The Thesis Committee for David Jeremy Sohl
Certifies that this is the approved version of the following thesis:

Determination of Precipitated Primary Non-Adherence after Step Therapy Intervention in 4 Classes of Therapy

APPROVED BY
SUPERVISING COMMITTEE:

Supervisor:

Kenneth A. Lawson

James P. Wilson

Joshua W. Devine

Determination of Precipitated Primary Non-Adherence after Step Therapy Intervention in 4 Classes of Therapy

by

David Jeremy Sohl, PharmD

Thesis

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Master of Science in Pharmacy

The University of Texas at Austin

August 2013

Dedication

I am truly grateful to my wife Janel, who has always pushed me to achieve something more. Without her continuing support and wisdom I feel I would not succeed in many of my endeavors.

Acknowledgements

This work would not have been possible without logistical, administrative and moral support from my colleagues at the Department of Defense. Particular thanks to Dr. Josh Devine, Dr. Shana Trice and Dr. Joseph Lawrence, for the huge part they played in completing this research.

Thank you also to the reviewing committee for your time and patience in my education. Dr. Lawson deserves extra appreciation, for his efforts conducting multiple reviews of this manuscript. Additionally, his patience in accommodating my resistance to using commas will always be remembered.

Abstract

Determination of Precipitated Primary Non-Adherence after Step Therapy Intervention in 4 Classes of Therapy

David Jeremy Sohl, M.S.Phr

The University of Texas at Austin, 2013

Supervisor: Kenneth A. Lawson

In light of drastically escalating costs for today's medications, pharmacy benefit managers are seeking a constant balance of effectiveness and cost control. Step Therapy helps to address these concerns with a try medication "A" before medication "B" logic. Like all medical interventions, the possibility of unintended consequences exists. The purpose of this study was to determine if non-adherence results from application of Step Therapy for selected medication classes (antihyperlipidemics (specifically the HMG Co-A reductase inhibitors), angiotensin receptor blockers, uro-selective alpha-blockers, and dipeptidyl peptidase-4 inhibitors) in the Department of Defense.

Using a retrospective database analysis, this study examined the primary adherence rate of subjects after they have been denied coverage due to Step Therapy intervention. Additionally, this study examined the association of demographic and service-related factors with the likelihood that a patient will be non-adherent after encountering the intervention. Finally, the study measured the time to adherence after intervention for those who were persistent after a Step Therapy claim rejection. STATA

version 10.0 was used to conduct logistic regression analyses to meet the study objectives.

After examination of 279,508 claims for 27,202 subjects, the estimated primary non-adherence rate following the Step Therapy intervention for all medication classes combined was 15.1%. Additionally, there was inter-class variability in this rate ranging between 13.1% and 19.5%. A statistical and practical difference was also noted in non-adherence rates between subjects who received care at the retail point of service versus those who received care at the mail order point of service. Subjects who received care through retail were nearly twice as likely to be non-adherent as those who received care in the mail order segment. For those subjects who were persistent with therapy, the median time-to-fill was estimated at 7 days.

The occurrence of non-adherence following a Step Therapy intervention was clearly demonstrated through this study. Although this study provides good framework for designing interventions after claim rejection, further research would help to determine the health impact of primary non-adherence as well as the economic consequences of the intervention.

Table of Contents

List of Tables

List of Figures

Chapter One: Introduction

With increasing drug benefit costs, insurers have continued to introduce new methods to ensure appropriate care for patients while at the same time providing the best value for their policy holders. These methods include restrictions on medication availability sometimes accompanied by educational interventions. The cost-saving interventions focused on limiting access to medications include use of formularies, tiered formularies, Prior Authorization (PA), and Step Therapy.

While outside the scope of this review, it is worth noting even the most basic intervention, restrictive formularies, are themselves not without contention.[1] The tiered formulary concept is an advancement on the basic formulary concept and is employed by some pharmacy benefit managers (PBMs) as an enforcement tool for implementation of other interventions. Additional, advanced interventions including quantity limits, therapeutic interchange, drug utilization review, drug rebates and medication therapy management (MTM) are sometimes employed as cost-saving or quality improvement measures. These items, however, are more health care provider-focused, involving less direct patient effort than the items described in this review.

Previous review articles published on PA and Step Therapy interventions have primarily focused on assessing cost-savings and identifying areas of future research.[2-9] Only a few of these articles include data on unintentional outcomes. Unintentional outcomes in this setting may include adverse clinical outcomes, or in the case of this study, precipitated non-adherence. Even in the few studies which have reported unintentional outcomes, they are presented as additional information rather than the primary focus of the review.

The Pharmacy Benefit Management Institute estimated the use of PA at 86% of plans and Step Therapy at 85% of plans in their 2012-2013 report.[10] These interventions are approaching the use of tiered formularies in terms of utilization and clearly have a large impact on beneficiaries throughout the United States. Therefore, the purpose of this review is to identify articles related to PA and Step Therapy with the intention of

examining reported unintended consequences of these interventions. While not a comprehensive review on the topic, this review is intended to describe areas for future research and provide support for the importance of post-implementation review of Prior Authorization and Step Therapy.

LITERATURE REVIEW

A review of the literature was conducted by the author using multiple databases and references. Initial identification of articles was made using the Academy of Managed Care Pharmacy (AMCP) Annotated Bibliography of Managed Care Pharmacy Interventions.[11] This was supplemented with PubMed, Medline and Google Scholar searches using the terms formulary, Prior Authorization and Step Therapy. Finally, contributing articles were identified by experts in managed care and an ancestral review of primary references. For the purpose of this review, articles regarding inpatient PA and Step Therapy are excluded.

To begin exploring PA and Step Therapy as interventions, we must first look at what differentiates the two. AMCP's somewhat complex definition for PA highlights its importance as a cost-saving tool in which approval is required for coverage of certain drugs under a benefit plan. For patients to receive these medications, exceptions to the plan limitations are needed. These exceptions are allowed under criteria developed by health care professionals associated with the plan. Closely tied to PA is the intervention known as Step Therapy. Categorically, this intervention is defined by AMCP as "The practice of beginning drug therapy for a medical condition with the most cost-effective and safest drug, and stepping up through a sequence of alternative drug therapies as preceding treatment options fail."[12] In its simplest form, Step Therapy requires that a first-line drug must be used before a second-line drug will be covered by the plan. This process is often automated through the PBM's online adjudication process.

Since the primary intent of these interventions is to control cost, one would reasonably expect that evaluations of both interventions would rely heavily on cost

assessment. In fact, Phillips and Larson suggested that methodology in 1997 as the primary method for measuring performance of Prior Authorization.[13]

Prior Authorization

In 1993, the first article to evaluate PA impact (Kotzan et al.) found Georgia's Non-Steroidal Anti-Inflammatory Drug (NSAID) intervention to be effective at reducing utilization of branded COX-2 inhibitor NSAIDs and reducing overall NSAID cost.[14] Their evaluation detected an increase in the use of non-branded NSAIDs, which was to be expected, but the increase did not directly correspond to the reduction in branded NSAIDs. When comparing the difference of these measurements, the unintended consequence of the PA program was a net decrease in NSAID prescriptions of 21% over the study period. This decrease was accompanied by an increase in other analgesic costs due to increased utilization (including opioid analgesics) although the authors did not explain if this change in utilization corresponded to the decrease in NSAID utilization. Finally, the authors expected an unintended increase in utilization of nondrug services; however, the observed increase was not significant.

In 1995, Smalley et al. supported these results with another NSAID PA study. [15] Their results, in a Medicaid population similar to Kotzan's, showed a significant 53% decrease in NSAID class expenditures. Likewise, they observed an overall 19% decrease in NSAID use with no increase in expenditures for other medical care. Numerous other studies have since validated these results for cost savings and discontinuation rates.[16-21]

In September of 2002, McCombs et al. published a strikingly different study on effects of PA when they reviewed the revocation of PA restrictions on antidepressants.[22] Their primary measurements indicated an immediate increase in SSRI utilization after the removal of PA criteria. Using regression they further estimated adherence with prescribed therapy, which they defined as 180 days of uninterrupted therapy. Surprisingly, McCombs et al. found a significant **decrease** in adherence following the removal of the PA criteria. Observing this unexpected result, they hypothesized that providers were less selective in their prescribing of antidepressants after the removal of

PA criteria and therefore, corresponding adherence rates were lower implying that PA criteria improve adherence.

Some efforts have been made to specifically address the effects of PA policies on outcomes other than cost. In 2002, Momani et al. published a quasi-experimental study on the effect of NSAID PA on Quality of Life (QoL).[23] Through a survey of 181 individuals using the Arthritis Impact Measurement Scale (AIMS), they were able to estimate QoL over a 2-month period following PA intervention. Their comparison groups were comprised of those who were mandated generic treatment by the intervention and those who received the brand-name product. Momani et al. demonstrated no significant effect on QoL after implementation of the PA program. Since the groups were comprised of subjects identified through receipt of medication, no weight or acknowledgement was given to the effect of the intervention on the patients' ability to receive medication. Therefore, this result may be better ascribed to a test of brand versus generic than the results of the intervention since their groups did not include members who received no medication due to the intervention.

Brown et al. have published information regarding physician burden based on focus groups and testing of a Burden of Prior Authorization of Psychotherapeutics (BoPAP) scale that the researchers developed.[24,25] Their information indicates an administrative and perceived patient care burden associated with the use of PA criteria. The literature on patient outcomes, however, is sparse compared to that of cost evaluation, and this has been identified in many reviews as a major gap in the current literature. [16-21]

Step Therapy

There is, unfortunately, less evaluative literature on Step Therapy than that for Prior Authorization. This is likely due, at least in part, to the recent addition of Step Therapy as a PBM intervention. It is important to recall that the intent of Step Therapy is not only to restrict the use of more expensive items, but also to guide therapy to safer and

equally or more effective products. Therefore, one would expect the research on this topic to include not only information on cost savings, but on patient outcomes as well.

Arguably, some of the best work in the area has been done by Motheral, Henderson and Cox on behalf of Express Scripts Inc.[26,27] Their original work in the area was published in two back-to-back articles in 2004. Both of their studies included claims data accompanied by specific survey data for those who were affected by a Step Therapy intervention. Their first study did not attempt to detect associations with drug cost control due to Step Therapy. Interestingly, they did make other assessments of the intervention with regard to member experience. They determined that 11% of patients who encountered the intervention received no medication and an additional 11% paid out-of-pocket for the medication. Cox et al. followed this with a separate survey of those who were believed to have received no medication after a Step Therapy intervention. Results of this survey indicate that 12% of those believed to have received no medication actually received no medication.[26] The remaining 88% indicated they had in fact received some form of medication through cash payment, use of an alternative agent or through an over-the-counter agent.

In their second study, Motheral et al. found an even higher primary non-adherence rate, which they defined as patients who received no medication after a Step Therapy intervention.[27] They indicated that 17% received no medication after a Step Therapy intervention and 16% paid full price out-of-pocket. In this study, economic analysis showed savings for the plan sponsor of approximately $0.83 per member per month (PMPM). This savings was determined across three classes (NSAID, Selective Serotonin Receptor Inhibitor [SSRI] and Proton Pump Inhibitor [PPI]) of which one (SSRI) showed no significant savings. Additionally, the savings included a $0.10 (PMPM) administrative fee for the intervention. Of important note, Motheral et al. did identify the need to include nondrug medical cost in future Step Therapy research.

In 2005, Panzer et al. modeled the research proposed by Motheral and concluded that there would be increased medical cost associated with SSRI Generic Step Therapy,[28] but it was Mark et al. in 2009 who ultimately studied the effect.[29] They too found a drug

cost savings of about 3.1%, but the unintended consequence was a 7.9% reduction in days of antihypertensive medication supplied and a primary non-adherence rate of 6.6%. Additionally, Mark et al. found an increased spending of $99 per user per quarter when incorporating all health expenditures.

A review of Step Therapy research would not be complete without mentioning the study by Yokoyama et al. in 2007.[30] Their review of Angiotensin Receptor Blocker (ARB) Step Therapy supported previous assertions of cost savings due to Step Therapy. Their observed savings of $0.03 PMPM in the 1-year review, however, was less than previously reported results. This well executed study by Yokoyama et al. also documented a 7% primary non-adherence rate. Finally, and quite interestingly, they showed that 45% of patients initially denied an ARB due to Step Therapy ultimately received an ARB within 12 months of the intervention.

Limitations of the Review

Review of the literature on pharmacy interventions is a somewhat challenging task because of the large amount of literature on the topic of managed care pharmacy interventions. Particularly, the literature on use of a formulary or use of a tiered formulary contains a large number of studies. Additionally, various outcome measurements and assessment methods are used to evaluate the interventions. Compounding the issue, many interventions overlap. For example, the use of PA can be enforced with use of a third formulary tier. In this scenario, non-preferred drug agents are placed in a higher copayment tier until the prior authorization criteria are met. After the PA criteria are met the item is moved down to a lower copayment tier. In examination of published articles, it is sometimes difficult to ascertain the effect that placing a drug in the third tier has versus complete lack of coverage.

Unfortunately, although there is a great deal of literature on some managed care pharmacy interventions the literature on PA and Step Therapy is sparse. The literature on PA and Step Therapy interventions may be lacking in outcomes research due to the complexity of the information required. Since these studies include outcomes, the

availability of claims and medical data is a likely limitation for many researchers. Additionally, cause:effect analyses of these interventions require longitudinal data for comparison. With multiple outcomes and multiple interventions taking place, it will likely be difficult to fully comprehend the full impact of any one formulary decision. All of these factors contribute to the lack of outcomes research on Prior Authorization and Step Therapy interventions.

