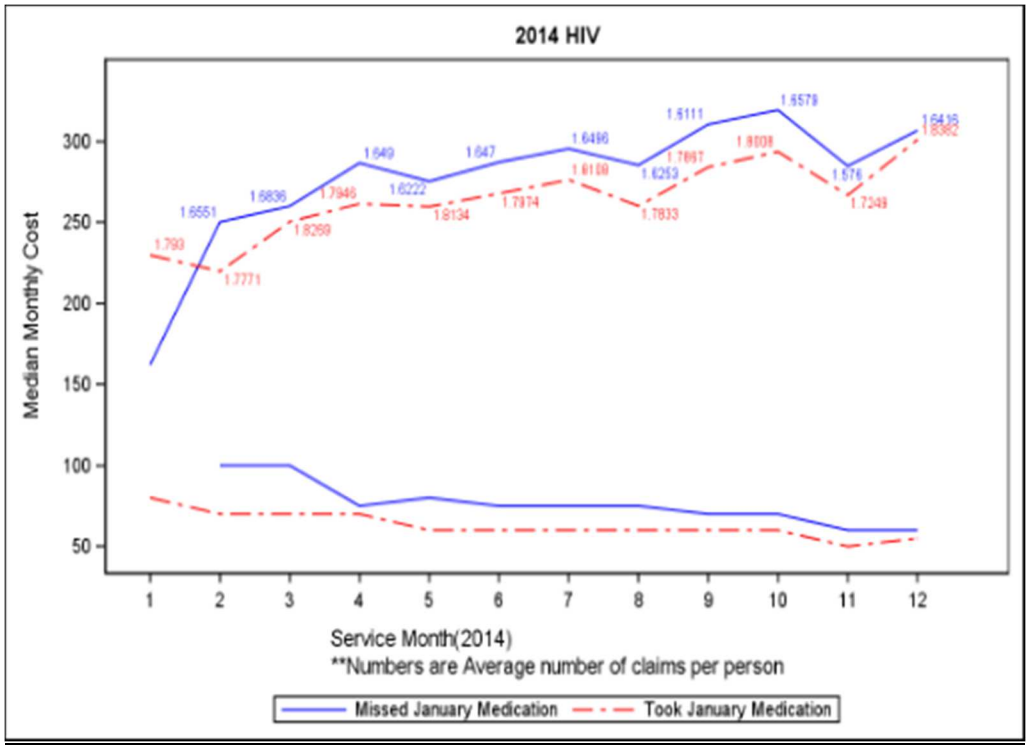

Figure 5.5: Total Healthcare Cost (Payer) and Specialty Drug (Patient) for HIV Patients for the two group in 2014

The median patient OOP was significantly higher in the patients missing their January medication. This is due to the patients needing to pay their deductible a month later, which essentially offset patient cost to the next month.

Discussion

Healthcare costs were observed for five diseases states to test for downstream effects of missing the January dose of high cost specialty drugs on total healthcare cost. We showed that PIDD and HIV disease states treated with more than ten drugs each had an increased total healthcare costs after patients missed their specialty drug dose. However, the ALPHA, EA and

CF cohort with one to three drugs did not show a significant increase in payer THC. We examined each cohort separately in the context of previous reports regarding the median cost-share claims for the year of 2014.

CF cohort

Patients with the CF cohort showed a higher payer THC in the patients who took their January medication compared to the patients who missed their January dose. Historically, CF patients are 61% compliant as shown by Siracusa et al (2015). Therefore, with patients having a low adherence rate the THC may reflect a population who is not compliant, which possibly explains the fluctuations between the groups in THC. Poor adherence can be attributed to poor knowledge by treatment guidelines by physicians, high out of pocket costs, and different perceptions of the severity of their own disease which made implications of their adherence verse. Previously, pre-2012 when Ivacaftor was not available patients used inhaled and oral medications, physiotherapy, exercise, pancreatic enzymes and inhaled coticosteroids to manage their disease (Dzuiban et al, 2010). Lung diseases in the form of recurrent exacerbations, progressive deterioration of the lung function explains to most common reasons for morbidity and mortality (Dzuiban et al, 2010).

ALPHA cohort

Patients with ALPHA are more susceptible to respiratory disorders of emphysema and chronic obstructive pulmonary disease (COPD). Iuga and McGuire (2014) found that patients who were adherent to COPD medications saw a reduction in emergency department visits and

hospitalizations which resulted in 2.2% reductions in healthcare costs. Additionally, this study reported that COPD patients who were 80% compliant with their primary medications experienced a decrease in annual Medicare expenditure by (-$2,185) by each patient. Further, ALPHA drugs are adjuvant therapy which has proven to be not cost-effective, but Stuart et al (2010) found that patients who used maintenance therapy were associated with lower hospitalization and rehospitalization leading to decreased Medicare expenditures.

