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Evaluation of Testosterone Prior Authorization and Step Therapy in the Department of Defense: Costs, Utilization, Adherence, and Persistence

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Evaluation of Testosterone Prior Authorization and Step Therapy in the Department of Defense: Costs, Utilization, Adherence, and Persistence

by

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Dedication

I dedicate this work to the men and women that are serving or have served in the United States Armed Forces and their families. Your commitment and sacrifice is an inspiration.

Disclaimer: "The views expressed in this document are those of the author and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U.S. Government."

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Evaluation of Testosterone Prior Authorization and Step Therapy in the Department of Defense: Costs, Utilization, Adherence, and Persistence

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Testosterone utilization rates have increased significantly in the last 10 years as demonstrated in the United Kingdom, Australia, United States, and by the US Department of Defense. Studies show that patients treated with testosterone may not be adherent or persistent, and exhibit patterns of restarting, switching, and cycling on testosterone therapy. These medication use behaviors may not be readily detected with traditional persistence measures. Managed care organizations and the Department of Defense responded to increased testosterone use by implementing prior authorization and step therapy programs in order to ensure safe, appropriate use of testosterone. Previous testosterone use studies failed to account for the widespread use of these utilization programs for testosterone products. The purpose of this study was to evaluate changes in testosterone costs, utilization, and medication use behavior before and after the March 1, 2013 implementation of prior authorization and step therapy programs by the Department of Defense.

This study included adult men, 18 years of age or older, from the Department of Defense Military Health System who received testosterone (other than injectable or implant) any time from March 1, 2012 through February 28, 2014. Data were extracted from the Department of Defense Pharmacy Data Transaction Service.

From March 1, 2012 to February 28, 2014, there were 78,623 patients in the Department of Defense using the included forms of testosterone. Of those patients, 26,464 (33.7%) had testosterone therapy only in the pre-index period, 18,111 (23.0%) had prescriptions only in the post-index period, while the remaining 34,048 (43.3%) patients had prescriptions both before and after implementation. Testosterone costs decreased by $27.5 million in the year following implementation of PA and ST programs. During the post-implementation year there were over 8,000 less patients started on testosterone treatments, and over 20,000 less testosterone prescriptions dispensed compared to the pre-intervention year. In the pre-PA/ST period, adherence (as measured by a medication possession ratio of 0.80 or greater) was 55.22%, and in the post-PA/ST period adherence was 53.46%. The percent of persistent patients using a 30-day gap, a 60-day gap and a gap of 1.5 times the previous days supply was calculated. In the pre-index period this rate was 64%, 75% and 58% respectively; similar to the rates in the post-index period (63%, 74% and 56% respectively). In the post-PA/ST period, 19.10% of patients switched products, 23.39% restarted therapy, and 18.60% of patients had cycles of therapy. When comparing only the 34,048 patients with prescriptions both before and after the PA/ST implementation, the mean gap period pre-index was 47 (SD

69) days but the gap at the point of implementation averaged 94 (SD 100) days (p <0.001).

Post PA/ST costs were lower, adherence and persistence rates were similar (although statistically significantly different) between the two periods, but the gap in receiving treatment after the PA/ST was implemented may be cause for concern. This study adds to the existing testosterone use literature, specifically how prior authorization and step therapy programs influence testosterone use behaviors. The effectiveness and impact of testosterone benefit design will inform future Department of Defense formulary decisions and deepen understanding of testosterone use behaviors.

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List of Abbreviations

ADAM	Androgen deficiency in the aging male
AHFS	American Hospital Formulary Service
AIDS	Acquired immune deficiency syndrome
AMCP	Academy of Managed Care Pharmacy
AMS	Aging Males' Symptoms
BMI	Body mass index
BPH	Benign prostatic hyperplasia
CDM	Clinformatics DataMart
DAX-1	Dosage sensitive sex-reversal (DSS), adrenal hypoplasia congenita (AHC) critical region on the X-chromosome, gene 1
DHA	Defense Health Agency
DoD	Department of Defense
DSA	Data Sharing Agreement
EBPWG	Evidence-Based Practice Guideline Work Group
ESI	Express Scripts, Incorporated
FDA	Food and Drug Administration
GCN	Generic code number
HIM	Hypogonadism in Males
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IM	Intramuscular
LOH	Late onset hypogonadism
MCO	Managed care organization
MHS	Military Health System
MI	Myocardial infarction
MMAS	Massachusetts Male Aging Study
MN	Medical necessity
MPR	Medication possession ratio
MTF	Military treatment facilities
P&T	Pharmacy and Therapeutics
PA	Prior authorization
PDC	Proportion of days covered
PDE-5	Phosphodiesterase-5
PDTS	Pharmacy Data Transaction Service
POE	Provider order entry

POS	Point of service
PRO	Patient reported outcomes
PRSD	Proportion of recommended starting dose
PSA	Prostate-specific antigen
ST	Step therapy
TBD	To be determined
TD	Testosterone deficiency
TDS	Testosterone deficiency syndrome
TMOP	Tricare Mail Order Pharmacy
TRT	Testosterone replacement therapy
TTh	Testosterone therapy
UF	Uniform formulary
UK	United Kingdom
US	United States
VA	Veteran’s Affairs
VHA	Veteran's Health Administration
VTE	Venous thromboembolism

Chapter 1: Introduction

Do you lack energy? Are you feeling grumpy? Do you fall asleep after dinner? Are you male? If you answered yes to any of these questions, there is a chance you suffer from a treatable condition known as Low-T. Talk to your doctor about Low-T and find out how testosterone therapy can help you.[1]

This is the message testosterone manufacturers are sending to American men in order to capitalize on a rapidly expanding market for testosterone replacement therapy (TRT) or testosterone therapy (TTh). In the United States (US), the testosterone market generated $1.9 billion in sales in 2012.[2] This market is projected to increase to $5.1 billion by 2018.[3] By 2025, there will be as many as 6.5 million men in the US, 30 to 79 years old, with symptomatic low testosterone. This is a 38% increase from 2000 estimates.[4]

Testosterone use in the US is increasing, however, testosterone patients may not be adherent or persistent, and exhibit patterns of restarting, switching, and cycling not detected with traditional persistence measures.[5–7] The reasons for this behavior remain unknown.[5,6] Simultaneously, managed care organizations (MCOs) are using utilization management tools such as prior authorization (PA) and step therapy (ST) to manage costs and utilization of testosterone. PA and ST strategies may have a negative impact on patient adherence, [8] however, the impact of PA and ST on testosterone use behaviors specifically has not been studied.

The Department of Defense (DoD) PA and ST programs are unique because all patients, even established testosterone users, were required to complete the PA and ST process. In addition, a “no-grandfathering” policy for PA and ST programs is atypical for the DoD. A review of the results of this deviation from normal conditions may impact future policy decisions. Finally, greater understanding of switching, restarting, and cycling behaviors is needed. This study expands the understanding of testosterone use behaviors by considering the presence of drug benefit controls that may contribute to previously documented non-persistence in testosterone use. This retrospective evaluation of utilization, costs, and medication use behaviors in testosterone therapy is warranted and will contribute significantly to the growing literature on testosterone use and the impacts of formulary management tools on medication use behaviors.

The following literature review explains the rationale and need for an examination of how benefit design impacts testosterone use behaviors. First, hypogonadism, or testosterone deficiency (TD), the condition known in marketing as “Low-T,” will be discussed, followed by a review of TTh and trends in TTh. Next, the behaviors of interest, persistence and adherence, as well as switching, restarting, and cycling, will be discussed followed by a review of PA and ST. In addition, there will be an examination of literature exploring the impacts of benefit design and formulary management on medication use behavior. Finally, the study setting, the DoD, and its testosterone utilization trends and utilization management tools will be described followed by the study methods, results, and discussion..

Chapter 2: Literature Review

This literature review will discuss the disease state of hypogonadism, testosterone therapy (TTh) use, TTh trends, and testosterone use behaviors such as adherence, persistence, switching, restarting, and cycling. The economic burden of TTh that drives managed care organizations (MCOs) to use prior authorization (PA) and step therapy (ST) to manage testosterone utilization will be discussed in detail. Finally, an example of testosterone PA and ST programs used by the Department of Defense (DoD) Military Health System (MHS) will be presented.