PHARMACY IN THE DEPARTMENT OF DEFENSE

In Fiscal Year (FY) 2005, the Department of Defense (DoD) implemented Congressional legislation mandating a formulary control program aimed at reducing pharmacy spending.[31] At that time, spending for the pharmacy benefit was approximately $5.4B with an average cost for each beneficiary of $587. [32] Since then the DoD has made aggressive moves to decrease per beneficiary spending. Through actions of the DoD Pharmacy and Therapeutics Committee (P&T), spending in FY11 was limited to $6.7B and $695 per beneficiary after retail rebates. When distributed across years evenly, this represents an annual increase of 4% for medication costs, which is comparable to the national average for drug cost inflation.[33] Their stringent formulary controls have been well outlined by Trice et al.[34] They explain the rigorous clinical and financial evaluation of agents the DoD applies in their use of Tiered Formulary, Prior Authorization and Step Therapy.

This review examines the effects of Step Therapy intervention in four specific classes of medications which have been reviewed by the DoD.[35-38] The four classes to be reviewed are: Antihyperlipidemics (specifically the HMG Co-A Reductase Inhibitors), Angiotensin Receptor Blockers (ARBs), uro-selective alpha-blockers, and Dipeptidyl Peptidase-4 Inhibitors (DPP-4s). These classes were selected because the criteria for Step Therapy have remained stable over time and there is sufficient longitudinal data for the review. Additionally, they have been selected due to the lack of over-the-counter (OTC) products available to treat the disease states. Presence of OTC products, such as with the PPI class, can make examination of non-adherence based on claims difficult to validate.

An overview of the Step Therapy classes is presented in Table 1.1. Step two agents will receive a rejection if a claim has not been processed for any of the first step agents. Claims will be paid if the patient has a previous paid prescription for the second step agent; therefore, this intervention is targeted at patients who are naïve to the therapy. The LIP-1 class expands on these criteria by also including a potency-based step approach. This criterion, however, has been excluded in this research because our primary measured outcome is discontinuation rates.

Class	Step Two Agents	First Step Agents	Implementation Date
Antihyperlidipemics (LIP-1)	fluvastatin lovastatin pitavastatin niacin/lovastatin amlodipine/atorvastatin niacin/simvastatin ezetimibe/simvastatin rosuvastatin	lovastatin pravastatin simvastatin atorvastatin	27-Sep-10
Uroselective Alpha Blockers	silodosin	alfuzosin tamsulosin	4-Aug-10
Dipeptidyl Peptidase-4 Inhibitors (DPP-4)	saxagliptin sitagliptin linagliptin	metformin chlorpropramide glimeprimide glipizide glyburide tolzamide tolbutamide pioglitazone/metformin rosiglitazone/metformin rosiglitazone/glimeprimide repaglinide/metformin pioglitazone/glimeprimde	13-Apr-11
Angiotensin Receptor Blockers (ARBs)	aliskiren (alone or in combo) candesartan (alone or in combo) eprosartan (alone or in combo) irbesartan (alone or in combo) olmesartan (alone or in combo) azilisartan (alone or in combo)	losartan (alone or in combo) telmisartan (alone or in combo) valsartan (alone or in combo)	12-Jan-11

Table 1.1: Medications classes subject to Step Therapy in the DoD

The DoD's implementation of Step Therapy includes real-time pharmacy adjudication of Step Therapy adherence and offers messaging to pharmacies on appropriate step guidelines. These guidelines have been established separately for each of the examined classes.[39-44] To date, no DoD data has been published on the effectiveness of Step Therapy from a clinical or financial standpoint. One study, by

Linton et al., examined utilization after implementation of PPI Prior Authorization. [21] While under the PA umbrella, these criteria functioned much like Step Therapy in that they required use of preferred PPIs before the non-preferred agent was covered. Non-preferred agents in Linton et al.'s study were not excluded from payment, as is the case with DoD Step Therapy, but rather fell into a third copayment tier. Their study reported that while PPI utilization rates increased, the use of the non-preferred agent decreased substantially following implementation of the intervention.

RATIONALE FOR THE STUDY

Over the past 20 years, the pharmacy benefit for many insurance companies has taken on increasing levels of complexity to control costs. With some contention,[45,46] there is strong evidence to suggest overall cost savings with Prior Authorization interventions. According to the PA literature, these savings appear to be attributed to decreased utilization of non-preferred agents and little to no increase in nondrug costs. Step Therapy research provides less clear cut conclusions but indicates a similar trend towards drug cost savings.

While the Step Therapy literature is yet to deliver solid evidence on intervention cost savings, researchers have begun to demonstrate stronger rigor in their assessment of PBM interventions. Particularly, researchers have highlighted an increasingly obvious subset of patients who do not receive therapy after encountering Step Therapy intervention. While those patients have been termed primary non-adherent, it is a somewhat inadequate term. Because those patients have been, in a sense, denied claim coverage, they are separate from those typically defined as non-adherent (i.e., those who choose to not receive medication). At the very least, the non-adherence of this population has been precipitated by the intervention of Step Therapy, hence the term Precipitated Primary Non-Adherence is applied in the current study. It is possible that this undefined group actually represents an overprescribed segment of the population not requiring medication as suggested by McCombs[22], but further research is needed in this area to support that conclusion. Regardless, it is clear that upwards of 8% of Step Therapy

patients do not receive prescribed treatment due to the Step Therapy intervention and the clinical impact of this is yet to be determined. Unfortunately, the literature is weak in the assessment of non-cost outcomes for patients. With cost savings thoroughly evaluated, the calls for more patient outcome-based investigation[16-21] must be answered.

Finally, it should be noted that a majority of the research in this area has been conducted in the NSAID, PPI and SSRI classes. In an effort to further control costs, however, Step Therapy and PA are now being applied to a variety of classes.[35-38] With Motheral finding varying results based on class[27], it is difficult to estimate effectiveness of the intervention. In 1996, Horn also suggested that outcomes will differ based on disease treatment class.[47] Finally, with documented PA approval rates above 95%[48], it is plausible to believe this intervention has a limited impact overall.

The intended metric would provide a method for timely identification of patients with precipitated primary non-adherence (PPNA). This would allow PBMs or pharmacies to make targeted interventions to ensure that the intended therapy is delivered. Additionally, PPNA rates across medication classes evaluated in this study will provide better insight for unintended consequences of Step Therapy interventions and provide information for the future evaluation of other medication classes.

PURPOSE AND OBJECTIVES

The purpose of this study is to evaluate PPNA for four medication classes in the DoD population. For these analyses, PPNA is defined as patients who did not receive a paid claim within the therapeutic class in the 180 days following rejection of a claim due to failure to meet Step Therapy criteria. Adherent patients will be those who receive a paid claim for a medication in a corresponding therapeutic class following rejection due to failure to meet Step Therapy criteria.

Objectives and Hypotheses

1. Compare the likelihood of PPNA by medication class.

    $H_0$1: The likelihood of PPNA for the specified **medication classes** does not differ significantly from the likelihood of PPNA for patients receiving a LIP-1 agent.

2. Compare the likelihood of PPNA by Age Category, Sex, Beneficiary Category, Branch of Service, and Service Category.

    $H_0$2: The likelihood of PPNA for the specified **age categories** does not differ significantly from the likelihood of PPNA for patients in the 18-44 age group in the **LIP-1** sample.

    $H_0$3: The likelihood of PPNA for the specified **age categories** does not differ significantly from the likelihood of PPNA for patients in the 18-44 age group in the **Alpha Blocker** sample.

    $H_0$4: The likelihood of PPNA for the specified **age categories** does not differ significantly from the likelihood of PPNA for patients in the 18-44 age group in the **DPP-4** sample.

    $H_0$5: The likelihood of PPNA for the specified **age categories** does not differ significantly from the likelihood of PPNA for patients in the 18-44 age group in the **ARB** sample.

    $H_0$6: The likelihood of PPNA for the specified **age categories** does not differ significantly from the likelihood of PPNA for patients in the 18-44 age group in the **combined** sample.

    $H_0$7: There is no difference in likelihood of PPNA associated with **gender** in the **LIP-1** sample.

    $H_0$8: There is no difference in likelihood of PPNA associated with **gender** in the **Alpha Blocker** sample.

    $H_0$9: There is no difference in likelihood of PPNA associated with **gender** in the **DPP-4** sample.

$H_0$10: There is no difference in likelihood of PPNA associated with **gender** in the **ARB** sample.

$H_0$11: There is no difference in likelihood of PPNA associated with **gender** in the **combined** sample.

$H_0$12: The likelihood of PPNA for the specified **beneficiary categories** does not differ significantly from the likelihood of PPNA for patients in the Active Duty Family member (ADF) group in the **LIP-1** sample.

$H_0$13: The likelihood of PPNA for the specified **beneficiary categories** does not differ significantly from the likelihood of PPNA for patients in the Active Duty Family member (ADF) group in the **Alpha Blocker** sample.

$H_0$14: The likelihood of PPNA for the specified **beneficiary categories** does not differ significantly from the likelihood of PPNA for patients in the Active Duty Family member (ADF) group in the **DPP-4** sample.

$H_0$15: The likelihood of PPNA for the specified **beneficiary categories** does not differ significantly from the likelihood of PPNA for patients in the Active Duty Family member (ADF) group in the **ARB** sample.

$H_0$16: The likelihood of PPNA for the specified **beneficiary categories** does not differ significantly from the likelihood of PPNA for patients in the Active Duty Family member (ADF) group in the **combined** sample.

$H_0$17: The likelihood of PPNA for the specified **branches of service** does not differ significantly from the likelihood of PPNA for patients in the Army in the **LIP-1** sample.

$H_0$18: The likelihood of PPNA for the specified **branches of service** does not differ significantly from the likelihood of PPNA for patients in the Army in the **Alpha Blocker** sample.

$H_0$19: The likelihood of PPNA for the specified **branches of service** does not differ significantly from the likelihood of PPNA for patients in the Army in the **DPP-4** sample.

$H_0$20: The likelihood of PPNA for the specified **branches of service** does not differ significantly from the likelihood of PPNA for patients in the Army in the **ARB** sample.

$H_0$21: The likelihood of PPNA for the specified **branches of service** does not differ significantly from the likelihood of PPNA for patients in the Army in the **combined** sample.

$H_0$22: There is no difference in likelihood of PPNA associated with **service category** in the **LIP-1** sample.

$H_0$23: There is no difference in likelihood of PPNA associated with **service category** in the **Alpha Blocker** sample.

$H_0$24: There is no difference in likelihood of PPNA associated with **service category** in the **DPP-4** sample.

$H_0$25: There is no difference in likelihood of PPNA associated with **service category** in the **ARB** sample.

$H_0$26: There is no difference in likelihood of PPNA associated with **service category** in the **combined** sample.

3. Within each drug class, determine the PPNA percentage for each of the drug agents.
4. For adherent patients, provide statistics describing the time between initial rejected claim and first subsequent paid claim. These statistics will include the mean, median, mode, standard deviation, 95^{th} and 99^{th} percentiles. Report for the combined sample as well as for each of the four classes of medication.

REFERENCES

1. Lexchin J. Effects of restrictive formularies in the ambulatory care setting. *Am J Manag Care.* Jan 2002;8(1):69-76.
2. MacKinnon NJ, Kumar R. Prior authorization programs: a critical review of the literature. *J Manag Care Pharm.* 2001;7(4):297.
3. Carroll NV. How effectively do managed care organizations influence prescribing and dispensing decisions? *Am J Manag Care.* Dec 2002;8(12):1041-1054.
4. Olson BM. Approaches to pharmacy benefit management and the impact of consumer cost sharing. *Clin Ther.* Jan 2003;25(1):250-272.
5. Pearson SA, Ross-Degnan D, Payson A, Soumerai SB. Changing medication use in managed care: a critical review of the available evidence. *Am J Manag Care.* Nov 2003;9(11):715-731.
6. Gibson TB, Ozminkowski RJ, Goetzel RZ. The effects of prescription drug cost sharing: a review of the evidence. *Am J Manag Care.* Nov 2005;11(11):730-740.
7. Lu CY, Ross-Degnan D, Soumerai SB, Pearson SA. Interventions designed to improve the quality and efficiency of medication use in managed care: a critical review of the literature - 2001-2007. *BMC Health Serv Res.* 2008;8:75.
8. McAdam-Marx C, Schaaf DT, Holtorf AP, Eng B, Oderda GM. Systematic analysis of outcomes evaluations applied to drug management programs. *Am J Manag Care.* Nov 2008;14(11 Suppl):SP36-45.
9. Shoemaker SJ, Pozniak A, Subramanian R, Mauch D. Effect of 6 managed care pharmacy tools: a review of the literature. *J Manag Care Pharm.* Jul 2010;16(6 Suppl):S3-20.
10. Prescription Drug Benefit Cost and Plan Design Online Report. *Prescription Drug Benefit Cost and Plan Design Online Report* 2012-2013; http://www.benefitdesignreport.com/ . Accessed 07/29/2013.
11. AMCP Annotated Bibliography of Managed Care Pharmacy Interventions. *AMCP Annotated Bibliography of Managed Care Pharmacy Interventions* 2010; http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=9276. Accessed 06/30/2011.
12. Managed Care Terms. 2011; http://www.amcp.org/ManagedCareTerms/. Accessed 11/11/2011, 2011.
13. Phillips CR, Larson L. Evaluating the operational performance and financial effects of a drug prior authorization program. *J Manag Care Pharm.* 1997;3:699-719.
14. Kotzan JA, McMillan JA, Jankel CA, Foster AL. Initial impact of a Medicaid prior authorization program for NSAID prescriptions. *J Res Pharm Econ.* 1993;5:25-41.
15. Smalley WE, Griffin MR, Fought RL, Sullivan L, Ray WA. Effect of a prior-authorization requirement on the use of nonsteroidal antiinflammatory drugs by Medicaid patients. *N Engl J Med.* Jun 15 1995;332(24):1612-1617.