EA cohort

The Asthma cohort of patients using Omalizumab showed an increased payer THC for patients who were compliant. On first glance an increased THC for compliant patients seem counterintuitive but a study by Mattke et al (2010) found that adherent asthma patients using leukotriene inhibitors or inhaled corticosteriods experienced an increased total payment, which included ed visits, hospital admissions and other non-drug payments. A possible explanation for higher THC in the compliant groups is that the compliant groups are less healthy patients, which need more healthcare expenditures (Mattke et al, 2010). This would make sense, as Omalizumab is used for severe allergic asthma (Caminati et al, 2016).

HIV cohort

Patients living with HIV face multiple barriers to adherence, which include forgetfulness, fear of disclosure, quality of life barriers, substance abuse, work-life responsibilities and access issues. (Kominski, 2019). Patients who miss their medication, risk the chance of drug resistance. Poor adherence leads to compromised treatment effectiveness, increased treatment for an unsuppressed virus and drug resistance would explain the increased in total healthcare cost for these non-adherent patients (Chen, Chen & Kalichman, 2016). In a study by Juday et al (2015),

the authors showed that completely adherent patients on cART (combination antiretroviral treatment) had lower hospitalizations, lower ER visits and lower healthcare costs. A possible explanation for non-adherence was stated by Juday et al (2015), that hill pill burden and frequent administration can contribute to non-adherence.

PIDD Cohort

There is a subset of patients who have disorders in antibody production who need PIDD medications every 3-4 weeks, otherwise they risk the incidence of serious and recurrent infections as pointed by Wasserman et al (2017). Therefore, our study supports the increased THC due to a missed dose. The PIDD cohort showed the biggest difference in the total healthcare cost between the groups. Within this study, we can use the total healthcare cost as a proxy to burden of disease to state the worsening of disease effects from missing doses.

Payer perspective

Stuart et al (2015) found that from a payer perspective, there was a significant decrease in the medical cost after patient were highly adherent to oral antidiabetic drugs, ACE inhibitors and statins over 2 years. These authors also concluded that the drug cost was more than compensated by savings on medical costs associated with non-adherence. Juday et al (2015) spoke about HIV combination therapy and stated that on a payer perspective, the value to coverage of HIV patients on cART is very important in order to keep total healthcare costs which are associated with HIV infections at a minimum. O'Connor (2006) suggested that payers should consider reducing or even eliminating copayment on statins, blood pressure medication as they are highly beneficial medications for patients with heart diseases, hypertension or diabetes. Goldman et al (2006) reported that given the beneficial nature of high cost specialty drugs, payers should manage

utilization by giving preferential access to patients who need these drugs, rather than having the same high copays for all patients on these specialty drugs

Specialty drug cost as a proportion of the total healthcare cost

There have been no studies investigating the five disease cohorts included in this study with respect to specialty drugs with relation to total healthcare costs. Joyce et al (2008), looked at studied the impact of specialty drugs on other medical services for patients having multiple sclerosis (MS) and rheumatoid arthritis (RA). Joyce's study found a reduction in the physician visits, hospitalizations and expensive procedures for Rheumatoid Arthritis patients. Expensive procedures were defined as procedures over $100. Also, patients taking MS and RA biologic drugs, which are considered under specialty drugs had a higher proportion of health spending ranging from 60% to 70%. When comparing these results to our study the spending on only specialty pharmaceuticals with respect to the total cost of all services ranged from 65% (HIV & EA) to 83% (CF). Therefore, our study showed that these specialty drug costs have at least stayed the same or increased compared to this data. It is possible that the price increase was due to an increase in price index over the years, but since the proportion involves dollars in the numerator (Specialty Drug) and denominator (THC) that increase due to yearly inflation is not possible. Similarly, Gleason et al (2013) reported the proportion of specialty drug to total health spending ranging from 50% (Inflammatory Bowel Disease) to 67% (Multiple Sclerosis)