HYPOGONADISM AND TESTOSTERONE DEFICIENCY

Hypogonadism is the failure of the testes to produce physiological levels of testosterone due to disruption of the hypothalamic-pituitary-testicular axis.[9] Hypogonadism is also known as androgen deficiency, testosterone deficiency syndrome (TDS), or low testosterone.[10] Patients with TDS experience sleep disturbance (33.0%), low physical performance (18.2%), low libido (11.6%), erectile dysfunction (16.3%), depressed mood (15.4%), lethargy (11.2%), and osteoporosis or osteoporotic fracture (1.4%).[4] They may also experience decreased volume of ejaculate, loss of body and facial hair, decreased lean body mass, increased body fat, poor concentration, and anemia, but the specific frequencies of these symptoms are not known.[9,11] These symptoms result in significant detriment to quality of life and can impact multiple organ systems.[12]

According to the Hypogonadism in Males (HIM) study, the prevalence of hypogonadism in the United States (US) in men 45 years or older is estimated to be

38.7%.[11] The prevalence of hypogonadism is 34.0% in ages 45 to 54, 40.2% in ages 55 to 64, 39.9% in ages 65 to 74, 45.5% in ages 75 to 84, and 50.0% in patients 85 years of age and over.[11] The Massachusetts Male Aging Study (MMAS) found lower prevalence rates of hypogonadism than the HIM. The MMAS found hypogonadism prevalence of 7.1% in men ages 48 to 59, 11.5% in ages 60 to 69, and 22.8% in ages 70 to 79.[13]

It is important to note, however, that the HIM and the MMAS used different definitions of hypogonadism. The HIM defined hypogonadism as evidence of one total testosterone level < 300 ng/dL or previous diagnosis of hypogonadism and receiving treatment regardless of measured total testosterone levels.[11] The MMAS had two methods of defining hypogonadism. Both methods required the presence of at least three signs or symptoms of hypogonadism. In addition, both methods also required laboratory evidence of low testosterone. Method one required one laboratory measure of total testosterone <200 ng/dL. Method two required one laboratory measure of total testosterone of 200 - 400 ng/dL and free testosterone < 8.91 ng/dL.[13]

The more strict definition of hypogonadism used in the MMAS explains why the prevalence in the MMAS is much lower than the HIM. The two studies do agree, however, that the prevalence of hypogonadism increases as age increases. Testosterone declines approximately 1% each year after the age of 30.[12,14,15] A clinically consequential decrease in testosterone due to aging is known as androgen deficiency of the aging male (ADAM), andropause, or late onset hypogonadism (LOH). While an exact total testosterone level for diagnosis is not specified, the Endocrine Society states that the lower limit for the normal range established by the reference laboratory should be used.

This value is usually around 300 ng/dL.[10] Diagnosis criteria are discussed further in the diagnosis section of this chapter.

The HIM explored prevalence by age as well as by comorbidities. For example, the prevalence of hypogonadism is 52.4% in obese patients and 50.0% in patients with diabetes.[11] Cardiovascular comorbidities such as obesity, metabolic syndrome, and type two diabetes mellitus are associated with low testosterone.[16] The burden of these comorbidities is thought to be the major cost driver for patients with low testosterone.[17]

One study using the Ingenix Employer Solutions database, which represents 55 large self-insured American companies, sought to compare direct and indirect healthcare costs for men with a diagnosis of hypogonadism and at least one testosterone prescription against a matched cohort without hypogonadism. In the study population of 4,269 men ages 35 to 64, the men with hypogonadism had higher rates of hyperlipidemia (50.2% vs. 25.3%), hypertension (37.7% vs. 21.1%), back or neck pain (32.0% vs. 15.7%), and human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS) (7.1% vs. 0.3%) (all $p<0.0001$). Even after adjusting for higher comorbidity rates in the hypogonadism group, the hypogonadism group had significantly higher mean direct costs during the study period compared to the control group ($9,291 [$10,202] vs. $5,248 [$5,762], $p < 0.0001$) and higher indirect costs ($2,729 [$2,111] vs. $1,840 [$1,423], $p < 0.001$) than the control group.[17]

Additionally, low testosterone may increase mortality. In a population of Veteran's Health Administration (VHA) men forty years old or older, testosterone levels less than 250 ng/dL were associated with increased risk of mortality (1.68, 95% CI, 1.14-2.48, p <

0.001) compared to men with normal testosterone.[18] A follow-up study conducted in a national VHA population compared mortality in men with hypogonadism treated with testosterone replacement therapy (TRT) to those without treatment. After adjusting for age, body mass index (BMI), testosterone level, medical morbidity, diabetes, and coronary heart disease, the overall mortality for treated men was associated with a decreased risk of mortality (0.61, 95% CI, 0.42 - 0.88).[19] In general, low testosterone is associated with increased morbidity and mortality, however, this association varies by the type of hypogonadism.

Types of Hypogonadism

There are three categories of hypogonadism: primary testicular failure, secondary testicular failure, and combined primary and secondary. Another preferred terminology is testosterone deficiency (TD). Each type has different causes and consequences. Primary testicular failure is caused by abnormalities of the hypothalamic-pituitary-thyroid axis at the testicular level and results in decreased testosterone levels, spermatogenesis impairment, and elevated gonadotropin levels.[10] Secondary hypogonadism occurs in defects of the central hypothalamus or pituitary axis which cause testicular failure and results in decreased testosterone levels, spermatogenesis impairment, and low to low-normal gonadotropin levels.[10] The third type, combined primary and secondary hypogonadism, results in low testosterone, impaired spermatogenesis, and variable gonadotropin levels.[10]

Combined primary and secondary hypogonadism occurs in hemochromatosis, sickle cell disease, thalassemia, glucocorticoid treatment, alcoholism, dosage sensitive sex-

reversal adrenal hypoplasia congenital critical region on the X-chromosome gene 1 (DAX-1) mutations, and in older men.[10] The decline in testosterone related to age is believed to result from defects in both testicular function and hypothalamic-pituitary function and therefore this mixed type of hypogonadism is generally the type experienced by aging men.[10]

Diagnosis

The Endocrine Society suggests making a diagnosis of androgen deficiency in men with consistent symptoms or signs of low testosterone and "unequivocally low serum testosterone levels." The Endocrine Society recommends a morning total testosterone test followed by a confirmatory morning test.[10] While an exact total testosterone level for diagnosis is not specified, the Endocrine Society states that the lower limit for the normal range established by the reference laboratory should be used. This value is usually around 300 ng/dL.[10]

According to the Endocrine Society, making a hypogonadism diagnosis can be difficult. First, signs and symptoms are nonspecific, and they are confounded by age, comorbidities, severity, and duration of deficiency. Additionally, laboratory measurement of testosterone presents many challenges. Testosterone levels vary with circadian cycles; therefore, testosterone laboratory testing should be conducted in the morning, but this recommendation is frequently not followed.[10,20] Complicating laboratory values further, there are multiple ways to measure testosterone such as free, bound, and total levels.[10] The guidelines are clear, however, on which patients should be treated with TRT.[10]

Treatment

The Endocrine Society recommends TRT for symptomatic men with classic androgen deficiency symptoms and low testosterone levels. The goal of treatment is to improve sexual function, improve sense of well-being, increase bone mineral density, induce or maintain secondary sex characteristics, improve fat free mass, and increase muscle strength.[10] Objectively, the success of TRT is determined by measuring testosterone levels pre and post treatment. The Endocrine Society recommends monitoring testosterone levels three to six months after initiation with target testosterone levels that vary depending on the testosterone form used. In general, a testosterone level between 350 and 750 ng/dL, which is considered a mid- to normal- range for healthy, young men is recommended.[10]

The Endocrine Society's 2010 clinical practice guidelines for androgen deficiency do not state a specific testosterone threshold for LOH treatment. The panel of authors could not agree on a threshold recommendation for TRT in older men – as a decline in testosterone is expected as men age. Instead, the panel recommended that additional research should be conducted. Panelists did agree, however, that older men should be treated depending on the severity of their symptoms.[10]