16. Kotzan JA, Perri M, Martin BC. Assessment of Medicaid prior-approval policies on prescription expenditures: market-share analysis of Medicaid and cash prescriptions. *J Manag Care Pharm.* 1996;2:651-656.
17. Hartung DM, Touchette DR, Ketchum KL, Haxby DG, Goldberg BW. Effects of a prior-authorization policy for celecoxib on medical service and prescription drug use in a managed care Medicaid population. *Clin Ther.* Sep 2004;26(9):1518-1532.
18. Fischer MA, Schneeweiss S, Avorn J, Solomon DH. Medicaid prior-authorization programs and the use of cyclooxygenase-2 inhibitors. *N Engl J Med.* Nov 18 2004;351(21):2187-2194.
19. Stacy J, Shaw E, Arledge MD, Howell-Smith D. Pharmacoeconomic modeling of prior-authorization intervention for COX-2 specific inhibitors in a 3-tier copay plan. *J Manag Care Pharm.* Jul-Aug 2003;9(4):327-334.
20. Delate T, Mager DE, Sheth J, Motheral BR. Clinical and financial outcomes associated with a proton pump inhibitor prior-authorization program in a Medicaid population. *Am J Manag Care.* Jan 2005;11(1):29-36.
21. Linton A, Bacon T, Peterson M. Proton-pump inhibitor utilization associated with the change to nonpreferred formulary status for esomeprazole in the TRICARE formulary. *J Manag Care Pharm.* Jan-Feb 2009;15(1):42-54.
22. McCombs JS, Shi L, Stimmel GL, Croghan TW. A retrospective analysis of the revocation of prior authorization restrictions and the use of antidepressant medications for treating major depressive disorder. *Clin Ther.* Nov 2002;24(11):1939-1959; discussion 1938.
23. Momani AA, Madhavan SS, Nau DP. Impact of NSAIDs prior authorization policy on patients' QoL. *Ann Pharmacother.* 2002;36(11):1686.
24. Brown CM, Richards K, Rascati KL, et al. Effects of a psychotherapeutic drug prior authorization (PA) requirement on patients and providers: a providers' perspective. *Adm Policy Ment Health.* May 2008;35(3):181-188.
25. Brown CM, Nwokeji E, Rascati KL, Zachry W, Phillips GA. Development of the burden of prior authorization of psychotherapeutics (BoPAP) scale to assess the effects of prior authorization among Texas Medicaid providers. *Adm Policy Ment Health.* Jul 2009;36(4):278-287.
26. Cox ER, Henderson R, Motheral BR. Health plan member experience with point-of-service prescription step therapy. *J Manag Care Pharm.* Jul-Aug 2004;10(4):291-298.
27. Motheral BR, Henderson R, Cox ER. Plan-sponsor savings and member experience with point-of-service prescription step therapy. *Am J Manag Care.* Jul 2004;10(7 Pt 1):457-464.
28. Panzer PE, Regan TS, Chiao E, Sarnes MW. Implications of an SSRI generic step therapy pharmacy benefit design: an economic model in anxiety disorders. *Am J Manag Care.* Oct 2005;11(12 Suppl):S370-379.

29. Mark TL, Gibson TB, McGuigan KA. The effects of antihypertensive step-therapy protocols on pharmaceutical and medical utilization and expenditures. *Am J Manag Care.* Feb 2009;15(2):123-131.

30. Yokoyama K, Yang W, Preblick R, Frech-Tamas F. Effects of a step-therapy program for angiotensin receptor blockers on antihypertensive medication utilization patterns and cost of drug therapy. *J Manag Care Pharm.* Apr 2007;13(3):235-244.

31. Charter DoD Pharmacy and Therapeutics Committee. http://pec.ha.osd.mil/P&T/PDF/Charter%20DoD%20P&T%20Committee%20May%202009%20-%20signed.pdf. Accessed 01/23/2012, 2012.

32. McGinnis TR. TRICARE Management Activity Pharmacy Update. 2011; http://www.jfpsinfo.org/index.cfm?do=ev.viewEv&ev=3263. Accessed 11/3/2011, 2011.

33. Nease B, Miller S, Frazee S, et al. *2010 Express Scripts Drug Trend Report*2010.

34. Trice S, Devine J, Mistry H, Moore E, Linton A. Formulary management in the Department of Defense. *J Manag Care Pharm.* Mar 2009;15(2):133-146.

35. Minutes and Decision Paper on the DoD Pharmacy and Therapeutics Committee Meeting - 16-17 November 2010 - Signed: 4 February 2010. http://pec.ha.osd.mil/PT_min_charter.php?submenuheader=5. Accessed October 20, 2011.

36. Minutes and Decision Paper on the DoD Pharmacy and Therapeutics Committee Meeting - 12-13 May 2010 - Signed: 23 July 2010. http://pec.ha.osd.mil/PT_min_charter.php?submenuheader=5. Accessed October 20, 2011.

37. Minutes and Decision Paper on the DoD Pharmacy and Therapeutics Committee Meeting - 11-12 August 2010 - Signed: 8 November 2010. http://pec.ha.osd.mil/PT_min_charter.php?submenuheader=5. Accessed October 20, 2011.

38. Minutes and Decision Paper on the DoD Pharmacy and Therapeutics Committee Meeting - 11-12 May 2011 - Signed: 5 Aug 2011. http://pec.ha.osd.mil/PT_min_charter.php?submenuheader=5. Accessed October 21, 2011.

39. Step Therapy/Prior Authorization Criteria for HMG-CoA Reductase Inhibitors (Statins), Niacin, Ezetimibe and Combinations. http://pec.ha.osd.mil/files/limits/PAC_ANTILIPIDEMICSI20101006.pdf. Accessed October 20, 2011.

40. Step Therapy/Prior Authorization Criteria for Renin Angiotensin Antihypertensive Agents (RAAs). http://pec.ha.osd.mil/files/limits/PAC_RAAS_20111105.pdf. Accessed October 20, 2011.

41. Step Therapy/Prior Authorization Criteria for Alpha Blockers for Benign Prostatic Hypertrophy.

http://pec.ha.osd.mil/files/limits/PAC_BPH_ALPHABLOCKERS20111105.pdf. Accessed October 20, 2011.

42. Exenatide (Byetta) Prior Authorization Criteria for the TRICARE Pharmacy (TPHARM) Program. http://pec.ha.osd.mil/files/limits/PAC_BYETTA_20111105.pdf. Accessed October 20, 2011.

43. Prior Authorization Criteria for the Dipeptidyl Peptidase Inhibitors (DPP4s) – Januvia, Janumet, Onglyza, Kombiglyze XR, Tradjenta. http://pec.ha.osd.mil/files/limits/PAC_DPP4s_20110601.pdf. Accessed October 20, 2011.

44. Liraglutide (Victoza) Prior Authorization Criteria for the TRICARE Pharmacy (TPHARM) Program. http://pec.ha.osd.mil/files/limits/PAC_VICTOZA_20111105.pdf. Accessed October 20, 2011, 2011.

45. Feldman SR, Fleischer AB, Jr., Chen GJ. Is prior authorization of topical tretinoin for acne cost effective? *Am J Manag Care.* Apr 1999;5(4):457-463.

46. Bukstein DA, Cherayil GA, Gepner AD, Luskin AT, Kooistra JB, Olson RM. The economic burden associated with prior authorizations in an allergist office. *Allergy Asthma Proc.* Mar-Apr 2006;27(2):119-122.

47. Horn SD. Unintended consequences of drug formularies. *Am J Health Syst Pharm.* Sep 15 1996;53(18):2204-2206.

48. LaPensee KT. Analysis of a prescription drug prior authorization program in a Medicaid health maintenance organization. *J Manag Care Pharm.* Jan-Feb 2003;9(1):36-44.

Chapter Two: Methods

This chapter describes the data source, study population, variables of interest, data manipulation, and data analyses that were used to meet the study objectives.

DATA SOURCE

The data source for this research was the DoD Pharmacy Data Transaction Service (PDTS) warehouse. This warehouse was established in 2000 as a source for pharmacy claims in the DoD system. In addition to holding claim transaction data, items are fed from various databases. Some elements attach to the claim data, while others reside in separate attached databases and are called forth on each query. The feeding databases for this warehouse include the National Council for Prescription Drug Programs (NCPDP), Defense Enrollment Eligibility Report System (DEERS), and First Data Bank (FDB).[1] The NCPDP database contains pharmacy identifying information, including: type of pharmacy (retail, community, mail order, etc.), pharmacy location, and NCPDP ID number. The DEERS database contains Tricare eligibility data and patient-specific information, including the DEERS ID, date of birth, service status, and sex. First Data Bank contains information relating to the drug. Specifically of interest here are National Drug Code (NDC), Generic Code 4 digit (GC4), and Generic Code Number (GCN).

STUDY POPULATION

The target population for this study was comprised of patients, 18 and older, with prescription claims information stored in the Department of Defense (DoD) Pharmacy Data Transaction Service (PDTS) warehouse who encountered a Step Therapy intervention (rejection) while seeking payment for prescription medications in the previously defined classes. This study included data for patients of all ages including Active Duty (AD) Service Members, Family Member Dependents, Retirees and Retiree Dependents who received their medication from a retail pharmacy or from home delivery (mail order) service. It did not include patients who received their prescriptions from a

Military Treatment Facility (MTF) because the MTF does not receive online adjudication of claims from PDTS. Patients who used Other Health Insurance (OHI) as their primary payer were not included in the research, since PDTS does not reject claims as the secondary payer. Additionally, patients who had processed paper claims for agents in the drug class were not included due to significant potential delays in processing. Subjects were identified if they experience a rejection within the first 90 days after implementation of the step therapy criteria. Those subjects were then followed for an additional 180 days after the rejection.

STUDY VARIABLES

Data for numerous variables were collected, recoded, and manipulated to create the analytic dataset used in this study. A complete list of variables and their definitions are described in Appendix A. Of particular interest are the following variables used to describe the sample and the results. Explanations here are a representation of formal database definitions as provided by the DoD.[1]

A majority of collected demographic data is populated in the PDTS database from the DEERS database. These elements include the subject's gender, beneficiary group, sponsor's (service member of the family) branch of service, and age category. For subject beneficiary group there are 3 primary classes each with 2 subsets. The primary classes are Active Duty, Retired and Non Active Duty. Active Duty members are those who are currently serving in one of the armed forces. Retired members are those who have completed 20 years of active military service, or have other special circumstances (e.g., Medal of Honor Hero) that make them eligible for lifetime medical care without 20 years of service. Finally, Non-Active Duty service members are those who are not fully active, but are temporarily eligible for Tricare benefits (e.g., Reservists currently active). Within each of these primary classes subjects are categorized as either service member (S) or family member (F). Family members are those who are eligible for services due to their relationship with the service member.

The sponsor's branch of service category is related to the service the eligible member is associated with. For retired subjects, this is the service from which he or she retired. The primary categories for this are Army, Air Force, Coast Guard, Department of Defense, Public Health Service, National Oceanic and Atmospheric Association (NOAA) and Navy. Due to low subject frequencies in the Coast Guard, Public Health Service and NOAA, these categories were aggregated by the researcher to form an "Other Services" category.

Age category is provided by DEERS in a number of subsets ranging from 0 to 65+. Given the disease states under consideration in this research, a majority of subjects fell within the 45-64 age category or the 65+ age category. With this in mind, split age categories less than 45 were combined to form an 18-44 age category.

Data was also collected on point of service for the claim. This data is based on pharmacy data populated from the claim and defined by the NCPDP pharmacy database. The categories examined in this research were Retail, Mail Order, Medical Treatment Facility (MTF), Veteran's Affairs (VA CHDR), and within Theater. Within Theater is comprised of soldiers receiving documented care while deployed.

Claim-specific data was populated directly to the database from the contracted claim adjudicator. The three primary elements used in defining the dataset were the claim status, reject code, and date of claim. Claim status and date of claim are true to their titles in that they indicate whether a claim was paid or rejected and on what date this event occurred. The reject code is used for rejected claims to indicate the reason the claims adjudicator did not approve payment for the claim. For this research, the reject code of interest is code 75, which indicates a claim was not paid due to failure to meet Step Therapy criteria. Additionally populated in the claim adjudication process are indicators for paper claims (DMRindicator) and coordination with a third party insurer (COBindicator). These elements were used in this research to operationalize exclusionary criteria.

Finally, drug class data within PDTS is built from linked data in the FDB database. This class data included GC4 codes as well as GCN numbers. GC4 codes

represent a primary ingredient for a medication. For example, a GC4 code of M4DA indicates a primary ingredient of simvastatin. This includes all doses and formulations of simvastatin. A GCN number is more specific in that it specifies certain formulations of a drug ingredient. This is particularly useful in medications that are available as a generic in one formulation, but brand name in another. For example, lovastatin (Mevacor) may be a covered item due to its generic availability, but lovastatin (Altoprev) is not a covered item. For purposes of this research, GCN# was used for analyses where a higher degree of differentiation was needed.

As noted in Chapter One, the DoD employs Step Therapy based on GC4 and GCN codes. During claim adjudication, all claims for a Step 2 agent are first examined to see if a Step 1 agent has been used. This process is completed using the GC4 or GCN# for the agent being adjudicated as well as agents within the subject's previous use profile. For purposes of this study, the GC4 codes and GCN#s used for adjudication are listed in Tables 2.1 through 2.4.