Wiley et al (2008) studied the OOP burden for severely ill patients who had chronic diseases versus patients using specialty medications between July 2000 to August 2004. Compared to our study that found that OOP ranged from $103 to $180 monthly, Wiley and colleagues saw annual costs averaged $579 (chronically ill) for its to $778 (severely ill). The severely ill patients were frequently on biologics $64 per month. Additionally, patients did have

an average $196 cost for the top 2.5% health spenders. Our study shows a much higher member-share costs for its biologics, although this study is expressed in 2005 dollars and our numbers are in 2014 dollars. Additionally, a similarity in the comparison of our study is that the biologic medication costs consisted of 10-31% of the total health costs. The current study did observe that the average specialty medication costs more than doubled the costs of the total healthcare costs for all cohorts except the EA cohort. Interestingly, the HIV cohort observed an average out of pocket costs for total healthcare at a staggering monthly $874. However, it must be noted that only 10% of the HIV patients reported total healthcare claims. This fact can show that HIV patients lead healthier lives but when they are hospitalized or seek services, they experience high OOP expenses.

The HIV cohort showed patients 95,000 patients with insurance. But it must be noted in The Ryan White Foundation data report of 2014 serving over half a million patients state that over quarter of their patients have no health care coverage. It did show that of the half a million-patient data report over 304,000 patients belonged to the 0-100% federal poverty line.

Limitations:

The HIV cohort was restrictive as the majority of HIV patients between the ages of 18-35 may not have insurance (Ryan White non-ADAP report, 2014). Hence this age group can potentially be misrepresented compared to the national estimates. Also, the data shows seasonality with respect to OOP costs as patients pay higher costs at the start of the year relative to the end of the year (for patients who have healthcost through the year through health insurance plans). Drug coupons or manufacturer coupons used widely in the market could not be measures. These discounts can alter the behavior as they artificially bump the affordable OOP. Additionally, in our study we did not control for any demographic or burden of disease factors.

Conclusions:

PIDD and HIV patients showed a significant THC increase possibly due to a worsening of their disease after missing a medication dose. Historically, CF patients are 61% compliant, with decreased compliance through the year, possibly explaining the inconsistent non-significant effect. Research has shown better medication adherence to medications had a positive economic impact for chronic diseases and our study agrees with this result. As the THC increases, payers need to find strategies to keep specialty drug patients compliant to reduce the impact on other healthcare cost. Payers could take suggestions from previous literature, which is giving differential patient cost-share pricing for patient who need them the most. Payers may need to visit the health plan design for patients who pay high out of pocket at the start of year due to a reset in the deductible, and possibly look at a average static copayment regardless of month of the year with other necessary adjustments to adjust for actual costs for the year. This might alleviate the patient stress at the start of the year and help patients plan their expenses for the full year.

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Chapter 6: Overall Conclusions

Conclusion

This dissertation illustrates the cost-share for patients, payers as well as the average wholesale price for specialty drugs in various markets treating the following diseases: cystic fibrosis (CF), alpha-1 antitrypsin deficiency (ALPHA), eosinophilic asthma (EA), primary humoral immunodeficiency (PIDD) and human immunodeficiency virus (HIV) in the first study. It also looked at the price elasticity of demand for these patients in the second study and studied the downstream effects on total healthcare cost after missing a specialty drug dose in the third study. There was a decrease in discounts (AWP - Payer cost share) in disease states with more available treatments Additionally, HIV that was not truly competitive due to the drugs representing different classes showed an estimated patient assistance of $150. Patients were more price inelastic to specialty drugs compared to the less expensive prescription drugs. After missing a specialty drug dose, patients treated for PIDD and HIV, experienced a significant increase in total healthcare due to possible worsening of symptoms or even development of drug resistance with respect to HIV.

Implications for Policy and Practice

This study is very relevant to issues faced by insurers, patients and drug manufacturers. In 2014, CVS Caremark predicted that specialty drugs spending is expected to quadruple by 2020, which is about $402 billion. Specialty drug spending comprised 44.7% of the total prescription drug costs in 2018 as compared to 40.8% in 2017 (Express Scripts Drug Report 2018). The volume of specialty drugs is increasing as well as the patient cost-share and payer cost-share. Poor drug adherence is related to poor health outcomes, and medication adherence is negatively impacted by increased patient cost sharing (Iuga & McGuire, 2014; Eaddy et al, 2012).

In fact, Eaddy et al (2012) demonstrated that decreased medication adherence adversely affected health outcomes. To date, we did not find any study that informed payers regarding the effect of missing a medication dose on total healthcare cost. This study demonstrates that some disease states (e.g. PIDD and HIV) might need more attention in keeping patients adherent to medications to avoid future downstream higher healthcare costs. In my third study, PIDD patients were shown to have significantly higher total healthcare costs ($500 or more) when missing their dose due to worsening of their diseases. Further, HIV patients had significantly higher total healthcare costs possibly due to drug resistance, reduced immunity and treatment failure (Parienti et al, 2010). Doctors can address any financial issues faced by patients and relay them to payers. Payers can use this information for addressing health plan designs and modifying them to work for patients.