There are many forms of TRT available. According to Lexi-comp, as of June 2015, testosterone forms available in the United States (US) include long-acting injectable, transdermal gel, transdermal solution, transdermal cream, transdermal ointment, transdermal patches, nasal gel, buccal adhesive tablets, and pellet implants.[21]

The particular product selected depends on patient preference, pharmacokinetics, treatment burden, and cost.[10]

One of the most popular testosterone products is Androgel. There are two strengths of Androgel available. The newer product of the two, Androgel 1.62%, requires the application of a smaller volume of gel for the starting dose than Androgel 1%, the older product. Androgel 1.62% is available in packets as well as a pump whereas the 1% is only available in packets.[22,23] Testosterone 1% gel was approved in a generic form in 2012. Androgel 1.62% became available in 2011.[24]

Each particular testosterone product has a recommended starting dose, maintenance dose, and dosing range that vary depending on dosage form and concentration.[22,23,25–28] Schoenfeld et al. categorized doses as low (< 50 mg/day), standard (50 mg/day), and high (> 50 mg/day) for Testim and Androgel. Other studies described dose as a proportion of recommended starting dose in order to standardize the daily dose across products. The dose as a proportion of recommended starting dose per day was calculated by first calculating the total number of milligrams of testosterone dispensed divided by the number of days supply for each prescription. This established the milligrams of testosterone per patient per day. The number of calculated milligrams of testosterone per day is then divided by the recommended number of milligrams recommended by the manufacturer as the starting dose per day to establish a proportion of the recommended starting dose.[29] The recommended starting dose is available for each individual product in the prescribing information.[22,23,25–28]

Known adverse events associated with testosterone include erythrocytosis, acne and oily skin, detection of subclinical prostate cancer, growth of metastatic prostate cancer, and reduced sperm production and fertility (without the addition of gonadotropin-releasing hormones).[10] In addition, each formulation has specific adverse events such as skin reactions for topical products (17% - 37%)[21], gum irritation for buccal products (9.2%)[30], and injection site irritation for injectable products (5%).[10] The impact of these adverse events and patient perception of treatment success can be measured using patient reported outcomes (PROs).

The subjective measure of TRT success, symptom relief, is best measured using PROs such as health related quality of life (HRQoL) measures.[31] Many instruments have been developed to measure HRQoL in men with LOH such as the Aging Males' Symptoms (AMS) scale, MMAS Questionnaire, and ADAM scale.[10,31] Each instrument varies in specificity to hypogonadism, objective, domains covered, reliability, validity, and responsiveness. The use of HRQoL studies for TRT captures how patients perceive the effectiveness of TRT, which may influence medication use behavior in this population.

Moore et al. used the AMS to assess treatment effects of testosterone after 12 weeks of TRT in Germany. They found that patients with the worst HRQoL (highest AMS score) before treatment experienced the greatest improvement in HRQoL (decrease in AMS score) with treatment. On average, patients experienced a 31.8% improvement overall in AMS scores.[32]

Behre et al. found that in British patients with low-normal testosterone, HRQoL as measured by the AMS improved with 1% testosterone gel treatment after six months compared to placebo. However, after 12 months there was no additional improvement in HRQoL.[33] This raises the question of whether topical testosterone produces sustained symptom relief which would encourage patients to continue therapy. The length of time needed to experience symptom relief may also influence TRT use behaviors.

In LOH, the effects of testosterone treatment are not immediately perceptible. Many effects are detectable after three weeks of treatment, but may take longer and vary widely from patient to patient.[34] Erection and ejaculation changes take up to six months for detectable differences.[34] In addition, many of the improvements from testosterone treatment plateau with continued use.[34] Symptoms related to HRQoL, such as sexual interest and improved mood, require three to six weeks to detect changes and plateau at six weeks and 18 to 30 weeks, respectively. Changes in fat mass, lean body mass, and muscle strength stabilize after six to 12 months.[34] Patients may struggle to see the benefits of treatment in a meaningful way and may become impatient and discontinue treatment due to lack of perceived benefits or sustained benefits. Additionally, continuously declining testosterone may present as a worsening of symptoms.[15] Another possible reason to reconsider TRT is the increasing safety concerns associated with TRT.

TESTOSTERONE SAFETY

While there is evidence of the benefits of testosterone therapy, the risks of testosterone treatment are a highly debated topic. Testosterone is contraindicated in men with prostate or breast cancer, men with a palpable prostate nodule or induration, or

prostate-specific antigen (PSA) greater than 3 ng/dL due to the association of testosterone therapy with an elevated risk of prostate events such as cancer and benign prostatic hyperplasia (BPH).[9] In addition to potential prostate problems, testosterone has been linked to cardiovascular risks including heart attack, stroke, and blood clots.[35,36]

The risks of cardiovascular events in TRT are controversial. In a retrospective study of a national cohort of men in the VHA system with testosterone levels < 300 ng/dL who underwent coronary angiography from 2005 – 2011, Vigen et al. aimed to assess the association between testosterone therapy and all-cause mortality, myocardial infarction (MI), and stroke. Initiation of testosterone therapy was defined as filling one prescription for testosterone gel, patch, or injection following coronary angiography. Therapy was assumed to be continued until an outcome event occurred or the end of the follow-up period. Patients were categorized in the testosterone treatment group after just one prescription.

Overall, the patients on testosterone therapy had an increased risk of adverse outcomes such as mortality, MI, and stroke. Of 8,709 men with testosterone lower than 300 ng/dL, 1,223 patients started testosterone therapy after a median of 531 days after coronary angiography. The Kaplan-Meier absolute risk difference of having one of the outcome events between the no testosterone group and the testosterone group was 5.8% (95% CI, -1.4% to 13.1%). After adjusting for presence of coronary artery disease, testosterone use was associated with increased risk of an adverse outcome (hazard ratio, 1.29, 95% CI, 1.04 to 1.58).

Of the 1,223 patients that initiated testosterone therapy, 17.6% only filled one prescription. Of the patients that filled more than one prescription, the mean number of days from the first fill to the last fill was 376 days. Of those prescribed testosterone, 60% had at least one testosterone level checked after testosterone initiation, and the mean level at that check was 332.2 ng/dL.[37]

While this does raise questions about a possible relationship between testosterone and cardiovascular events, the assumption that one prescription constitutes adequate exposure to testosterone and therefore, a long enough exposure to be associated with adverse outcomes is a tenuous assumption. Of the patients that filled more than one prescription, it is not known if the patient used testosterone continuously from the first fill to the last fill. The definition of the testosterone group may have been too broad to indicate testosterone therapy is associated with increased risk of adverse outcomes.

This study prompted multiple responses. One response from an endocrinologist stated that the Vigen et al. study contributed to the mounting evidence of a signal of cardiovascular risk with testosterone. However, without large, long-term, randomized trials to conclusively assess long-term benefits and risks of testosterone therapy, this study alone is not enough to show a significant association with increased risk of cardiovascular events. In addition, the Vigen et al. study had limited generalizability because of the uniqueness and specificity of the VHA population.[38] Another issue that erodes the quality of this study is the necessity to publish a correction to the text and figures due to misclassification of patients and publishing of incorrect data.[39]

In men 65 years and older, Finkle et al. found an increased rate of MI up to ninety days after filling a prescription for testosterone, compared to the twelve months prior to initiating testosterone. Comparing the incidence of MI after testosterone to before testosterone, the rate ratio for MI was 2.19 (95% CI, 1.27 to 3.77).[40] Critics of this study felt that the reported excess risk is clinically insignificant and pointed to the possibility that patients newly diagnosed with low testosterone are at risk for cardiovascular events, and that the risk of events may have diminished outside of the 90-day follow-up period.[41]

Consequently, cardiovascular risks are not known, but the Food and Drug Administration (FDA) found this trend compelling enough to issue a safety communication alert for testosterone products and the risk for stroke, heart attack, and death.[42] The FDA also issued a warning about the potential for blood clots.[35] Lastly, concerns of topical product transfer to women and children prompted the FDA to require a Risk Evaluation and Mitigation Strategy Medication Guide, as well as label changes, reflecting this risk.[36]

In September 2014, The Bone, Reproductive and Urologic Drugs Advisory Committee of the Drug Safety and Risk Management Advisory Committee of the FDA voted to further restrict FDA indications for testosterone in order to reduce the number of patients using testosterone for “age-related” purposes rather than previously approved indications.[43] Furthermore, the committee recommended that the FDA not approve an application from Clarus Therapeutics for a new oral testosterone product named Rextoro.[44] The committee expressed concerns that an oral form of testosterone may be susceptible to abuse and emphasized general concerns of testosterone safety.[44]

In light of ongoing controversy surrounding testosterone safety, there is a clear need for conclusive studies about testosterone safety. In the absence of large, randomized, controlled studies assessing testosterone benefits and risks, the trend of increasing testosterone use is concerning. Millions of men are in what has been called, "A mass, uncontrolled experiment that invites men to expose themselves to the harms of a treatment unlikely to fix problems that may be wholly unrelated to testosterone levels."[45] The extent of this increase in testosterone utilization is discussed further in the following section.