Step 2 (Rejected) GC4s	**Step 2 (Rejected) GCN #s**	**First Step (Prior Attempt) GC4s**	**First Step GCN #s**
M4DD (fluvastatin) M4DH (pitavastatin) A9AJ (atorvastatin/amlodipine) CGNN (niacin/lovastatin or niacin/simvastatin) M4FR (simvastatin/ezetimibe) M4DG (rosuvastatin)	17650 (lovastatin - Altoprev) 17651 (lovastatin - Altoprev) 17652 (lovastatin - Altoprev) 17654 (lovastatin - Altoprev)	M4DA (simvastatin) M4DB (lovastatin - Mevacor) M4DC (pravastatin) M4DE (atorvastatin)	None

Table 2.1: Data codes for LIP-1 class

Step 2 (Rejected) GC4s	**Step 2 (Rejected) GCN #s**	**First Step (Prior Attempt) GC4s**	**First Step GCN #s**
None	16857 (silodosin) 16858 (silodosin)	*None*	92024 (alfuzosin) 48191 (tamsulosin)

Table 2.2: Data codes for Uro-selective Alpha Blockers

Step 2 (Rejected) GC4s	Step 2 (Rejected) GCN #s	First Step (Prior Attempt) GC4s	First Step GCN #s
C4JC (saxagliptin & combinations) C4JA (sitagliptin & combinations) C4JD (linagliptin & combinations)	*None*	C4LB (metformin) C4KC (chlorpropamide C4KJ (glimeprimide) C4KF (glipizide combinations) C4KE (glyburide) C4KD (tolzamide) C4KB (tolbutamide)	25445 (pioglitazone/metformin) 25444 (pioglitazone/metformin) 28622 (pioglitazone/metformin) 28620 (pioglitazone/metformin) 20313 (rosiglitazone/metformin) 20314 (rosiglitazone/metformin) 91741 (rosiglitazone/metformin) 91742 (rosiglitazone/metformin) 91743 (rosiglitazone/metformin) 98489 (rosiglitazone/glimeprimide) 97648 (rosiglitazone/glimeprimide) 26126 (rosiglitazone/glimeprimide) 26127 (rosiglitazone/glimeprimide) 16085 (repaglinide/metformin) 16084 (repaglinide/metformin) 97181 (pioglitazone/glimeprimide) 97180 (pioglitazone/glimeprimide)

Table 2.3: Data codes for DPP-4s

Step 2 (Rejected) GC4s	Step 2 (Rejected) GCN #s	First Step (Prior Attempt) GC4s	First Step GCN #s
A4TA (aliskiren & combinations)	98936 (olmesartan/amlodipine)	A4FA (losartan & combinations)	97963 (valsartan/amlodipine)
A4FE (candesartan & combinations)	98937 (olmesartan/amlodipine)	ARFF (telmisartan & combinations)	97962 (valsartan/amlodipine)
ARFD (eprosartan & combinations)	98938 (olmesartan/amlodipine)	ARFB (valsartan & combinations)	98579 (valsartan/amlodipine)
A4FC (irbesartan & combinations)	98939 (olmesartan/amlodipine)		98580 (valsartan/amlodipine)
A4FG (olmesartan & combinations)			22625 (valsartan/amlodipine/hctz)
A4FH (azilsartan)			22648 (valsartan/amlodipine/hctz)
			22631 (valsartan/amlodipine/hctz)
			22649 (valsartan/amlodipine/hctz)
			22705 (valsartan/amlodipine/hctz)

Table 2.4: Data codes for ARBs

DATA ANALYSIS

STATA version 11 was used for data analyses. The complete data analysis sequence is available in Appendix 2 and STATA coding for the analysis in Appendix 3.

Initially, data were cleaned to remove observations that met exclusionary criteria after which demographic data for the subjects was compiled. Following this, the criteria for defining PPNA were operationalized creating a dichotomous variable. Subjects who did not receive a paid claim within days of initial rejection were classified as PPNA.

Subjects who did have a paid claim within the specified time were determined as adherent and a time to fill variable was calculated.

With PPNA defined, likelihood of PPNA for each medication class was compared to the reference category to determine differences. Within each class, logistic regression analysis was used to determine association between demographic data and PPNA. The regression models were tested for goodness of fit as well as violation of assumptions. Finally, for patients who were determined to be adherent, time to fill statistics were analyzed.

REVIEW OF HYPOTHESES

Logistic regression analyses were used to test all comparative hypotheses. Alpha was set at 0.01. This value for alpha was selected to provide a strong control of type I error. Concerns about power were overridden because of the relatively large sample size.

REFERENCES

1. Hardy P. DOD POC Business Objects Data Dictionary. 2008. Accessed 11/16/2011, 2011.

Chapter Three: Results

This chapter describes the results of analysis for rejected drug claims due to Step Therapy failure in each individual drug class, as well as an aggregation of individuals from all classes.

BASIC COMPOSITION OF THE DATASETS

Table 3.1 shows the breakdown of processed claims by point of service. Reflective of the general DoD claims distribution, a majority of the claims were processed through the retail pharmacy channel. This sample includes all processed claims within the specified time period, in the specified medications classes, for patients who experienced a Step Therapy rejection in the study period.

Class	Retail Claims (%)	Mail Order Claims (%)	Military Treatment Facility Claims (%)	Veteran's Affairs Claims (%)	Theater Claims (%)	Total (%)
LIP-1	144,261 (78.6)	33,683 (18.5)	4,869 (2.7)	411 (0.2)	5 (<0.1)	182,229 (100.1)*
Alpha Blockers	5,493 (88.1)	636 (10.2)	105 (1.7)	0 (0)	0 (0)	6,234 (100.0)
DPP-4	16,116 (83.7)	2,829 (14.7)	516 (2.7)	157 (0.8)	3 (<0.1)	19,261 (102)*
ARB	56,865 (80.7)	12,212 (17.3)	1,311 (1.9)	44 (<0.1)	0 (0)	70,432 (100.0)
Total	222,735 (79.7)	49,360 (17.7)	6,801 (2.4)	612 (0.2)	8 (<0.1)	279,508 (100.1)*

*Total not equal to 100% due to rounding

Table 3.1 Frequency of Processed Claims by Point of Service and Medication Class.

Exclusion Criteria

After collection of data predefined exclusion criteria were applied. Table 3.2 lists the criteria applied and the number of subjects excluded for each criterion. Below the listed frequency, in parentheses, is the percentage of total subjects. The first column listed shows subjects who were included in the initial data pull, but did not meet age

criteria defined in the study proposal. The second column shows the number of subjects who were excluded if they filed a claim with other health insurance (OHI) at any point during the study period. Subjects with OHI were excluded because they are exempt from Step Therapy criteria. A relatively small number of subjects were excluded because gender or beneficiary group information was not available. Those who had filed a paper claim were excluded because substantial delays between medication dispensing and adjudication may exist as allowed by the pharmacy benefit. Subjects who had a branch of service outside of the U.S. military were excluded, as this was not the population of interest. Finally, the primary exclusion was for subjects whose claim was rejected outside of the study window previously defined as within 90 days of Step Therapy implementation. For the combined data set, all subjects were included even if they occurred in more than one class. Post-hoc analysis showed that 137 subjects were present in 2 classes, but no subjects were in more than 2 classes. Given the small number of subjects in more than one class, it was believed assumptions of independence would be upheld.

Class	Age Under 18 (%)	Other Health Insurance (%)	Unknown Beneficiary Group (%)	Unknown Gender (%)	Filed Paper Claim (%)	Branch of Service (%)	Outside Study Period (%)	Met All Criteria (%)	Total (%)
LIP-1	13 (<0.1)	718 (3.2)	33 (0.1)	1 (<0.1)	111 (0.5)	11 (<0.1)	4,940 (22.1)	16,511 (73.9)	22,338 (100.1) *
Alpha Blocker	0 (0)	26 (2.9)	0 (0)	0 (0)	2 (0.2)	0 (0)	200 (22.5)	660 (74.3)	888 (99.9)*
DPP-4	3 (0.1)	94 (3.5)	5 (0.2)	0 (0)	23 (0.2)	0 (0)	436 (16.3)	2,121 (79.1)	2,682 (99.5)*
ARB	11 (0.1)	339 (3.5)	20 (0.2)	0 (0)	31 (0.3)	0 (0)	1,336 (13.8)	7,910 (82.0)	9,647 (99.9)*

*Total not equal to 100% due to rounding

Table 3.2 Frequencies of Subjects Excluded by Exclusion Criteria and Medication Class

Demographic Data

Following the removal of subjects based on the exclusion criteria, analyses were conducted on the remaining subjects to describe the general demographics of the sample.

Age categories were combined as previously described; as anticipated, a majority of all subjects analyzed were 65 years old or older. Table 3.3 describes the breakdown of subjects by age for each class as well as the combined sample. For each of these groups, it is important to note that all of these subjects received a rejection for failure to meet Step Therapy criteria.

Class	**Ages 18-44 (%)**	**Ages 45-64 (%)**	**Ages 65+ (%)**	**Total (%)**
LIP-1	1,001 (6.1)	6,610 (40.0)	8,900 (53.9)	16,511 (100.0)
Alpha Blockers	12 (1.8)	128 (19.4)	520 (78.8)	660 (100.0)
DPP-4	116 (5.5)	778 (36.7)	1,227 (57.9)	2,121 (100.1)*
ARB	406 (5.1)	2,707 (34.2)	4,797 (60.6)	7,910 (99.9)*

*Total not equal to 100% due to rounding

Table 3.3 Frequencies of Subjects in the Study Sample by Age Group and Medication Class

Patient gender, as demonstrated in Table 3.4, was distributed near 50/50 in the LIP-1 class and in the DPP-4 class. There was a slight skew towards females in the ARB class with only 40% being male. As expected the Alpha Blocker class was predominately male due to the primary indication for these agents in a male-specific condition.

Class	Male (%)	Female (%)	Total (%)
LIP-1	9,011 (45.4)	7,500 (54.6)	16,511 (100.0)
Alpha Blockers	631 (95.6)	29 (4.4)	660 (100.0)
DPP-4	1,052 (49.6)	1,069 (50.4)	2,121 (100.0)
ARB	3,255 (41.1)	4,655 (58.9)	7,910 (100.0)

Table 3.4 Frequencies of Subjects in the Study Sample by Gender and Medication Class

Beneficiary group data (Table 3.5) and branch of service data (Table 3.6) showed no surprising results, with a majority of all subjects being retirees. Specifically, the Alpha Blockers were almost exclusively retired service members. This matches expectations due to etiology of the disease and the observation that most service members in the retiree segment are male. The distribution of subjects was relatively even across branches of service with the exceptions being the Marine Corps and Other services. This was expected, as these branches represent a smaller proportion of the Armed Forces.

Class	Active Duty Family Member (%)	Active Duty Service Member (%)	Non-Active Duty Family Member (%)	Non-Active Duty Service Member (%)	Retired Service Member (%)	Retired Family Member (%)	Total (%)
LIP-1	460 (2.8)	388 (2.4)	70 (0.4)	395 (2.4)	7,071 (42.8)	8,127 (49.2)	16,511 (100.0)
Alpha Blockers	7 (1.1)	0 (0)	0 (0)	3 (0.5)	618 (93.6)	32 (4.8)	660 (100.0)
DPP-4	61 (2.9)	24 (1.1)	12 (0.6)	41 (1.9)	1,020 (48.1)	963 (45.4)	2,121 (100.0)
ARB	220 (2.8)	122 (1.5)	55 (0.7)	209 (2.6)	3,100 (39.2)	4,204 (53.2)	7,910 (100.0)

Table 3.5 Frequencies of Subjects in the Study Sample by Beneficiary Group and Medication Class

Class	Army (%)	Air Force (%)	Marine Corps (%)	Navy (%)	Other Services (%)	Total (%)
LIP-1	6,214 (37.6)	5,269 (31.9)	811 (4.9)	3,827 (23.2)	390 (2.4)	16,511 (100.0)
Alpha Blockers	200 (30.3)	256 (38.8)	33 (5.0)	156 (23.6)	15 (2.3)	660 (100.0)
DPP-4	813 (38.3)	637 (30)	119 (5.6)	513 (24.2)	39 (1.8)	2,121 (99.9)*
ARB	2,955 (37.4)	2,631 (33.3)	392 (5.0)	1,738 (22.0)	194 (2.5)	7,910 (100.2)*

*Total not equal to 100% due to rounding

Table 3.6 Frequencies of Subjects in the Study Sample by Sponsor's Branch of Service and Medication Class

ANALYSIS OF OBJECTIVES

After initial description of each class, objectives and hypotheses were addressed sequentially. Each of the objectives, with corresponding hypotheses, is listed below.

Objective 1

The purpose of objective 1 was to calculate the likelihood of PPNA in each of the medication classes as well as for the combined sample and compare to the likelihood for the LIP-1 class. The combined sample contained 27,202 subjects who experienced a rejection, of whom 4,107 (15.1%) were determined to be primary non adherent. The PPNA proportions varied across medication classes from 13.1% to 19.5% with the lowest non-adherence rates belonging to the LIP-1 class and the highest to the Alpha Blocker class.

The null hypothesis for this objective stated the likelihood of PPNA for the specified **medication classes** did not differ significantly from the likelihood of PPNA for patients receiving a LIP-1 agent. Based on the logistic regression analysis by class, we can reject this hypothesis. In fact, subjects in the Alpha Blocker, DPP-4, and ARB classes all were statistically more likely to be PPNA when compared to the LIP-1 class.

Subjects who received a rejection on their Alpha Blocker medication were 60% more likely to be non-adherent than subjects in LIP-1 class.

Class	Subjects with a Rejection	Number of Subjects PPNA	Proportion of Subjects PPNA	OR	99% CI
LIP-1	16,511	2,166	13.1%	-Ref-	-Ref-
Alpha Blockers	660	129	19.5%	1.60*	1.22 - 2.09
DPP-4	2,121	384	18.1%	1.43*	1.22 – 1.68
ARB	7,910	1,428	18.1%	1.47*	1.34 – 1.62
Combined	**27,202**	**4,107**	**15.1%**	**N/A**	**N/A**

*Denotes statistical significance

Table 3.7 Logistic Regression Results: PPNA by Medication Class

Objective 2

The second objective was to determine the association of various demographic variables with PPNA. Five independent variables were analyzed for this objective: age, gender, beneficiary group, branch of service, and claim point of service. These analyses were conducted by medication class using a logistic regression analysis to determine odds ratios and test for differences. Since there was the potential for multicollinearity between age and beneficiary category, all of the analyses were initially tested using the variance inflation factor (VIF). VIF values (Table 3.8) are all far below 10, so the influence of multicollinearity was not determined to be significant.