Further, we did not find any reports on price elasticity of demand for the five diseases states selected in my study treated with specialty medications. The majority of studies to date have focused on diseases such as kidney diseases, multiple sclerosis and rheumatoid arthritis. (Goldman et al, 2006; Gatwood et al, 2014). Insurers and manufacturers know that patients will need to continue taking their medication as they are price inelastic to the increase in patient cost-sharing. In fact, these patients are more price inelastic as compared to patients on prescription medications. Therefore, the price elasticity estimates shown in my second study, which were (3.13%) to (0.07%), states that regulation is required to make sure that patient cost-sharing is checked by policy makers, and ensuring payers are not pressuring patients into higher cost-sharing. If drug prices continue increasing, it would increase patient cost-sharing, leading to non-adherence and higher cost to the system in total healthcare cost.

Another policy perspective which is related to the pricing in my first study is the multiple payers present in the United States marketplace that are responsible to buy drugs. Conversely, the UK's National Health Service has a single buyer (monopsony) system for each of the four regions, where the price of the drug must be justified by the incremental therapeutic value, which

is measures in Quality Adjusted Life years (QALY). Unfortunately, with a multiple payer system in the US, it is difficult to assess the value of new drugs. Therefore, the need for common data which can be shared among insurance companies to judge the effectiveness will be important. In fact, the New York state medicaid program has started to use this concept to drive price negotiations with drug manufacturers (Bergethon & Wasfy, 2019). On the other hand, drug manufacturers are using this tool to prove therapeutic value with payers by negotiating prices improving access to patients and recouping any loss by slight lower prices, but higher patient volume (Bergethon & Wasfy, 2019).

The first study investigated patient assistance, which is present in the form rebates and discounts. Manufacturer Coupons are commonly used to cover patient cost sharing. In fact, in 2013 an estimated $21.2 million of $35.3 million out of pocket expenses was subsidized by coupons (Starner et al, 2014). However, the problem with coupons was that patients ended up using the more expensive drugs and this can lead to higher expenditures. To curb these coupons from adding more pressure on payers, kick-back statute was used to stop manufacturers from rolling out coupons in federal programs (e.g. Medicare Part D) (Kirchoff, 2015). Therefore, coupons can be a solution as well as a problem on the long-term. This is because as patients buy these expensive drugs with coupons it will only increase the premiums the next year, which could have a snowball effect over time.

One suggestion which could help with patient cost burden is to have equal payments set for each month for patients who need their specialty drug dose (e.g. PIDD) every month. With this model, patients will be able to plan their expenses and not be burdened with an enormous payment at the start of the calendar year. Another option is to allow the Secretary of Health and Human Services to negotiate prices because if they are treating a lot of patients over aged 65 using specialty drugs then the private payers will be using those negotiated amounts and pay a lower price, effectively bringing patient's premiums and cost-share lower. This is because by law,

Medicare is not allowed to negotiate reimbursement pricing for drugs covered under Medicare Part B (physician office based) and Part D (Pharmaceitical based). The law states that under Section 1861 of the Social Security Act, Medicare is mandated to cover reasonable and necessary cost, before insurance coverage can consider any cost or cost-effectiveness of pharmaceutical drugs.

Manufacturer sets prices high due to losses from State and federal Medicaid programs mandate manufacturers to give at least a 23.1% discount after accounting for yearly consumer price inflation for innovator drugs (Lee et al, 2016). These discounts are given to eligible institutions (e.g. Non-profit hospital) in the 340-B programs. The problem with this program is that manufacturers will need to keep the prices high for the rest of the buyers of drugs to reduce any losses from this 340-B program and Medicaid. Actual pricing is also set by Payer-manufacturer negotiations occur to obtain effective pricing. For example, manufacturer can offer payers discounts if they place their drug under a lower cost-share compared to other drugs. Based on volume, payers with a larger pool of patients receive better pricing compared to payers with a smaller patient pool because negotiating power is lower, which gives the manufacturer an advantage (Lee et al, 2016). These negotiations of pricing for drug placement on cost-share spectrum is not publicly available and are not regulated (Ridley, 2015). Therefore, if these payer-manufacturer negotiations were regulated, payers with smaller patient pools would benefit. Hence, these negotiations relate to our study, as such regulation would provide a fair and less variable pricing reimbursements between all payers, as opposed to the data in my study which arrives from large as well as small payers with variable reimbursement. Though, it must be noted payers have attempted to address the higher prices with effectiveness concerns too. CVS Health recently announced that after price negotiations, if newer drugs do not meet their standard of effectiveness then these drugs will not be covered (Bergethon & Wasfy, 2019).