TESTOSTERONE TRENDS

It is projected that the US will have 25 million men with LOH by 2025.[46] Testosterone replacement manufacturers are working hard to capture this market. AbbVie, the makers of Androgel, launched a campaign known as "Is it Low-T?" aimed to raise awareness of low testosterone symptoms. AbbVie is especially focused on aging men experiencing symptoms of low testosterone due to routine aging.

The "Low-T" campaign uses a modified form of the AMS as a screening tool for patients and spouses to encourage them to talk to their doctor about TRT. The AMS is not designed to be a screening tool.[47] In addition, the Endocrine Society recommends against screening for androgen deficiency in the general population due to lack of data on the how available screening tools perform and because the benefits and adverse consequences of TRT are unclear.[10] Low-T "quizzes" lack specificity for low testosterone. A "positive" quiz may trigger a patient to seek treatment for low testosterone.[45]

Through population-wide disease awareness marketing, AbbVie successfully increased Androgel market share by 19% from November 1, 2011 through October 31, 2012 resulting in $1.37 billion in sales. Androgel represented 72% of the $1.9 billion US testosterone market during that time.[2] There are many skeptics of this marketing activity, and many see these campaigns as the commercialization of a disease.[45]

Even in countries that prohibit direct-to-consumer advertising, the use of testosterone is growing. In the United Kingdom (UK), testosterone prescribing increased 90% in 10 years from 157,602 prescriptions in 2001 to 298,134 in 2010.[48] In Australia, testosterone prescribing doubled from 1992 to 2010, driving annual expenditures up nine-fold to $12.7 million per year.[49]

The VHA, which authors considered "relatively insulated from marketing," exhibited increasing rates of exogenous testosterone use from October 1, 2010 through September 30, 2011 in men who did not test positive for HIV and with at least one outpatient visit or hospitalization in the VHA system.[50] Researchers found that 1.67% of the men included in the study received exogenous testosterone from a VHA pharmacy during the study period. Rates of testosterone use varied from 0.3% to 3.7% depending on the VHA site. Injectable, topical, and oral capsules of testosterone were included.

Total spending on those testosterone products during that time period was $20.9 million. The authors emphasized that rates of utilization varied widely between each VHA site and there may have been high rates of off-label prescribing of testosterone.[50] The authors recognized that their findings bring to light the need for standardized practices VHA wide that are consistent with existing evidence and guidelines.[50] As of

November 2014, the Veteran's Affairs (VA)/DoD Evidence-Based Practice Guideline Work Group (EBPWG) has not established a clinical practice guideline for testosterone use.[51] The authors mentioned that they plan to conduct a follow-up study examining patient-level and site-level predictors of testosterone use.[50]

Even in health care systems with standardized guidelines, there are concerning trends in testosterone use. In Saskatchewan, Canada, from 1976 to 2008, Hall et al. identified 11,521 testosterone users who received a median of two prescriptions for testosterone.[52] In 1976 the number of testosterone users per 1,000 men in the Saskatchewan population was 1.6. From 1994 to 1999 the annual rate of use increased on average by 24.7%, peaking at 4.2 testosterone users per 1,000 men in the Saskatchewan population. [45]

Rates of testosterone use declined from 2002 to 2008, possibly due to the new availability of phosphodiesterase-5 (PDE-5) inhibitors, such as sildenafil, during that time.[52] Until 1999, androgen products were prescribed for erectile dysfunction. When PDE-5 inhibitors became available, patients may have switched to them instead of using testosterone.[52] Also, in 2006, Health Canada informed testosterone manufacturers that testosterone could not be indicated for general purposes such as "andropause." This change may have contributed to the decrease in testosterone use from 2006 to 2008.[52] Differences in health care delivery between Canada and the US make this study difficult to generalize to US patients.

Specific studies in the US show dramatic increases in testosterone use starting in 2001. Testosterone trends were studied using a large, commercially insured population

via Clinformatics DataMart (CDM). Prevalence of testosterone use in men increased more than three-fold from 0.81% in 2001 to 2.91% in 2011. Use of topical testosterone gel increased five-fold. The median number of days the subjects had a supply of testosterone available in the first twelve months following initiation of therapy was 150 days. Approximately 18.6% of incident users only filled one prescription.[53]

The proportion of days patients had a supply of testosterone in the first 12 months following initiation was only 0.41.[53] This raises concerns that men initiating testosterone may not be adherent with the prescribed regimen. Additional studies that specifically describe testosterone medication use behaviors such as persistence and adherence are available. Before reviewing those studies, the next section will examine persistence and adherence in general.

MEDICATION USE BEHAVIORS: ADHERENCE AND PERSISTENCE

Adherence

Two concepts are generally used to describe medication use behaviors, adherence and persistence. Adherence measures how a patient complies with, or adheres to, a prescribed medication regimen.[54] The full benefit of medications can only occur if patients follow their medication regimen reasonably closely.[54] Therefore, it is important to understand how a patient adheres to a medication regimen in order to realize benefits from the therapy.

The specific information captured by adherence measures varies by measurement type. For example, with indirect measures captured by prescription claims in a database, it is not known if the patient took the correct dose at the correct time. Other measures

such as directly observing therapy through blood markers demonstrates the drug was taken but the exact amount and schedule is still not known.[54] It is common to use prescription claims data to assess patient adherence. If a patient has a paid claim for a prescription, it is assumed that the patient is adherent to the medication regimen. Of the claims-based methods of measuring adherence, the two most commonly used are medication possession ratio (MPR) and proportion of days covered (PDC).[55]

The MPR is the sum of the days supply for all claims during a defined period of time divided by the number of days in the period.[56] There are multiple ways of applying this measure to claims, and therefore multiple MPR methodologies. Patients with an MPR of 80% or higher are generally considered adherent.[57]

PDC tends to be more conservative than MPR when used for multiple medications at one time, switches between drugs, or therapeutic duplication for a single condition.[58] PDC is the proportion of the number of days a patient has the medication available in specified period.[58] PDC always ranges from zero to one because it avoids double-counting covered days. It can also be dichotomized similarly to MPR.[59] Each day is assessed for the presence or absence of the medication in question and a binary measure of presence or absence is determined.[58]

Assessing adherence using claims data has many strengths.[56] Using claims information avoids the "Hawthorne Effect" in which patients behave differently because they know they are being observed.[56] In addition, evaluating adherence using claims is inexpensive compared to other methods of adherence assessment. There are, however, limitations to using claims data measures. It is possible for each method of assessment to

yield a different result.[56] In addition, there is an underlying assumption that when a prescription is filled the patient is taking the medication as prescribed.

Persistence

Persistence aims to capture "the duration of time from initiation to discontinuation of therapy."[60] Persistence as a continuous measure is the number of days from initiation of therapy (or a certain point of time in chronic treatment) to a point in time defined by the end of the observation period or until the patient exceeds the permissible gap, whichever comes first.[61] A permissible gap reflects the amount of time during which a patient may not fill or refill a prescription but is still considered to be using the therapy.

If a patient exceeds the permissible gap between refills, the patient is considered to be non-persistent. The permissible gap depends on the specific therapy and situation being studied but gaps such as 30 days, 60 days, or 1.5 times the previous days supply have been used.[55,60] Persistence can also be reported as a dichotomous measure. Patients persistent without an unacceptable gap in therapy are classified as persistent and patients with an unacceptable gap are classified as non-persistent.