VIF	LIP-1	Alpha Blockers	DPP-4	ARB	Combined
Beneficiary Group	1.41	1.05	1.32	1.42	1.41
Sex	1.19	1.05	1.19	1.20	1.20
Service Category	1.04	1.01	1.02	1.03	1.03
Age	1.22	1.09	1.16	1.24	1.22
Sponsor Branch of Service	1.01	1.01	1.00	1.01	1.01
Mean VIF	1.18	1.04	1.14	1.18	1.17

Table 3.8 Variance Inflation Factors for Independent Variables by Medication Class in the Logistic Regression Models

To test hypotheses on age difference, subjects were stratified into three separate age categories and tested by class (Table 3.9). For each class, we tested the hypothesis that the older age categories were not significantly different in PPNA compared to the 18-44 age category. For the LIP-1 class, this hypothesis was rejected as a significantly lower proportion of subjects were non-adherent in the 64+ class when compared to the reference 18-44 age category. The OR of 0.75 (99% CI = 0.57-0.99) indicates the older category was 25% less likely to be non-adherent when compared to the younger category. This was the only individual class that showed a statistical difference between age categories, however, the combined sample showed a similar result with a OR of 0.78 (99% CI = 0.63 – 0.96) indicating PPNA rates were significantly lower in the 64+ age group compared to the 18-44 age group.

Class	Ages 18-44 Subjects with Reject	Ages 18-44 PPNA (Proportion)	Ages 45-64 Subjects with Reject	Ages 45-64 PPNA (Proportion) (OR) (99% CI)	Ages 64+ Subjects with Reject	Ages 64+ PPNA (Proportion) (OR) (99% CI)
LIP-1	1,001	176 (17.6) -ref-	6,610	944 (14.3) (0.87) (0.67-1.14)	8,900	1,046 (11.8) (0.75)* (0.57-0.99)
Alpha Blockers	12	5 (41.7) -ref-	128	25 (19.5) (0.69) (0.09-5.00)	520	99 (19.0) (0.70) (0.10-5.00)
DPP-4	116	22 (19.0) -ref-	778	134 (17.2) (1.18) (0.53-2.65)	1,227	228 (18.6) (1.30) (0.58-2.93)
ARB	406	108 (26.6) -ref-	2,707	521 (19.2) (0.79) (0.55-1.15)	4,797	799 (16.7) (0.73) (0.50-1.06)
Combined	1,535	311 (20.3) -ref-	10,223	1,624 (15.9) (0.86) (0.70-1.06)	15,444	2,172 (14.1) (0.78)* (0.63-0.96)

*Denotes statistical significance

Table 3.9 Logistic Regression Results: PPNA by Age Group for Each Medication Class

The likelihood of PPNA by gender was tested using logistic regression with Male subjects being the reference category. Across each class and in the combined sample, no significant differences in likelihood of PPNA were detected (Table 3.10).

Class	Male Subjects with Reject	Male PPNA (Proportion)	Female Subjects with Reject	Female PPNA (Proportion) (OR) (99% CI)
LIP-1	9,011	943 (10.5) -ref-	7,500	1,223 (16.3) (0.92) (0.66-1.27)
Alpha Blockers	631	121 (19.2) -ref-	29	8 (27.6) (0.70) (0.08-6.24)
DPP-4	1,052	190 (18.1) -ref-	1,069	194 (18.1) (0.88) (0.36-2.18)
ARB	3,255	572 (17.6) -ref-	4,655	856 (18.4) (0.86) (0.55-1.34)
Combined	12,438	1,826 (14.7) -ref-	14,764	2,281 (15.4) (0.90) (0.70-1.15)

*Denotes statistical significance

Table 3.10 Logistic Regression Results: PPNA by Gender for Each Medication Class

Testing for beneficiary category differences looked across six different categories for differences (Table 3.11). The reference category for this test was active duty family members (ADF). For subjects in the Alpha Blocker, ARB, and DPP-4 classes there were no detected significant differences. Similarly, there were no detectable differences for Active Duty Service members (ADS), Non-Active Duty Family members (NADF) or Retirees (RET) in the individual medication classes. In the LIP-1 class and the combined sample, ORs were significantly lower for the Non-Active Duty Service members (NADS) (0.55 and 0.60, respectively). A significant difference was also detected in the combined sample for Retiree Family members (RETF) (OR = 0.69, 99% CI = 0.54 – 0.90).

The test by branch of service (Table 3.12) only yielded one significant result across all medication classes and service categories. That difference was demonstrated in the LIP-1 class, and showed that Air Force subjects were less likely than Army subjects to be primary non-adherent (OR = 0.85). This difference was not reproduced in any other classes, or the combined sample.

Class	ADF with Reject	ADF PPNA (Proportion)	ADS with Reject	ADS PPNA (Proportion) (OR) (99% CI)	NADF with Reject	NADF PPNA (Proportion) (OR) (99% CI)	NADS with Reject	NADS PPNA (Proportion) (OR) (99% CI)	RET with Reject	RET PPNA (Proportion) (OR)	RETF with Reject	RETF PPNA (Proportion) (OR) (99% CI)
LIP-1	460	94 (20.4) -ref-	388	58 (14.9) (0.71) (0.41-1.23)	70	11 (15.7) (0.75) (0.31-1.85)	395	42 (10.6) (0.55)* (0.32-0.95)	7,071	882 (12.5) (0.79) (0.50-1.24)	8,127	1,079 (13.3) (0.78) (0.55-1.09)
Alpha Blockers	7	4 (57.1) -ref-	0	0	0	0	3	1 (33.3) (0.42) (0.01-19.54)	618	118 (19.1) (0.24) (0.02-3.33)	32	6 (18.8) (0.19) (0.01-2.40)
DPP-4	61	16 (26.2) -ref-	24	5 (20.8) (0.83) (0.16-4.33)	12	2 (16.7) (0.52) (0.06-4.47)	41	5 (12.2) (0.37) (0.08-1.67)	1,020	185 (18.1) (0.60) (0.18-1.98)	963	171 (17.8) (0.51) (0.20-1.29)
ARB	220	67 (30.5) -ref-	122	25 (20.5) (0.62) (0.28-1.35)	55	11 (20) (0.56) (0.22-1.46)	209	42 (20) (0.72) (0.39-1.33)	3,100	541 (17.4) (0.74) (0.40-1.36)	4,204	742 (17.6) (0.65) (0.41-1.01)
Combined	748	181 (24.2) -ref-	534	88 (16.5) (0.68) (0.44-1.04)	137	24 (17.5) (0.65) (0.35-1.21)	648	90 (13.9) (0.60)* (0.41-0.88)	11,809	1,726 (14.6) (0.74) (0.53-1.05)	13,326	1,998 (15.0) (0.69)* (0.54-0.90)

*Denotes statistical significance

Table 3.11 Logistic Regression Results: PPNA by Beneficiary Group for Each Medication Class

Class	Army with Reject	Army PPNA (Proportion)	Air Force with Reject	Air Force PPNA (Proportion) (OR) (99% CI)	Marine Corps with Reject	Marine Corps PPNA (Proportion) (OR) (99% CI)	Navy with Reject	Navy PPNA (Proportion) (OR) (99% CI)	Other Service with Reject	Other Service PPNA (Proportion) (OR) (99% CI)
LIP-1	6,214	901 (14.5) -ref-	5,269	630 (12.0) (0.85)* (0.74-0.99)	811	113 (13.9) (0.94) (0.71-1.24)	3,827	474 (12.4) (0.86) (0.73-1.00)	390	48 (12.3) (0.85) (0.56-1.28)
Alpha Blockers	200	29 (11.3) -ref-	256	55 (20.8) (1.71) (0.88-3.33)	33	10 (30.3) (2.60) (0.84-8.07)	156	32 (20.5) (1.55) (0.74-3.25)	15	3 (20) (1.71) (0.29-9.92)
DPP-4	813	153 (18.9) -ref-	837	119 (14.2) (1.00) (0.70-1.42)	119	18 (15.1) (0.75) (0.37-1.52)	513	91 (17.8) (0.93) (0.63-1.36)	39	3 (7.7) (0.36) (0.07-1.73)
ARB	2,955	546 (18.4) -ref-	2,631	457 (17.4) (1.01) (0.84-1.21)	392	87 (22.2) (1.28) (0.91-1.79)	1,738	297 (17.1) (0.96) (0.78-1.19)	194	41 (21.9) (1.31) (0.81-2.11)
Combined	10,184	1,629 (16.0) -ref-	8,792	1,261 (14.3) (0.93) (0.86-1.01)	1,355	228 (16.8) (1.06) (0.91-1.23)	6,235	894 (14.3) (0.91) (0.83-0.99)	636	95 (14.9) (0.97) (0.77-1.01)

*Denotes statistical significance

Table 3.12 Logistic Regression Results: PPNA by Branch of Service for Each Medication Class

The final analysis of this objective was to examine differences between the Retail and Mail Order points of service (Table 3.13). In both of the largest classes, LIP-1 and ARB, differences were detected. Each case demonstrated Retail subjects to be nearly twice as likely to be non-adherent when compared to Mail Order subjects. This result was confirmed with a statistically significant result (OR = 1.90, 95% CI = 1.69 – 2.13) in the combined sample.

Class	Mail Order Subjects with Reject	Mail Order PPNA (Proportion)	Retail Subjects with Reject	Retail PPNA (Proportion) (OR) (99% CI)
LIP-1	4,422	373 (8.4) -ref-	16,089	1,793 (11.1) (1.80)* (1.54-2.10)
Alpha Blockers	90	11 (12.2) -ref-	570	118 (20.7) (1.89) (0.78-4.57)
DPP-4	455	71 (15.6) -ref-	1,666	313 (18.8) (1.28) (0.88-1.87)
ARB	2,090	207 (9.9) -ref-	5,820	1,221 (21.0) (2.32)* (1.89-2.86)
Combined	7,056	662 (9.4) -ref-	20,146	3,445 (17.1) (1.90)* (1.69-2.13)

*Denotes statistical significance

Table 3.13 Logistic Regression Results: PPNA by Service Category for Each Medication Class

Objective 3

The third objective was, for each class, to describe the proportion of subjects who were PPNA for each of the medications. The data provides important insight as to the most commonly rejected medications and the resilience of the subjects to adhere to

therapy following the rejection. Tables 3.14 through 3.17 present the data for each class and the agents within that class. Generally, agents within the class appeared representative of the overall PPNA proportion for the class.

Generic Name	Number of Subjects with Reject	Number of Subjects PPNA	Proportion of Subjects PPNA
amlodipine/atorvastatin	276	40	14.5%
ezetimibe/simvastatin	2,547	308	12.1%
fluvastatin sodium	177	18	10.2%
lovastatin	17	0	0.0%
niacin/lovastatin	86	10	11.6%
niacin/simvastatin	565	78	13.8%
pitavastatin calcium	867	179	20.6%
rosuvastatin calcium	11,976	1,533	12.8%
OVERALL	**16,511**	**2,166**	**13.1%**

Table 3.14 PPNA Proportions for Medications in the LIP-1 Class

Generic Name	Number of Subjects with Reject	Number of Subjects PPNA	Proportion of Subjects PPNA
silodosin	660	129	19.5%
OVERALL	**660**	**129**	**19.5%**

Table 3.15 PPNA Proportions for Medications in the Alpha Blocker Class

Generic Name	Number of Subjects with Reject	Number of Subjects PPNA	Proportion of Subjects PPNA
linagliptin	39	7	17.9%
pioglitazone/glimeprimide	1	0	0.0%
pioglitazone/metformin	7	1	14.3%
rosiglitazone/metformin	2	0	0.0%
saxagliptin	312	66	21.2%
saxagliptin/metformin	114	19	16.7%
sitagliptin/metformin	519	78	15.0%
sitagliptin	1,127	213	18.9%
OVERALL	**2,121**	**384**	**18.1%**

Table 3.16 PPNA Proportions for Medications in the DPP-4 Class

Generic Name	Number of Subjects with Reject	Number of Subjects PPNA	Proportion of Subjects PPNA
aliskiren hemifurate	748	181	24.2%
aliskiren/amlodipine	34	7	20.6%
aliskiren/amldopine/HCTZ	4	2	50.0%
aliskiren/HCTZ	143	25	17.5%
aliskiren/valsarten	262	65	24.8%
amlodipine/olmesartan	616	141	22.9%
azilsartan medoxomil	6	1	16.7%
candesarten cilexetil	491	70	14.3%
eprosartan	9	6	66.7%
eprosartan/HCTZ	5	5	100.0%
irbesartan	999	161	16.1%
irbesartan/HCTZ	268	53	19.8%
olmesartan/amlodipine	295	84	28.5%
olmesartan medoxomil	2,222	387	17.4%
olmesartan/HCTZ	1,604	219	13.7%
OVERALL	**7,910**	**1,428**	**13.1%**

Table 3.17 PPNA Proportions for Medications in the ARB Class

Objective 4

The final objective is designed to describe the days to fill for subjects who were met with a rejection, but later filled a prescription for an agent in the same therapeutic class. Most importantly, this objective seeks to determine the mathematical characteristics of the time between rejection and first fill.

Table 3.18 describes the values for the time to fill statistic and Figures 3.1 through 3.5 demonstrate the distribution of values. The histograms show values to be strongly skewed to the right. Statistical values confirm this with a median value of 7 days, but a 95th percentile not being reached until over 90 days for the combined sample.