Future Research

This study encourages one to study other aspects further studies on pricing, adherence and price elasticity of demand for patients using specialty drugs for other diseases. There has been adherence studies with respect to prescription medication and few studies with specialty medications (Goldman et al, 2006; Gatwood et al, 2014). Additionally, as previous study by Gleason et al (2009) has investigated the prescription abandonment by different levels of cost sharing, similarly, we could investigate our third study based on different thresholds of cost-sharing and assess its effects on total healthcare costs.

This study had the limitation of only looking at a claims database, and researchers can invesigate claims as well as Electronic Health Record to quantify the disease burden (e.g. Charlson comorbidity index and Elixhauser comorbidity index) and better understand patient adherence habits while adjust for price elasticity for these drugs. Patient assistance in the form of coupons can be also studied with relation to adherence of drugs. For example, our findings of higher patient assistance for patients under monopolistic markets of cystic fibrosis makes us wonder whether the 61% patient adherence would lead to manufacturers rolling more patient assistance to keep patients to adhere to medication, thereby increasing sale volume (Siracusa et al, 2015).

Limitations

This study had the limitation of having only claims data and no access to electronic health record to quantify the Charlson comorbidity index (CCI) for these patients. Therefore, if both claims as well as electronic health records were used together, the burden of disease can quantify a better estimate with respect to price elasticity of demand. The CCI would also be useful with studying adherence and its total healthcare cost implication. One can imagine a study

looking at the severity of CCI and the total healthcare cost and health implications of missing a specialty drug dose for each CCI level.

Secondly, another limitation related to drug coupons and the amount it contributed to patient out-of-pocket expenses. Patients may use assistance which would contribute to the patient cost-share that is recorded in the claims database, but in reality, the patient may have been assisted by a 3rd party. This may influence our results, as the price elasticity of demand for patients may show an underestimated estimate because if patients were subjected to the total out of pocket without assistance, a larger utilization decrease might be plausible. Patient assistance in the form of Foundation support is characterized by direct support for customers with respect to access to care and promotion of individualized care. For example, the Healthwell Foundation provides annual assistance to CF patients with a yearly maximum of $15,000 for prescription drug copayments, deductibles, and health insurance premiums, provided that they fall under 500% of the federal poverty line (Healthwell Foundation, April 2017). Patients enrolled in clinical trials, for example PIDD patients, can acquire support inquire with the Immunodeficiency Foundation, which can route them to a drug clinical trial; hence, treatment utilization will not account for these patients.

A third limitation is the health expenditures and utilization might be incomplete. This is since the claims database has data for patients who filed a claim and used the drug. Patients may even obtain drugs through coupons from manufacturers without filing a claim (Grosse et al, 2018). Additionally, rebates passed from manufacturers to health plans and pharmacies as incentive for selling the drug may show as an overestimated payment recorded at pharmacies (Grosse et al, 2018)

A fourth limitation is the Marketscan commercial claims database is a convenience sample of privately insured patients. Therefore, we are missing individuals who are only covered by Medicare, Medicaid and patients paying solely out-of-pocket. With respect to the CF

population it was reported at 56% have private insurance therefore we do not study the entire CF population (Grosse et al, 2018). Additionally, HIV patients between 0-18 may have been underrepresented as they have shown to have no insurance and therefore that part of the HIV population is misrepresented too. (Ryan White Programs Services Report, 2014)

A fifth limitation is the pricing for the drugs used in this study. The first study used the average wholesale price (AWP), which is historically used as the primary benchmark for which pharmacies are reimbursed for drugs (Bin Sawad et al, 2016). In reality the pharmacies are reimbursed the AWP minus a percentage discount (Bin Sawad et al, 2016). Therefore, the patient assistance (difference between the price and payer cost-share) used in our first study would represent at most the higher end, or an underestimate of the patient assistance in the form of discount and rebates. Since, the Marketscan claims database contains solely the AWP as the pricing benchmark we were limited. Pricing benchmarks for example Wholesale Acquisition Cost would be a better alternative as they are closer to the pricing pharmacies purchase drugs from wholesale agents.

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