Factors Influencing Medication Use Behaviors

Patient, provider, and system-wide factors all influence medication adherence.[54] Patient-level barriers to adherence are common. The number one reason patients cite as a reason for non-adherence is forgetfulness, which is cited by 30% of non-adherent patients. Having other priorities (16%), making a decision to omit doses (11%), lack of information (9%), and emotional factors (7%) are other patient reasons for non-adherence.[54]

Patients who do not understand the disease state, benefits and risks of treatment, and proper use of the medication are less likely to be adherent.[54] The complexity of the drug regimen is inversely related to adherence. In other words, the more complicated the regimen, such as frequency of dosing, the less likely the patient is to be adherent.[54] Physicians can also contribute to non-adherence. When providers are not familiar with drug cost or the individual patient's pharmacy benefits, they may chose medications that the patient will have difficulty accessing or affording.[54]

The patient's experience within the health care system impacts adherence. When patients miss appointments, receive poor treatment from clinical staff, are switched to a new drug due to formulary restrictions, cannot access the pharmacy, or cannot afford the medication, adherence tends to decrease.[54]

Motheral's 2011 review of the ST literature raises questions about the impact of ST on multiple types of outcomes. Motheral's review found a gap in the literature regarding the evaluation of the ST effect on medication discontinuation and appropriateness of use.[62] Similarly, in 2014 Seabury et al. called for further research on the factors driving non-adherence, including cost sharing and financial disincentives for patients that may be driving non-adherent behavior.[63] Benefit design may play an important role in understanding medication use behaviors, but additional studies are needed to explore this relationship.

Medication adherence is known to have significant financial impact on patients, manufacturers, and health care payers. From a patient perspective, adherence may mean better disease control, increased adverse events, or higher out-of-pocket costs. According

to Capgemini Consulting, pharmaceutical manufacturers lose $188 billion in annual revenues in the US due to patient non-adherence. For health care payers, adherence means spending more on medications; however, payers are likely to realize savings related to improved disease control and ideally lowered overall health care costs.[64]

Adherence and persistence are unique when it comes to testosterone use. The following section examines literature that specifically addresses testosterone use behaviors.

ADHERENCE, PERSISTENCE, AND OTHER BEHAVIORS IN TESTOSTERONE REPLACEMENT THERAPY

The literature on testosterone use behaviors continues to expand and gain interest. An FDA Advisory Panel noted the typical length of treatment for testosterone products has been reported to be between three and four months.[65] The panel noted that this is a major characteristic of the overall pattern of testosterone use in the US.[65] This conclusion is backed by a series of studies addressing testosterone use behaviors.[5,53]

One of the earliest examinations of testosterone therapy duration was a retrospective chart review that identified 127 men with testosterone deficiency initiating treatment from June 2000 to 2001. The authors did not state the location of the study. Injectable testosterone, Androgel 1%, and Androderm were included. Patients had follow-up appointments with physicians after three months of therapy. At that time, patients who were not responding to treatment were encouraged to quit therapy. After three months, 30% of the original 127 men discontinued treatment. After 12 months of therapy, 63% of the original 127 remained on therapy. Of those, 70% reported symptom

resolution.[6] Therefore, of the original 127, 44% experienced symptom resolution after 12 months of therapy. It is unknown at what point in time between the initial physician follow-up at three months and the final follow-up at 12 months patients had changes in symptoms. This study does not describe traditional measures of adherence or persistence, has a very small number of participants, and omits nine months of potentially important observations. The description of the treatment setting lacks details, adding to the difficulties of interpreting this study.[6]

Baillargeon et al. examined testosterone trends in a population of 10,739,815 men identified from CDM data from 2001 to 2011. The authors found that the median number of days covered by androgen prescriptions following treatment initiation in 2010 was 150 days. In initiating patients, about 18.63% filled only one prescription for a maximum of a 30-day supply. CDM is comprised of commercially insured individuals in the US, and includes prescription claims data.[53] It encompasses multiple MCOs and plan types. The utilization management tools used, such as PA or ST, for testosterone products were not investigated in this study, but could have contributed to therapy discontinuation and the number of patients that only filled one prescription if a PA or ST was initiated during the study period.

Recognizing the lack of information about TRT adherence, Schoenfeld et al. examined 15,435 hypogonadal men from the Thomson Reuters MarketScan Database for adherence and persistence patterns for the year 2009. The authors defined adherence using an MPR of greater than 0.8. They defined persistence as “the duration of therapy from the index date to the earliest of the following events: end date of the last

prescription, date of the first gap of more than 30 days between prescriptions, or end of the study period (12 months)."[5] The authors also examined dose escalation, switching, restarting, continuation, and discontinuation.

Continuation was defined as having index drug refills throughout the study period with no gaps between refills of greater than or equal to 30 days. Discontinuation was defined as not having a refill of the index drug within 30 days of the last day of the most recent fill of the index drug. Switching was defined as filling a prescription for a medication other than the previous agent (including brand or administration route) without refilling the previous agent. Restarting was defined as a refill of the index drug after a discontinuation of more than 30 days.[5]

They found that 75% of the patients initiating testosterone therapy were using Androgel (concentration not specified in study). Adherence rates (percentage of patients with MPR >0.80) overall were low (32.7% for specific hypogonadism and 29.4% for nonspecific hypogonadism). The overall average MPR was 56% over six months. Specific and nonspecific hypogonadism groups used testosterone for a short average length of therapy (146 days for specific hypogonadism and 137 days for nonspecific hypogonadism). There was no difference in length of therapy by age group, initial dose, or product type. Termination and switching patterns appeared to be the same for Androgel and Testim.[5]

Overall, 66.4% of patients discontinued therapy after two months. Of those who discontinued, approximately 50% restarted. Those who restarted within one to two months of discontinuing discontinued again at a mean of 32 days. Those who restarted

within six to eight months of discontinuing discontinued again at a mean of 207 days. Only 5% of men who restarted switched to another product.[5]

The authors concluded that age does not predict adherence for Androgel or Testim. Additionally, the authors speculated that the low switching rate may be attributable to patient satisfaction with their current product. The patient may perceive greater efficacy from their current product, be more familiar with product use, and may have had a prescription with refills already at the pharmacy which would make refilling that product more convenient.[5]

The authors described the patient population represented by MarketScan, but did not take into consideration that the benefit design for each plan represented in MarketScan is different. This level of detail is not possible with large databases, such as MarketScan, that represent multiple insurers. In this study, the patients were Medicare-insured, US patients, but the specific benefit design for testosterone products is unknown. Therefore, it is possible that benefit design, such as PA or ST, impacted patient behavior and may partially explain restarting behaviors if therapy was disrupted by the PA or ST process. The fact that 50% of men restarted after discontinuation highlights the need for further investigation of medication use behaviors beyond adherence and persistence.[5]

Another MarketScan study was conducted using patients who received their first TRT prescription during 2009. Patients were followed for 12 to 30 months following initiation. There were 15,435 men identified on topical treatment and 517 on short-lasting injectable testosterone.

Several treatment patterns were identified. Interruption was defined as not having a refill within 30 days of the last prescription. Of those with interruptions, patients may have restarted therapy after 30 days or more or discontinued therapy entirely. If patients restarted more than once, they were deemed cyclic users. If patients switched products but did not have a gap of more than 30 days they were considered to be on continuous therapy.[7] A subgroup analysis further divided patients into long-term users (more than 12 months of continuous treatment), complete discontinuation, and cyclic users. Age, physician specialty, copays, diagnosis, comorbidities, and use of PDE-5 inhibitors were evaluated.

At three months after initiation, 54% of topical patients and 37% of injectable patients were still using TRT. One year after initiation of therapy, only 18% of topical and 5% of injectable patients were considered to have continuous treatment.