Med Class	Number of Adherent Patients (% of subjects)	Mean Days to Fill	Median Days to Fill	Std. Deviation	95th Percentile (Days)	99th Percentile (Days)
LIP-1	14,345 (86.9)	20.6	7	32.2	96	157
Alpha Blockers	531 (80.5)	17.3	6	29.0	81	152
DPP-4	1,737 (81.9)	19.1	7	31.6	91	158
ARB	6,482 (81.9)	18.1	6	29.3	84	149
Combined	23,095 (84.9)	19.7	7	31.5	92	155

Table 3.18 Days to Fill Statistics for Adherent Patients

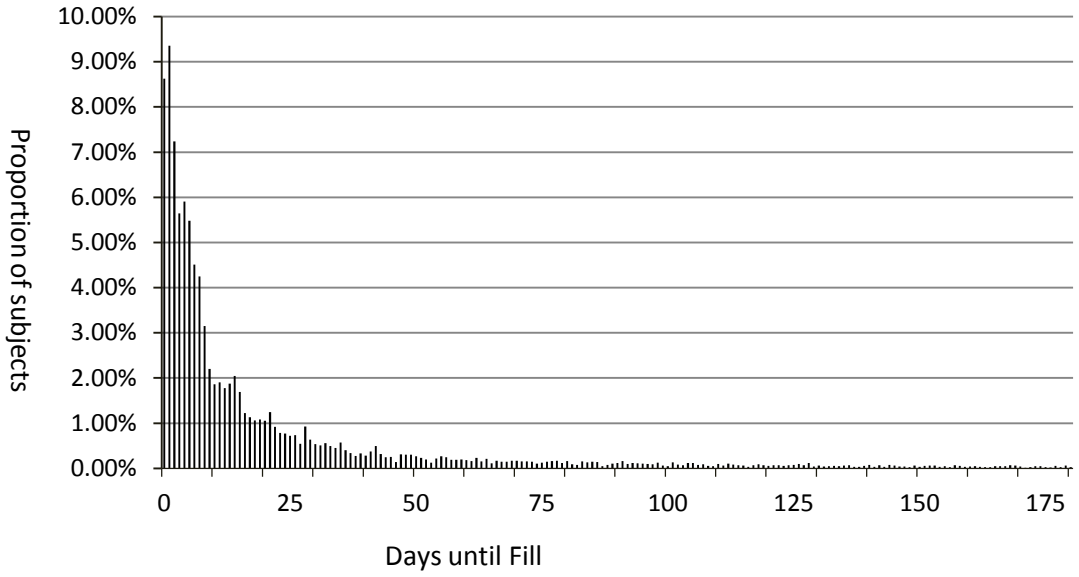

Figure 3.1 Histogram of Days until Adherence for the LIP-1 Class

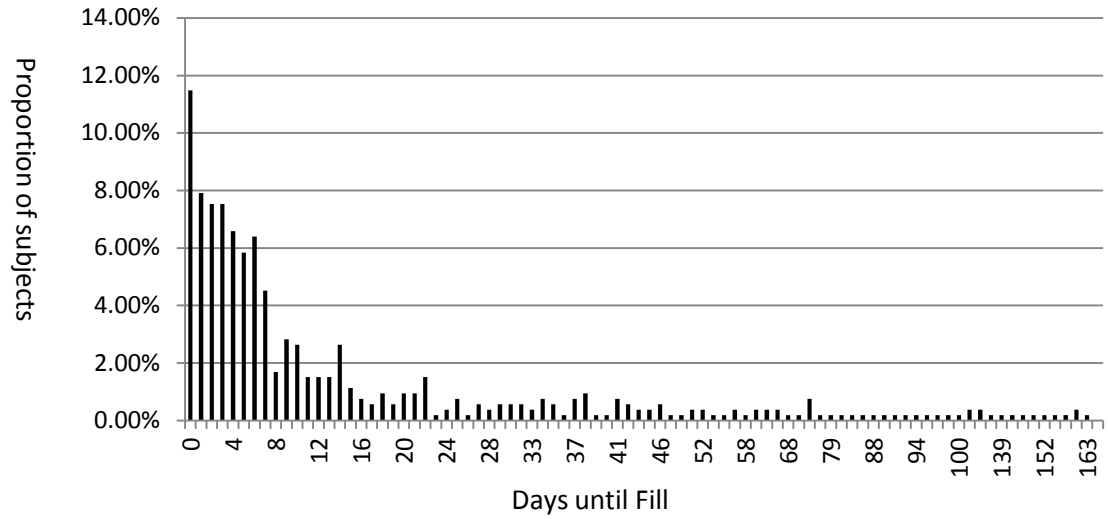

Figure 3.2 Histogram of Days until Adherence for the Alpha Blocker Class

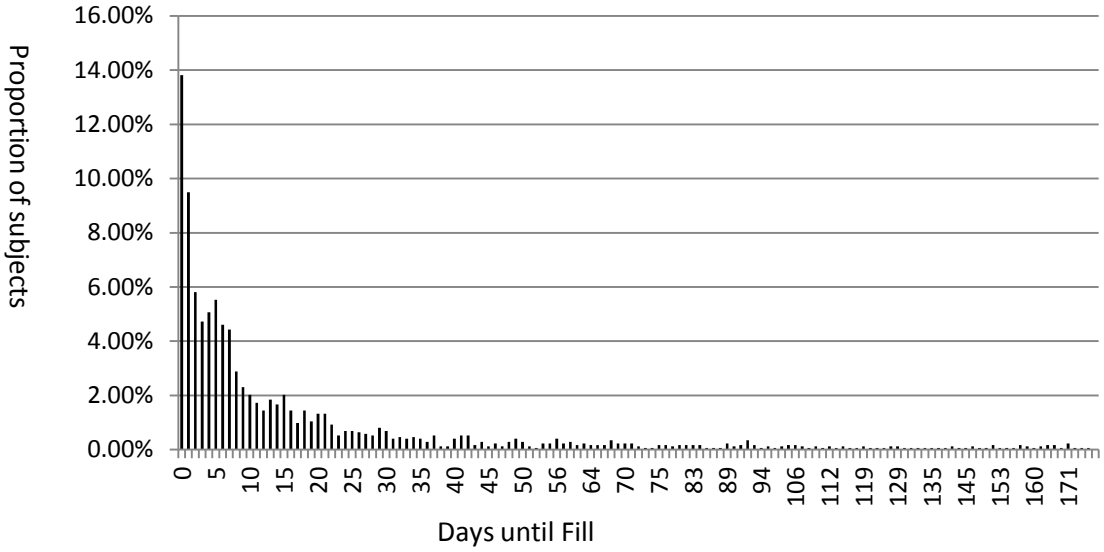

Figure 3.3 Histogram of Days until Adherence for the DPP4 Class

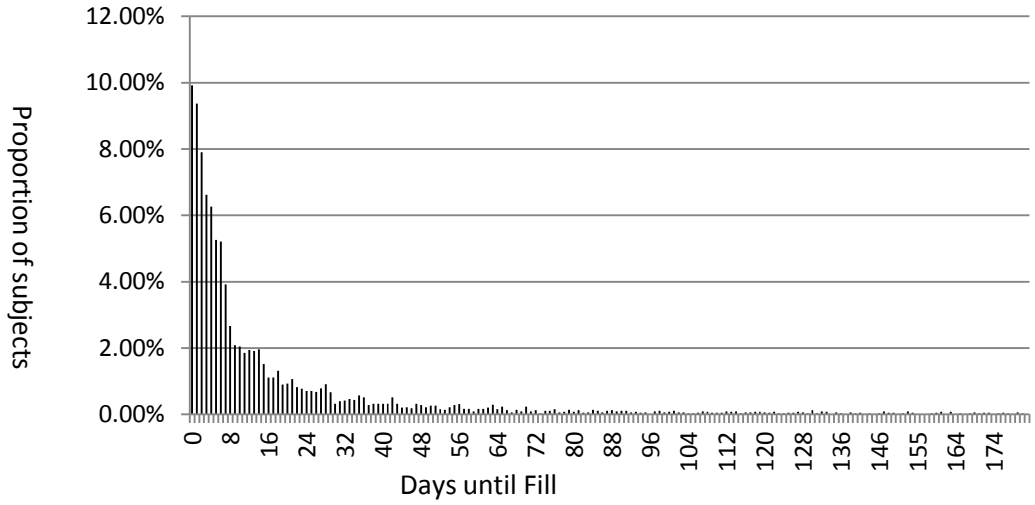

Figure 3.4 Histogram of Days until Adherence for the ARB Class

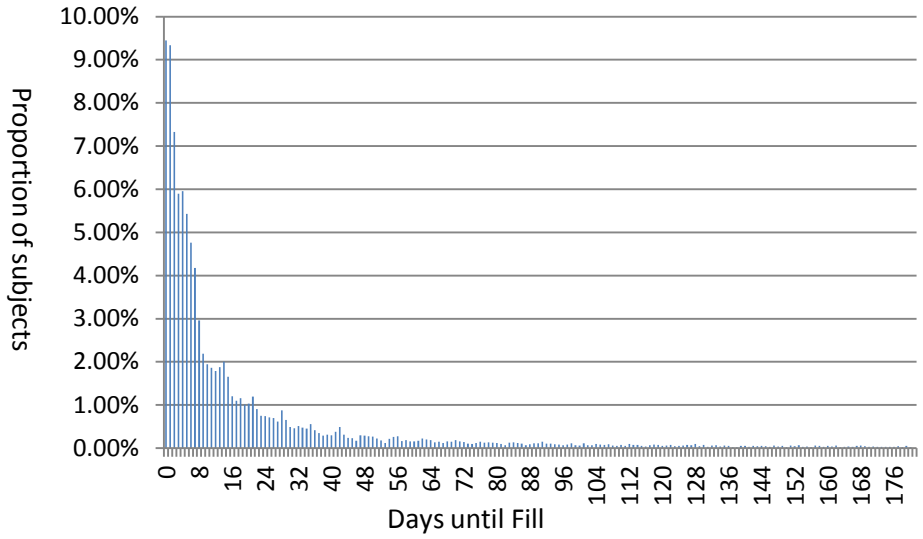

Figure 3.5 Histogram of Days until Adherence for the Combined Data

Summary of Hypotheses

Table 3.19 contains a summary of the hypotheses tests. For a majority of hypotheses, we failed to reject the null hypothesis. Significant differences were found between medication classes as well as in multiple samples for age category, beneficiary category, and point of service.

	Hypothesis	**Result**
$H_0$1	The likelihood of PPNA for the specified **medication classes** does not differ significantly from the likelihood of PPNA for patients receiving a LIP-1 agent.	Rejected
$H_0$2	The likelihood of PPNA for the specified **age categories** does not differ significantly from the likelihood of PPNA for patients in the 18-44 age group in the **LIP-1** sample.	Rejected

Table 3.19 Results of Hypothesis Tests

$H_0$3	The likelihood of PPNA for the specified **age categories** does not differ significantly from the likelihood of PPNA for patients in the 18-44 age group in the **Alpha Blocker** sample.	Failed to Reject
$H_0$4	The likelihood of PPNA for the specified **age categories** does not differ significantly from the likelihood of PPNA for patients in the 18-44 age group in the **DPP-4** sample.	Failed to Reject
$H_0$5	The likelihood of PPNA for the specified **age categories** does not differ significantly from the likelihood of PPNA for patients in the 18-44 age group in the **ARB** sample.	Failed to Reject
$H_0$6	The likelihood of PPNA for the specified **age categories** does not differ significantly from the likelihood of PPNA for patients in the 18-44 age group in the **combined** sample.	Rejected
$H_0$7	There is no difference in likelihood of PPNA associated with **gender** in the **LIP-1** sample.	Failed to Reject
$H_0$8	There is no difference in likelihood of PPNA associated with **gender** in the **Alpha Blocker** sample.	Failed to Reject
$H_0$9	There is no difference in likelihood of PPNA associated with **gender** in the **DPP-4** sample.	Failed to Reject
$H_0$10	There is no difference in likelihood of PPNA associated with **gender** in the **ARB** sample.	Failed to Reject
$H_0$11	There is no difference in likelihood of PPNA associated with **gender** in the **combined** sample.	Failed to Reject
$H_0$12	The likelihood of PPNA for the specified **beneficiary categories** does not differ significantly from the likelihood of PPNA for patients in the Active Duty Family member (ADF) group in the **LIP-1** sample.	Rejected
$H_0$13	The likelihood of PPNA for the specified **beneficiary categories** does not differ significantly from the likelihood of PPNA for patients in the Active Duty Family member (ADF) group in the **Alpha Blocker** sample.	Failed to Reject
$H_0$14	The likelihood of PPNA for the specified **beneficiary categories** does not differ significantly from the likelihood of PPNA for patients in the Active Duty Family member (ADF) group in the **DPP-4** sample.	Failed to Reject

Table 3.19 Continued

$H_0$15	The likelihood of PPNA for the specified **beneficiary categories** does not differ significantly from the likelihood of PPNA for patients in the Active Duty Family member (ADF) group in the **ARB** sample.	Failed to Reject
$H_0$16	The likelihood of PPNA for the specified **beneficiary categories** does not differ significantly from the likelihood of PPNA for patients in the Active Duty Family member (ADF) group in the **combined** sample.	Rejected
$H_0$17	The likelihood of PPNA for the specified **branches of service** does not differ significantly from the likelihood of PPNA for patients in the Army in the **LIP-1** sample.	Rejected
$H_0$18	The likelihood of PPNA for the specified **branches of service** does not differ significantly from the likelihood of PPNA for patients in the Army in the **Alpha Blocker** sample.	Failed to Reject
$H_0$19	The likelihood of PPNA for the specified **branches of service** does not differ significantly from the likelihood of PPNA for patients in the Army in the **DPP-4** sample.	Failed to Reject
$H_0$20	The likelihood of PPNA for the specified **branches of service** does not differ significantly from the likelihood of PPNA for patients in the Army in the **ARB** sample.	Failed to Reject
$H_0$21	The likelihood of PPNA for the specified **branches of service** does not differ significantly from the likelihood of PPNA for patients in the Army in the **combined** sample	Failed to Reject
$H_0$22	There is no difference in likelihood of PPNA associated with **service category** in the **LIP-1** sample.	Rejected
$H_0$23	There is no difference in likelihood of PPNA associated with **service category** in the **Alpha Blocker** sample.	Failed to Reject
$H_0$24	There is no difference in likelihood of PPNA associated with **service category** in the **DPP-4** sample.	Failed to Reject
$H_0$25	There is no difference in likelihood of PPNA associated with **service category** in the **ARB** sample.	Rejected
$H_0$26	There is no difference in likelihood of PPNA associated with **service category** in the **combined** sample.	Rejected

Table 3.19 Continued

Chapter Four: Discussion

The final chapter of this thesis provides interpretations of the results related to the objectives, seeks to identify the strengths and limitations of the research methodology, discusses the implications of the results, and identifies opportunities for future research.