Cyclical patients made up the majority of subjects (60% for topical and 64% of injectable). These are the users that restarted therapy at least 30 days after the end of the last day of the previous prescription, possibly multiple times. After each gap greater than 30 days after the end of the previous prescription, 40-50% of cyclical transitioned to "discontinued" status. In the sub-analysis, the authors were not able to detect meaningful differences between long-term, short-term, and cyclic users by age, physician specialty, copays, diagnosis, comorbidities, and use of PDE-5 inhibitors before and during testosterone therapy.[7]

Similarities between the injectable and topical forms in terms of therapy continuation suggest that treatment patterns with testosterone are disease driven rather

than product driven. The authors recommend educating patients on realistic expectations of treatment and monitoring of testosterone levels to encourage patients to continue therapy.[7]

The authors recognize that their measure of interruption may have been too strict.[38] Because of not taking into account the previous prescriptions' days supply, and using 30 days as the threshold for interruption, the adherence rates may be artificially low. A sensitivity analysis using different gaps such as 1.5 times previous days supply would strengthen this study. The concept of cyclical treatment recognizes that testosterone behavior goes beyond measuring restarting. Most of the patients in this study exhibited some type of cycling or restarting behavior that would not be detected using traditional adherence and persistence measures.

Puenpatom et al. conducted one study evaluating adherence and switching and another study evaluating persistence of TRT in the US from 2005 to 2011. Both studies used MarketScan data and included men, ages 18 to 65, that initiated TRT during the study period and had a hypogonadism diagnosis. Subjects were required to have a minimum of six months continuous enrollment before and 12 months after the TRT index date. In the adherence study, MPR and PDC were both measured. In the persistence study, the percentage of patients who remained persistent with their index therapy was measured using the product-limit method.[66,67]

The adherence study identified 106,039 patients. The mean MPR and PDC were 0.47 and 0.44 respectively. The overall adherence rate was 21.4%. About 13% of patients switched to a different testosterone product during the study.[66] Patients receiving pellets

had the highest PDC (0.59), followed by those receiving gels (0.43), short-acting injections (0.39), buccal (0.28) and patches (0.27). Statistical significance was reported ($p<0.001$), but the type of test used was not.[66]

In the persistence study, the authors identified 140,098 patients. About half of the patients were persistent at four months of therapy, 36.9% at six months, 24.4% at 12 months, 13.6% at 24 months, and 8.9% at 36 months. After 12 months, 25% of patients using gel or pellet forms of TRT continued on their initial therapy. Of patients using short-acting injections, 17.1% continued on initial therapy and of patients using a patch, 7.8% continued on initial therapy.[66]

Layton et al. compared testosterone dosage forms to determine if patches, injections, and gels have similar associations with cardiovascular events. As part of the study, authors measured treatment duration days. From January 1, 2000 to December 31, 2012, the authors identified 544,115 testosterone initiators from the MarketScan and Medicare databases in the US, and Clinical Practice Research Datalink and general practitioner records in the UK. The mean treatment duration for gel was 122 (SD 112) days, injection was 105 (SD 104) days, and patches were 96 (SD 91) days.[68] Injections were associated with a greater risk of cardiovascular events (1.26, 1.18-1.35), hospitalizations (1.16, 1.13-1.19), and deaths (1.34, 1.15-1.56) compared with gels in hazard ratio analysis with a 95% confidence interval. Injections did not have a higher risk of venous thromboembolism (VTE) compared to gels (0.92, 0.76-1.11). Gels and patches had similar risks of cardiovascular events (1.10, 0.94-1.29), hospitalizations (1.04, 1.00-1.08), death (1.02, 0.77-1.33), and VTE (1.08, 0.79-1.47). If in fact injections are

associated with higher risks of adverse events, long-term use of injections may be undesirable and persistent use unadvisable.

Testosterone level monitoring is recommended at baseline and after three to six months of therapy. Follow-up monitoring allows for dose adjustment in order to reach appropriate testosterone level goals.[10] Muram et al. evaluated dose titration and testosterone level assessments in patients using topical testosterone. Using OptumHelath Reporting and Insights claims data, Muram et al. identified 4,416 men that started a topical testosterone agent from January 1, 2011 to March 31, 2012. Inclusion criteria required 12 months of continuous enrollment and at least six months of study observation time. Patients were required to have an initial dose of testosterone at the recommended starting dose. Outcome measures included maintenance dose attainment month, time to stopping index product, or time to a claim for a non-index product, and proportion of patients with a testosterone assay or hypogonadism diagnosis in the study period. The recommended starting doses per day for the included products are Axiron 60 mg, Androgel 1% 50 mg, Androgel 1.62% 40.5 mg, Fortesta 40 mg, and Testim 50 mg.[29] These recommended starting doses are consistent with the manufacturers' prescribing information.[22,23,25,27,69] Maintenance dose was attained in month four at 115.2% of the recommended starting dose. Baseline testosterone levels were obtained in 46% of patients. The patients with a baseline testosterone level were more likely to have a hypogonadism diagnosis in the first six months following the index date (44.7% vs. 35.8%, $p < 0.001$) and to have a follow-up testosterone level (50.6% vs. 28.3%, $p < 0.001$). During the six months after initiation, 63.2% of patients stopped refilling the

index product or filled a prescription for a non-index product. There were no significant differences in the time to stop refilling index treatment or filling a non-index product between the groups that either had a baseline testosterone assay (1229, 64.5%) and those that did not (1391, 62.1%)($p = 0.113$). The mean time to stopping refills of an index product or filling a non-index product was 72.7 days in patients with a baseline essay and 70.9 in those without ($p = 0.477$).

Overall, 43.4% of all patients stopped refilling the index product. Patients with a baseline assay were significantly less likely to stop filling the index product (41.3% vs. 45.2%, $p < 0.001$) and more likely to continue treatment by filling a prescription for a non-index product (12.4% vs. 9.2%, $p = 0.002$) compared to patients without a baseline testosterone assay. This study suggests that a baseline testosterone assay improves treatment benefits by increasing the likelihood of follow-up testosterone level monitoring, continuation of index treatment, continuation of a non-index treatment, and decreases the likelihood of stopping treatment with the index product.[29]

The current situation of TRT in the US has reached a critical point. Utilization is increasing despite conflicting opinions on testosterone safety and necessity. Marketing is encouraging patients to seek testosterone therapy, but not all patients are appropriate for treatment. At the same time, barriers to testosterone use such as PA and ST may be limiting access to needed testosterone. Other avenues not captured in claims data may be used, such as cash payment or use of clinics. The patients that are appropriate may not be consistent in TRT use. MCOs are left to deal with increased costs related to TRT as well

as ensuring appropriate use of TRT. One way MCOs can manage a situation where safety, appropriate use, and costs of a therapy are in question is the use of PA.

PRIOR AUTHORIZATION (PA)

According to The Academy of Managed Care Pharmacy (AMCP), prior authorization (PA) is an essential tool used by MCOs to control utilization of and expenditures for selected medications. Usually these medications are very expensive, have serious side effects, or a less expensive but similarly effective option that is preferred by the MCO is available. Once a medication has been identified for the PA process, the MCO determines the requirements for coverage of the medication using evidence-based clinical need and therapeutic rationale. Individual PA parameters vary by plan and medication. In most cases, if PA criteria are not met, the payer either does not cover the medication or the medication may be subject to higher copay.[70]

AMCP considers PA an overarching strategy with multiple subtypes and uses.[70] Each type of PA addresses a different aspect of an MCO's appropriate drug use criteria. PAs can be used to gather necessary medical information on a patient, administer ST, enforce quantity management guidelines, optimize generic utilization, and manage specialty medications. Most employers use PA, ST, quantity limits, and 'refill too soon' limits. The rates of utilization of these strategies increased from 2011 to 2012 by the following amounts: PA increased 10%, ST increased 9% and quantity limits increased 7%.[71]

A literature review of ST in 2011 found that PA and ST processes are not distinctly unique throughout the literature.[62] However, in 2014 a literature review of formulary restrictions on multiple outcomes treated ST and PA as separate formulary management

techniques.[8] Therefore, a separate review of ST is necessary.