RESULTS RELATIVE TO OBJECTIVES

Objective 1

The observed rate of PPNA for this objective overall (15.1%) initially seems in line with previous results. The rates for the Motheral and Cox studies were similar at 11% and 17% respectively, but these studies were conducted through survey methodology. [1,2] The only other claims-based study, by Yokoyama et al., found the rate to be 7%, about half the observed rate of this study.[3] If we focus on the ARB class, which was the class used by Yokoyama et al., we see a PPNA rate of over 18%.

This drastic difference in rates is attributed to three primary factors. First, in the Yokoyama study the follow-on to initial rejection was 1 year versus the 180-day follow-on for this study.[3] Second, Yokoyama documented PPNA as failure to receive any antihypertensive medication. In this study, PPNA was documented as failure to receive a step-appropriate agent. Finally, the Yokoyama study was comprised of 8,904 subjects who experienced a rejection versus this study which was comprised of 27,202 subjects.

Examining the first factor, follow-on period, one could assert that the 180-day follow-on is more clinically appropriate than a 1-year follow-on. For antihypertensive therapy, it seems undesirable that patient therapy would be delayed for more than 6 months. Regarding the second factor, the intention of step therapy should be examined. Not only is the intent to control cost, but also to guide prescribing to the best therapeutic alternative. The use of any antihypertensive is not always a suitable alternative for use of an ARB. The Yokoyama study assumed that ARB therapy could be replaced with any antihypertensive.[3] For this study, it was assumed that only an ACEI or an ARB would be a suitable substitute for the initially prescribed ARB. Finally, consideration should be given to the fact that this study encompassed multiple classes and a large sample size,

which helps to mitigate clinical considerations such as those described in ARB substitution. Considering all of these factors, the combined PPNA rate of 15.1% seems to be a reasonable representation of the overall PPNA rate for Step Therapy intervention.

To the author's knowledge, this is the largest evaluation of non-adherence following step therapy ever conducted. Additionally, it was the only identified claims-based study that examined multiple medication classes. In light of this, it is not currently possible to couch results of this study in previous findings. Interestingly, different PPNA rates were observed when comparing the Alpha Blocker, DPP-4, and ARB classes to the LIP-1 class. Given the etiology of each disease, it could be expected that the LIP-1 class would have the highest PPNA rate, however, the inverse is true. This could be attributed to two possible reasons. First, the LIP-1 class was the first of these classes to have step therapy implemented. It is possible that patients and providers responded more acutely in the initial rollout of this program. Second, LIP-1 agents have a very large amount of direct-to-consumer advertising. Therefore, these agents could be viewed by patients as more necessary than drugs in the other classes. If this is in fact the case, then future research could evaluate the effect of advertising expenditures on PPNA rate. The LIP-1 PPNA rate clearly influences the combined PPNA rate due to its difference from the other agents and the large sample size. Because of this large sample size, it should certainly be included in the combined rate despite its outlier status. As a class, LIP-1s accounted for over 65% of the total sample while ARBs as the second largest class only accounted for about 25%.

Objective 2

For this objective, again there was no identified literature which examined the association between various demographic factors and likelihood of PPNA. Due to the scarcity of previous research, these results must once again stand alone for interpretation. Looking first at the non-significant findings, gender and branch of service did not seem to be associated with any difference in likelihood for PPNA. Age 64+ and retired family members did seem to have a somewhat lower likelihood of PPNA than the younger and

active duty family member populations, respectively. The association here was identified in the combined sample, but not uniformly in the drug classes, indicating there could be a small association not readily identified in smaller group sizes. The appearance of the association in these groups could be attributed to a higher self awareness of health, or possibly more free time to navigate the requirements of the step therapy process.

The most drastic and uniform association was the nearly double likelihood of PPNA in retail claims compared to mail order claims. The cause of this association is not clearly evident, but possibly lies within the varying procedures to address step therapy rejections. It is known that standard operating procedure exists in the mail order pharmacy to address these rejections, but it is less consistent for the retail sector. Regardless of cause, the association is drastic and further consideration and research should be given to this topic.

Objective 3

This objective did not reveal any particularly surprising statistics, however will serve as a good DoD reference for the utilization and rejection rates of these agents.

Objective 4

The final objective looked at the adherent proportion of this sample. Specifically, the objective identified the time to adherence after an initial rejection. Not surprisingly, a large segment of those who are adherent reach adherence in the first week as indicated by a median of 6 to 7 days. After the initial surge, the rate of adherence drops significantly with 95^{th} and 99^{th} percentiles not reached until 90 and 150 days, respectively. This information could prove useful as consideration is given to interventions aimed at lowering the PPNA rate. Particularly, it identifies a point of intervention that would be most impactful 7 days or later after the rejection.

LIMITATIONS

First, and most apparently, this study is limited by the design. As a retrospective database analysis, no causality assumptions can be made. Additionally, randomization

did not occur and the groups cannot be assumed to be equivalent. The DoD sample also may also not be representative of the general population for these diseases.

The calculation of PPNA rates also cannot be assumed to be exact. There is the possibility that some patients identified as PPNA did in fact receive therapy. This could have been through another medication that was not included in analysis or through use of another payment source not identified (e.g., cash).

Finally, there was no measurement of the consequence of PPNA. Clearly the most important consideration of adherence is the impact on the health of the non-adherent subjects. No assessment was made in this study and no assertions can be made due to that design. In addition to health, no economic impacts were studied. From this study, it cannot be determined if step therapy resulted in overall plan cost avoidance.

FUTURE RESEARCH

This study demonstrated a need for further research on the unintentional consequences of step therapy. Now that a group has been identified who is non-adherent after the intervention, it would be interesting to note if this resulted in adverse clinical outcomes. One possible approach to this would be to examine blood glucose differences in subjects identified as PPNA for the DPP-4 category. A comparison could also be made to determine the level of blood glucose control for patients who were switched to metformin as a result of the step therapy.

Additionally, there appears to be a strong association between point of service and PPNA. Future research should be directed to this difference and possibly testing of new interventions to affect the difference. It would appear from the data presented here that the highest impact interventions would focus on patients who have not received an agent within 7 days of rejection and received care in the retail sector.

CONCLUSIONS

It appears that over 15% of patients who experience a step therapy rejection will not receive a similar medication within 180 days. Those who receive their care from a retail pharmacy are nearly twice as likely to be non-adherent when compared to mail

order patients. Finally, of the group who become adherent after the initial rejection, half of them will receive a medication with the first 7 days after the rejection. The remaining non-adherent subjects represent a subset that deserves further consideration. Particularly, research should begin on the clinical implications of non-adherence. Pharmacy Benefit Managers should give consideration to this and the financial implication of non-adherence when implementing Step Therapy in their plans.

REFERENCES

1. Motheral BR, Henderson R, Cox ER. Plan-sponsor savings and member experience with point-of-service prescription step therapy. *Am J Manag Care.* Jul 2004;10(7 Pt 1):457-464.
2. Cox ER, Henderson R, Motheral BR. Health plan member experience with point-of-service prescription step therapy. *J Manag Care Pharm.* Jul-Aug 2004;10(4):291-298.
3. Yokoyama K, Yang W, Preblick R, Frech-Tamas F. Effects of a step-therapy program for angiotensin receptor blockers on antihypertensive medication utilization patterns and cost of drug therapy. *J Manag Care Pharm.* Apr 2007;13(3):235-244.

APPENDIX A: COMPLETE LIST OF VARIABLES USED

Database Variable Name	**Variable Type**	**Database Variable Description**	**Values (examples)**
age	String	Age category of the beneficiary at the time of the claim.	0-4 5-14 15-17 18-24 25-34 35-44 45-64 65+
age_rec	Numeric	Recoded Age	1 = 0-4 2 = 5-14 7 = 15-17 3 = 18-24 4 = 25-34 5 = 35-44 6 = 45-64 8 = 65+
Authorizationnumber	String	Unique ID for each transaction	U000000000

Database Variable Name	Variable Type	Database Variable Description	Values (examples)
bengroup	String	The patient's beneficiary group	ADF ADS NADF NADS RET RETF UNK
bengroup_rec	Numeric	Recode of bengroup	1 = ADF 2 = ADS 3 = NADF 4 = NADS 5 = RET 6 = RETF 7 = UNK
birthdate	String	Patient's Date of Birth - Dropped from all data sets	5/2/1979
brandname	String	The brand name of the drug for claim filed	Lipitor
claimstatus	String	For each claim indicates Paid or Rejected	Paid Rejected
claimstatus_rec	Numeric	Recode of claimstatus	1 = Paid 2 = Rejected
cobindicator2	String	Coordination of benefit indicator. Indicates if the claim was filed with other health insurance.	Y = Yes N = No

Database Variable Name	Variable Type	Database Variable Description	Values (examples)
cobindicator_rec	Numeric	Recode of cobindicator2	1 = No 2 = Yes
cobindicator_rev	Numeric	A reverse of the cobindicator, used to place claims with other health insurance first for purpose of exclusion of subjects from sample	1 = Yes 2 = No
compoundcode	String	Indicates if the product dispensed was a compounded product	N = No Y = Yes NS = Not Sent
comptime	Numeric	Researcher calculated variable measuring the time, in days, between initial claim rejection and subsequent paid claim.	7
cutoffdate	Numeric	Researcher calculated variable set as the date of implementation plus 90	
datedispensed	String	Date prescription was filled	10/12/2010
datedispensed_rec	Date/Time	Recode of the date dispensed variable to fit STATA time	10/12/2010
date_paid	Date/Time	Value of datedispensed_rec for Paid Claims	10/12/2010

Database Variable Name	Variable Type	Database Variable Description	Values (examples)
date_rej	Date/Time	Value of datedispensed_rec for Rejected Claims	10/5/2010
dayssupply	Numeric	Days supply of the prescription calculated by the transmitting site's system	90
deersid	String	Patient's unique ID number for claims processing	123456789
dmrindicator	String	Indicates if the claim was processed as a paper filed claim, rather than electronically.	N = No Y = Yes
dmrindicator_rec	Numeric	Recode of dmrindicator	1 = No 2 = Yes
dmrindicator_rev	Numeric	A reverse of the dmrindicator, used to paper filed claims are listed first for purposes of subject removal	1 = Yes 2 = No
dosageform	String	Description of the drug form	Tablet
dropindicator	Numeric	Researcher defined variable indicating if the patient meets criteria to be dropped from the study sample	0 = No 1 = Yes

Database Variable Name	**Variable Type**	**Database Variable Description**	**Values (examples)**
firstmerge	String	Stata defined variable which indicates the results of the first merge procedure during analysis	_1 = Only present in Master _2 = Present other than Master _3 = Present in more than 1 dataset
gc3description	String	Description of drug grouping	Cardiovascular
gc4	String	Code indicating primary ingredient within First Data Bank (FDB)	A1AA
GCN	Numeric	Generic Code Number which is specific to the generic ingredient, dosage form and strength	35741
gcnsequencenumber	Numeric	Random number from PDTS representing the generic formulation	8348
genericindicator	String	Identifies drug as multi-source or single source. Brand or Generic	N = Unavailable O = Originator, generics available Y = Generic
genericname	String	Generic name of the drug filed with the claim	atorvastatin
genericname_paid	String	Generic name value for paid claims	atorvastatin
genericname_rej	String	Generic name value for rejected claims	rosuvastatin

Database Variable Name	Variable Type	Database Variable Description	Values (examples)
ndc	Numeric	National Drug Code as filed with the FDA	12345678901
otcindicator	String	Indetifies the drug filed as non-legend	Y = Yes N = No
pastcutoff	Numeric	Researcher defined variable indicating if the datedispensed is past the defined cutoff date	0 = No 1 = Yes
ppna	Numeric	Researcher defined variable indicating if the patient meets the criteria of precipitated primary non-adherence as evidenced by a rejected claim with no subsequent paid claim with 180 days	0 = No 1 = Yes
processeddatetime	String	Date and time the claim was processed by the adjudicator	10/12/2010 14:23
quantitydispensed	Numeric	Quantity of medication processed with the claim	90
rejcomp	Numeric	Researcher defined variable indicating the patient encountered a rejection and received a paid claim for another agent within 180 days	0 = No 1 = Yes

Database Variable Name	Variable Type	Database Variable Description	Values (examples)
rejectcode1	Numeric	For rejected claims, indicates the reason for rejection	75 = Failure of Step Therapy
rejectcode2	Numeric	For rejected claims, indicates the reason for rejection	75 = Failure of Step Therapy
rejectcode3	Numeric	For rejected claims, indicates the reason for rejection	75 = Failure of Step Therapy
servicecategoryclaim	String	Indicates the point of service the claim was processed at	MTF = Military Treatment Facility Mail Order Retail Theater = By military personnel at a location other than MTF VA CHDR = Processed by the VA for patients who are eligible for both VA and DOD benefits
servicecategoryclaim_paid	Numeric	Value of the servicecategoryclaim_rec for paid claims	1 = MTF 2 = Mail Order 3 = Retail 4 = Theater 5 = VA CHDR

Database Variable Name	Variable Type	Database Variable Description	Values (examples)
servicecategoryclaim_rec	Numeric	Recode of servicecategoryclaim	1 = MTF 2 = Mail Order 3 = Retail 4 = Theater 5 = VA CHDR
servicecategoryclaim_rej	Numeric	Value of the servicecategoryclaim_rec for rejected claims	1 = MTF 2 = Mail Order 3 = Retail 4 = Theater 5 = VA CHDR
sex	String	Gender of the patient at the time of the last PDTS transaction	F = Female M = Male . = Not on file
sex_rec	Numeric	Recode of sex	1 = Female 2 = Male
sponsorbranchofservice	String	The branch of service to which the sponsor belongs at the time of the last PDTS transaction	A = Army C = Coast Guard D = Office of SecDef F = Air Force H = Public Health Service M = Marine Corps N = Navy O = Nat Oceanic/Atmos 1 = Foreign Army 2 = Foreign Navy 3 = Foreign Marine Corps 4 = Foreign Air Force X = Not Applicable . = Not on file

Database Variable Name	Variable Type	Database Variable Description	Values (examples)
sponsorbranchofservice_rec	Numeric	Recode of sponsorbranchofservice	1 = A 2 = C 3 = D 4 = F 5 = H 6 = M 7 = N 8 = O 9 = X . = .
strength	String	The strength of the medication processed in the claim	10
_merge	Numeric	Stata defined variable which indicates the results of the second merge procedure during analysis	_1 = Only present in Master _2 = Present other than Master _3 = Present in more than 1 dataset

Table A1: Variables included in data analysis

APPENDIX B Complete Analysis Sequence

Recoding of the String Variables

1. Working from the original working 1 table, variables listed below were recoded from their original string form to a numeric or date form for use in the dataset.
    - Age
    - Bengroup
    - Claimstatus
    - Cobindicator
    - Datedispensed
    - Dmrindicator
    - Servicecategoryclaim
    - Sponsorbranchofservice
2. Original, unrecoded, variables or variables not of interest to final analysis were dropped from the table.
3. Table saved as working 2.