Step Therapy

As of 2012, ST was used by 74% of large employers and 56% of small employers.[71] The use of ST is common among Medicare Part D plans.[62] ST requires a trial with a first-line medication prior to receiving coverage for a second-line agent. For example, the first-line medication may be a generic. The second-line medication may be the preferred brand name drug. Another example occurs when the first-line medication is a preferred brand name drug and the non-preferred brand is the second-line medication. ST prioritizes established and cost-effective therapy use prior to progressing to other therapies that may not have well established safety, effectiveness, or value.[62]

ST can be administered using online adjudication with automated logic to review the patient's prescription profile. In the case of ST, if the patient already has an adequate trial of the first-line therapy, the second-line may be approved automatically. This method minimizes patient, physician, and pharmacist disruption and ensures that preferred products are dispensed.[62]

Evaluation of Prior Authorization Effectiveness

The measure of effectiveness of a PA program depends on the initial goal of the PA program and the perspective of the evaluation. While cost and utilization are usually the main focus, there are many unintended consequences of a PA program that should also be considered. Administrative costs and impacts, changes in patient adherence and outcomes, costs to physicians and costs to pharmacists may also be considered.[72] A 2009 literature review on PA programs found that quality measures are rarely, if ever, used to

evaluate drug management programs.[72] Plan- or payer-focused endpoints were most common (68%). Among those endpoints, evaluation of plan drug cost (62%) and plan drug utilization (30%) occurred most frequently. Among studies that evaluated benefit restrictions, 40% evaluated patient-focused outcomes such as patient satisfaction, and 38% had clinically-focused outcomes such as a clinical marker.[72]

PA programs have significant administrative consequences. PA programs cost $15-$25 per claim processed yet administrative costs for restriction programs are not consistently included in the evaluation of drug management programs.[72] Consequently, the financial impact of administering the program often goes unrecognized by the payer.

PA is a way for MCOs to adhere to contractual obligations to pharmaceutical manufacturers. There are increasing numbers of agreements between payers and manufacturers based on market share or formulary position for medications. In order for payers to continue to receive preferential pricing, they must adhere to the terms of their contracts, which may require some type of drug preference program.[73] As these contracts become increasingly important to payers, the use of PA to enforce drug preference programs and meet contractual requirements will also become more important. This means that it is likely that PA programs will be needed by payers unless a better system is developed.

PA is most likely to reduce costs and utilization in drug classes with the following characteristics: generic products are available, treatment of a condition with mild to moderately severe symptoms, and availability of brand name drugs with limited advantages over generics in that class.[74] In an ideal situation, PA programs should have a

favorable effect on cost and quality of care, but they should not cause negative health outcomes. However, an analysis by Carroll in 2002 found that most PA programs do not meet these ideal conditions and that negative health outcomes as a result of PA are possible.[74]

Utilization management mechanisms such as PA and ST have been linked to non-adherence. In 2004, Motheral et al. studied the effects of ST programs on patients. They surveyed patients who experienced ST for either proton pump inhibitors, non-steroidal anti-inflammatory medications, or selective serotonin receptor inhibitors within 7 months of the ST experience. They found that 17% of patients received no medication following the ST experience.[75]

Another study used pharmacy claims to track patients attempting to receive aliskiren for hypertension.[76] The need for aliskiren was assumed to indicate the current therapy was not meeting goals and additional therapy was needed. PA, ST, or non-formulary placement utilization management tools were in effect during the study. After receiving a rejected claim, 28.4% of the patients did not receive any type of additional antihypertensive, dose escalation, or combination of additional and escalation. Therefore, despite the assumed need for additional therapy, the therapeutic needs of those patients may not have been met because of the utilization management tools in place.[76]

A 2014 meta-analysis of managed care formulary restrictions found that PA negatively impacted adherence in 68% of studies.[8] The authors also found no distinct trends in the relationships between PA and broad economic measures such as total medical costs, total costs, and total pharmacy costs. Overall, the authors found a lack of

research assessing the impact of formulary restrictions on medication adherence among other outcomes.[8]

In summary, PA programs offer the possibility of cost savings and utilization control, but those benefits may come at a cost. As of July 1, 2014, the top two pharmacy benefit managers in the US, ESI-Medco and CVS Caremark, have some form of PA in place for testosterone products.[77,78] Until now, evaluations of testosterone use behaviors have not taken into account how pharmacy benefit design, such as the use of PAs or ST, impact testosterone patients despite widespread use. The implementation of PA and ST for testosterone in the DoD MHS offers a unique setting to evaluate how these utilization management tools impact TRT patients.

THE DEPARTMENT OF DEFENSE MILITARY HEALTH SYSTEM

The DoD is responsible for the health care for 9.5 million beneficiaries. In 2014, 78.9% of those eligible used MHS services.[79] The DoD MHS is a separate medical system from the VHA. Patients qualify for medical benefits in the MHS either by serving on active duty or through 30 days of active service in the National Guard or Reserve. Spouses and children of those who serve are also eligible. Following 20 years of active service, active duty members are eligible to retire. Medical benefits for retirees and their spouses continue for life. If an active duty member separates from the military (rather than retiring), they are not eligible for continued medical benefits unless special circumstances have occurred such as significant medical disability due to service. Patients who separate may be eligible for care through the VHA.[80] Only 17% of military

members will retire.[81] The remaining 83% separate from the military and therefore no longer qualify for medical benefits under the MHS.[81]

The MHS has the following four overarching goals: increase readiness, keep people healthy through population health initiatives, provide the best experience of care possible, and lower per capita costs through a focus on quality and eliminating waste.[82] The mission of the MHS is unique compared to other health care payers. One of the major responsibilities of the MHS is maintaining the war fighter's ability to deploy. Another unique quality is the proportion of patients who are retirees and their families over the age of 65 (23%), retirees and their families under 65 (34%) and the fact that the MHS is responsible for the health care of these patients for life.[82] By 2020, the MHS projects 43% of the MHS population will be males 45 years old or older.[79]

The MHS is comprised of military treatment facilities (MTF) and purchased care through civilian facilities. Tricare, the program that administers the DoD health care program, integrates MHS resources as well as purchased care from civilian health care providers. Beneficiaries can choose from different Tricare health plans.[79] Tricare Prime and Tricare for Life make up 66% and 28% of the enrolled MHS population, respectively.[79]

Individuals eligible for Tricare Prime include active duty service members and their families, retired service members and their families (that are not using Tricare For Life), activated Guard and Reservists and their families, and other miscellaneous groups of beneficiaries. Tricare Prime provides primary care managers, preventative health services, arrangement for specialty provider services, and pharmacy benefits. Tricare for

Life is a Medicare wraparound coverage and secondary payer for beneficiaries 65 years or older who have Medicare Parts A and B. The majority of beneficiaries 65 years or older are covered by Tricare for Life as their supplemental plan. Approximately two million beneficiaries are enrolled in Tricare for Life comprising 28% of all enrollees.[79]

Pharmacy benefits are available at MTFs, a retail pharmacy network of 55,000 pharmacies, and a Tricare Mail Order Pharmacy (TMOP).[83] In 2012, the DoD spent $7 billion on drug expenditures after accounting for pharmaceutical manufacturer refunds.[83] The annual budget for the entire DoD medical program for fiscal year 2015 was $58.5 billion.[79]

DoD beneficiaries, including Tricare Prime and Tricare for Life, can use four main pharmacy points of service. MTF, TMOP, retail network, and non-network retail pharmacies are available and have varying copays. At MTF patients may receive up to a 90-day supply of medication and there is no copay. Through TMOP, patients may receive up to a 90-day supply of medication. This includes schedule III-V controlled substances as allowed by the prescriber. Network retail pharmacies include major pharmacy chains throughout the US. The copays for each point of service are available in Table 2.1.

Non-network pharmacies are the most expensive for patients and will not be included in this study. If patients use pharmacies outside the network, the patient files a claim for reimbursement and is subject to deductibles, out-of-network cost-shares, and copays of 20% to 50% of total cost depending on the beneficiary type. This results in significantly higher out-of-pocket costs for the patient compared to the other three points

of service.[84] Additionally, the manual claim submitted by the patient may not be available in the patient's military prescription claims database.