Description of the Complete Sample

1. Starting with the table working 2, observations were sorted first by deersid and then within deersid by beneficiary group, paper claim indicator, and other health insurance (OHI) indicator.
2. Only the first observation was retained for each deersid, certain to retain a claim that was a paper claim and/or was as an OHI claim, if one existed.
3. Descriptive variables were tabulated to describe the complete sample.
4. After initial analysis, a drop variable was constructed and populated with a value of 1 for individuals who met the following criteria:
    - Subjects with a cobindicator_rec value indicating the use of OHI.
    - Subjects with a dmrindicator_rec value indicating they had filed a paper claim.
    - Subjects with in an age category below 18 years old.

- Subjects with a missing gender value.
- Subjects with in a beneficiary group listed as “other”.
- Subjects whose sponsor branch of service was listed as NOAA, not applicable or missing.

5. Table saved as working 3.

Construction of the Study Sample

1. Starting with the working 2 table, values of the for the drop indicator were merged into each observation using the deersid as the link.
2. All observations containing a drop indicator of 1 were removed.
3. Table saved as working 4.

Description of the Study Sample

1. Starting with the table working 4, observations were sorted by deersid.
2. The first observation was retained for each deersid.
3. Descriptive variables were tabulated to describe the study sample.
4. The constructed table was saved as working 5.

Construction of the Reject Table

1. Starting with the table working 4, only rejected claims were retained.
2. Claims were then sorted by deersid and date dispensed.
3. The first observation for each deersid was retained for analysis.
4. A cutoffdate variable was created for each observation equal to the date of implementation plus 90 days.
5. A variable was created and populated with 1 for observations with a date processed greater than the cutoff date.
6. Variables for date processed, service category, and generic name were recoded for association with rejected claims.

7. Using “Keep” logic, retain only the first rejection for each patient. This step is used to eliminate redundant submission of a rejected claim resulting in a single claim for each patient in a given class.
8. Descriptive variables were tabulated to describe the sample of subjects with rejected claims, not including those who had rejection date beyond the cutoff period.
9. This table saved as reject 1 included the claims which were beyond the cutoff period.

Construction of the Paid Table

1. Starting with the table working 4, only paid claims were retained.
2. Variables for date processed, service category, and generic name were recoded for association with paid claims.
3. The table was saved as paid 1.

Merger of the Paid and Rejected Tables

1. Starting with the table paid 1, the unique rejected claim from reject 1 was merged to any matching paid claims by deersid.
2. Observations with a pastcutoff value of 1 from the rejected table were dropped from the analysis.
3. Variable for time to adherence (comptime) was created and calculated by taking the difference of the paid date and the rejected date.
4. Observations were sorted by deersid and comptime.
5. The first observation for each deersid with the lowest comptime was retained.
6. For subjects with no paid date or a comptime greater than 180 days, a PPNA variable was created and populated with 1.
7. For subjects other than PPNA a variable (rejcomp) was created and populated with a 1.
8. Table was saved as merged.

Analysis of the PPNA Subjects

1. Starting with the merged table, only subjects with a PPNA value equal to 1 were retained.
2. Descriptive variables were tabulated to describe the sample of subjects.
3. Table saved as PPNA.

Analysis of the Adherent Subjects

1. Starting with the merged table, only subjects with a PPNA value equal to 1 were retained.
2. Descriptive variables were tabulated to describe the sample of subjects.
3. The comptime variable was described according to range, mean, and standard deviations.
4. The comptime variable was analyzed by percentiles and plotted as a histograph for further description
5. Table saved as rejcomp.

Appendix 3: Sample of STATA Code

```
*coding.do
clear
insheet using "Q:\Step Therapy Analysis Data\LIP-1\working1.txt"
save "Q:\Step Therapy Analysis Data\LIP-1\Working1.dta", replace
use "Q:\Step Therapy Analysis Data\LIP-1\Working1.dta", clear
describe
summarize
codebook age
codebook bengroup
codebook sponsorbranchofservice
codebook cobindicator2
summarize sex
codebook sex
codebook servicecategoryclaim
codebook claimstatus
codebook dmrindicator
codebook genericindicator
codebook compoundcode
encode age, generate (age_rec)
replace age_rec = 3 if (age_rec == 4)
replace age_rec = 3 if (age_rec == 5)
label define agel 1 "Ages 0 - 4" 2 "Ages 15 - 17" 3 "Ages 18 - 44" 6
"Ages 45-64" 7 "Ages 5 - 14" 8 "Ages 65+"
label values age_rec agel
codebook age_rec
encode cobindicator, generate (cobindicator_rec)
codebook cobindicator_rec
encode sex, generate (sex_rec)
codebook sex_rec
encode servicecategoryclaim, generate (servicecategoryclaim_rec)
codebook servicecategoryclaim_rec
encode claimstatus, generate (claimstatus_rec)
codebook claimstatus_rec
encode bengroup, generate (bengroup_rec)
codebook bengroup_rec
encode sponsorbranchofservice, generate (sponsorbranchofservice_rec)
*recode the branch of service groups to combine smaller groups then
relabel
replace sponsorbranchofservice_rec = 2 if (sponsorbranchofservice_rec
== 3)
replace sponsorbranchofservice_rec = 2 if (sponsorbranchofservice_rec
== 5)
replace sponsorbranchofservice_rec = 2 if (sponsorbranchofservice_rec
== 8)
label define bosl 1 "Army" 2 "Other Service" 4 "Air Force" 6 "Marine
Corps" 7 "Navy" 9 "Not Applicable"
label values sponsorbranchofservice_rec bosl
codebook sponsorbranchofservice_rec
encode dmrindicator, generate (dmrindicator_rec)
codebook dmrindicator_rec
```

```
tabulate claimstatus_rec
tabulate bengroup_rec claimstatus_rec, row
generate datedispensed_rec=date(datedispensed, "MDY")
format datedispensed_rec %d
drop age bengroup datedispensed sponsorbranchofservice cobindicator2
sex servicecategoryclaim claimstatus dateprocessed genericindicator
dmrindicator compoundcode birthdate
save "Q:\Step Therapy Analysis Data\LIP-1\Working2.dta", replace

*working3.do
use "Q:\Step Therapy Analysis Data\LIP-1\Working2.dta", clear
gen dmrindicator_rev = .
replace dmrindicator_rev = 1 if dmrindicator_rec ==2
replace dmrindicator_rev = 2 if dmrindicator_rec ==1
gen cobindicator_rev = .
replace cobindicator_rev = 1 if cobindicator_rec ==2
replace cobindicator_rev = 2 if cobindicator_rec ==1
sort deersid age_rec bengroup_rec dmrindicator_rev cobindicator_rev
quietly by deersid: keep if _n==1
keep deersid age_rec  cobindicator_rec sex_rec bengroup_rec
sponsorbranchofservice_rec dmrindicator_rec
gen cobdropindicator = 0
replace cobdropindicator = 1 if cobindicator_rec ==2
gen dmrdropindicator = 0
replace dmrdropindicator = 1 if dmrindicator_rec ==2
gen agedropindicator = 0
replace agedropindicator = 1 if inlist(age_rec, 1,2,7)
gen sexdropindicator = 0
replace sexdropindicator = 1 if sex_rec ==.
gen bendropindicator = 0
replace bendropindicator = 1 if  bengroup_rec == 7
gen bosdropindicator = 0
replace bosdropindicator = 1 if inlist(sponsorbranchofservice_rec, 9,.)
codebook age_rec
tab age_rec
codebook bengroup_rec
tab bengroup_rec
codebook sex_rec
tab sex_rec
codebook sponsorbranchofservice_rec
tab sponsorbranchofservice_rec
codebook dmrindicator_rec
tab dmrindicator_rec
codebook cobindicator_rec
tab cobindicator_rec
save "Q:\Step Therapy Analysis Data\LIP-1\working3.dta", replace
drop if agedropindicator ==1
drop if bendropindicator ==1
drop if dmrdropindicator ==1
drop if cobdropindicator ==1
drop if bosdropindicator ==1
```

```
*working4.do
use "Q:\Step Therapy Analysis Data\LIP-1\Working2.dta", clear
sort deersid
drop  age_rec cobindicator_rec dmrindicator_rec sex_rec bengroup_rec
sponsorbranchofservice_rec
merge deersid using "Q:\Step Therapy Analysis Data\LIP-1\working3.dta"
drop if agedropindicator ==1
drop if bendropindicator ==1
drop if dmrdropindicator ==1
drop if cobdropindicator ==1
drop if bosdropindicator ==1
codebook authorizationnumber
gen firstmerge = _merge
drop _merge
save "Q:\Step Therapy Analysis Data\LIP-1\working4.dta", replace
```

```
*working5.do
*this describes the dataset without drops for out of range
*use this and subtract reject number to get total number dropped for
range
use "Q:\Step Therapy Analysis Data\LIP-1\Working4.dta", clear
keep deersid age_rec bengroup_rec sex_rec sponsorbranchofservice_rec
sort deersid age_rec bengroup_rec
quietly by deersid: keep if _n==1
describe deersid
codebook age_rec
tab age_rec
codebook bengroup_rec
tab bengroup_rec
codebook sex_rec
tab sex_rec
codebook sponsorbranchofservice_rec
tab sponsorbranchofservice_rec
save "Q:\Step Therapy Analysis Data\LIP-1\working5.dta", replace
```

```
*rejectfile
*builds the rejected claim database and describes users
use "Q:\Step Therapy Analysis Data\LIP-1\Working4.dta" if
claimstatus_rec==2, clear
codebook claimstatus_rec
sort deersid datedispensed_rec
quietly by deersid: keep if _n==1
gen cutoffdate = td(6Oct2010) +90
format cutoffdate %d
generate pastcutoff = 0
replace pastcutoff = 1 if datedispensed_rec > cutoffdate
describe
save "Q:\Step Therapy Analysis Data\LIP-1\Reject1.dta", replace
gen date_rej = datedispensed_rec
gen servicecategoryclaim_rej = servicecategoryclaim_rec
gen genericname_rej = genericname
format date_rej %d
keep sponsorbranchofservice_rec pastcutoff deersid age_rec bengroup_rec
sex_rec date_rej servicecategoryclaim_rej genericname_rej
save "Q:\Step Therapy Analysis Data\LIP-1\Reject1.dta", replace
drop if pastcutoff == 1
tab age_rec
tab bengroup_rec
tab sex_rec
tab servicecategoryclaim_rej
tab genericname_rej
tab sponsorbranchofservice_rec
save "Q:\Step Therapy Analysis Data\LIP-1\Reject2.dta", replace
```

```
*paidfile
use "Q:\Step Therapy Analysis Data\LIP-1\Working4.dta" if
claimstatus_rec==1, clear
codebook claimstatus_rec
sort deersid datedispensed_rec
gen date_paid = datedispensed_rec
gen servicecategoryclaim_paid = servicecategoryclaim_rec
gen genericname_paid = genericname
format date_paid %d
keep sponsorbranchofservice_rec date_paid deersid
servicecategoryclaim_paid genericname_paid
save "Q:\Step Therapy Analysis Data\LIP-1\Paid1.dta", replace
```

```
*merge.do
use "Q:\Step Therapy Analysis Data\LIP-1\paid1.dta", clear
merge deersid using "Q:\Step Therapy Analysis Data\LIP-1\reject1.dta"
drop if pastcutoff == 1
gen ppna = 0
gen nonrej = 0
gen rejcomp = 0
gen comptime = .
replace comptime = (date_paid - date_rej)
replace comptime = 9999 if comptime < 0
sort deersid comptime
quietly by deersid: keep if _n==1
replace ppna = 1 if missing(date_paid)& date_rej > 0
replace nonrej = 1 if missing(date_rej)
replace ppna = 1 if comptime > 180
replace rejcomp = 1 if nonrej < 1& ppna < 1
replace comptime = . if comptime >180
save "Q:\Step Therapy Analysis Data\LIP-1\merged.dta", replace
```

```
*describeppna
use "Q:\Step Therapy Analysis Data\LIP-1\merged.dta"
keep if ppna == 1
tab age_rec
tab bengroup_rec
tab sex_rec
tab servicecategoryclaim_rej
tab genericname_rej
tab sponsorbranchofservice_rec
save "Q:\Step Therapy Analysis Data\LIP-1\ppna.dta", replace
```

```
*describerejcomp
use "Q:\Step Therapy Analysis Data\LIP-1\merged.dta"
keep if rejcomp == 1
tab age_rec
tab bengroup_rec
tab sex_rec
tab servicecategoryclaim_rej
tab genericname_rej
tab servicecategoryclaim_paid
tab genericname_paid
tab sponsorbranchofservice_rec
summarize comptime, detail
hist comptime, frac
save "Q:\Step Therapy Analysis Data\LIP-1\rejcomp.dta", replace
```

```
*logistic
use "Q:\Step Therapy Analysis Data\LIP-1\merged.dta", clear

collin  bengroup_rec sex_rec servicecategoryclaim_rej age_rec
sponsorbranchofservice_rec

xi: logistic  ppna i.bengroup_rec i.sex_rec i.servicecategoryclaim_rej
i.age_rec i.sponsorbranchofservice_rec
```