On February 1, 2013 the DoD adjusted copays at all pharmacy points of service.[85] Table 2.1 summarizes the copayment structure before and after the adjustment.[82,84] The goal of the change was to incentivize use of the MTF and TMOP options by offering $0 copays for generic drugs at those points of service. By lowering the copayments to $0, financial barriers are removed for obtaining medications in those categories. This also means the copays for the other points of service, especially for brand or non-formulary medications, became very high (in comparison) which could negatively impact adherence rates for those medications.[86]

Table 2.1: Department of Defense Copay Structure

	October 1, 2011– February 1, 2013[1]	February 1, 2013– February 28, 2014[2]
Military Treatment Facility		
Generic	$0	$0
Brand	$0	$0
Non-formulary	n/a	n/a
Home Delivery/Tricare Mail Order Pharmacy *(90-day supply)*		
Generic	$3	$0
Brand	$9	$13
Non-formulary	$25	$43
Network Retail Pharmacy *(30-day supply)*		
Generic	$5	$5
Brand	$12	$17
Non-formulary	$25	$44

Note: Active duty service members have no copay at any point of service for formulary medications. Non-formulary medications require medical necessity approval. If approved there is no copay.

[1] Evaluation of the Tricare Program: Access, Cost, and Quality. 2013. Available at: http://www.tricare.mil/tma/dhcape/program/downloads/TRICARE2013%2002_28_13%20v2.pdf. Accessed November 25, 2013.
[2] Tricare Pharmacy Program Handbook. 2014. Available at: http://www.tricare.mil/~/media/Files/TRICARE/Publications/Handbooks/Pharmacy_HBK.pdf. Accessed July 9, 2014.

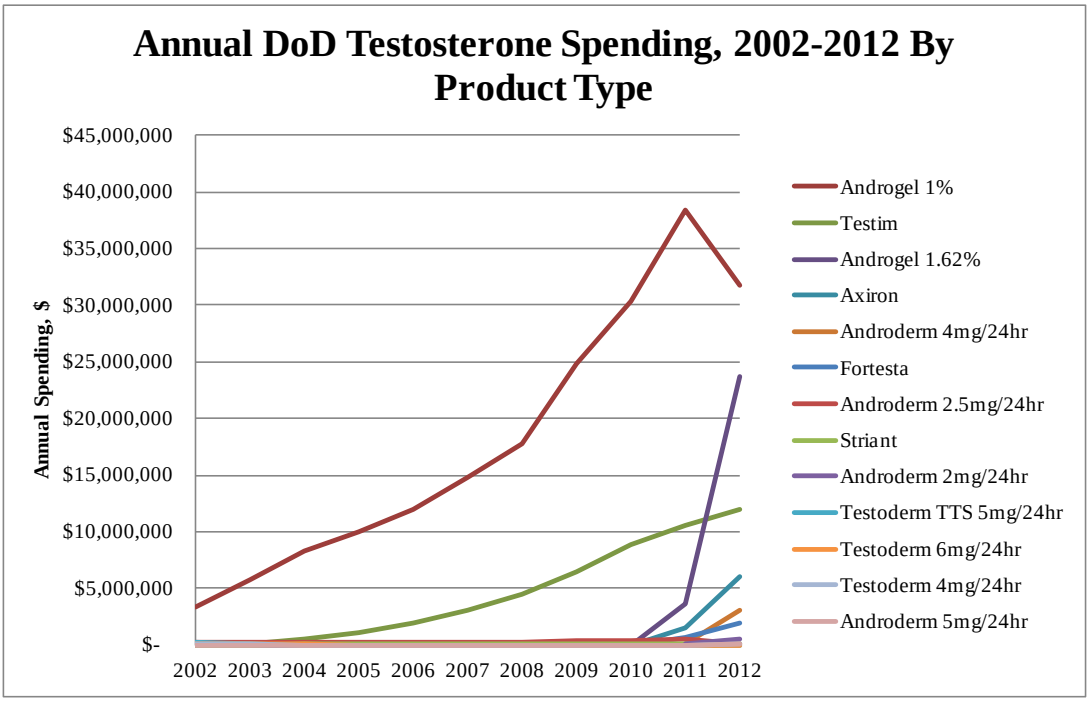
MHS patients are subjected uniformly to the same guidelines, copays, and formularies on the same timeline. Claims data from military, mail order, and retail pharmacies are available. These data can be used retrospectively to evaluate drug benefit trends MHS wide. Recently these were used to evaluate overall trends and persistence of testosterone therapy in the DoD.

Testosterone in the Department of Defense Military Health System

Trends in testosterone use that occur in civilian populations have also occurred in the DoD population. A 2015 study by Canup et al. found that prescriptions for androgens (all forms) dispensed at MTFs increased dramatically from 19,143 in 2007 to 44,860 in 2011.[87] The authors found the largest increase in use in patients 35 to 44 years old. Finally, the authors examined changes in coding for testicular hypofunction from the Defense Medical Epidemiology Database. While coding for testicular hypofunction increased 45.5% annually from 2007 to 2011, the increased rate of androgen use was only 23% per year. The number of androgen prescriptions to hypofunction diagnosis decreased throughout the study period. One reason authors believe this ratio may have decreased is the possibility of treatment with testosterone without a diagnosis or initial testosterone level testing.[87]

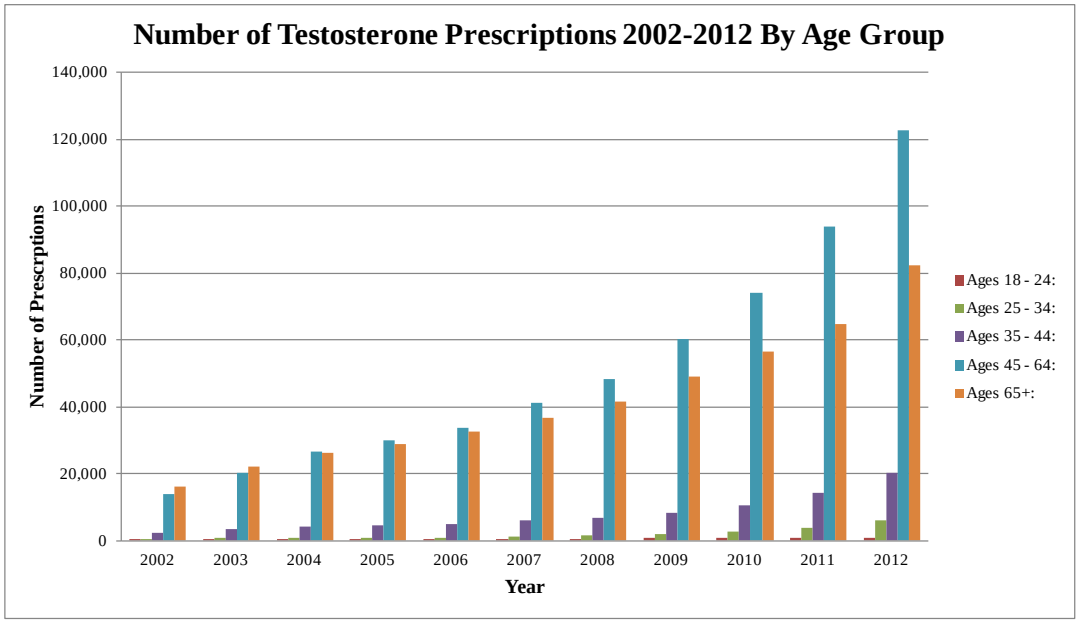
Another testosterone study in the DoD is a 2013 retrospective study of testosterone utilization and persistence behaviors from 2002 – 2012. From 2002 – 2012, the number of men receiving prescriptions for testosterone (topical and buccal) each year grew from 8,124 in 2002 to 63,014 in 2012 resulting in an increase in prevalence from 0.35% to 1.91%. Costs grew from $4.9M annually in 2002 to $79.5M in 2012. From 2011 to 2012 alone, costs increased 35%.[88] Figure 2.1 shows the total cost for each product type dispensed by year. Figure 2.2 shows the number of prescriptions dispensed in each age group annually from 2002 – 2012. During the 2010 to 2012 study period, there were no pharmacy benefit restrictions (such as PA, ST, medical necessity (MN) requirements, or formulary restrictions) on testosterone prescriptions.[89]

Figure 2.1: Testosterone Spending, 2002 – 2012, by Product Type



Roska E, Wilson J. Testosterone Prescribing and Persistence Trends in the Department of Defense, 2002-2012: A Retrospective Analysis. 2014.

Figure 2.2: Testosterone Prescriptions, 2002 – 2012, by Age Group



Roska E, Wilson J. Testosterone Prescribing and Persistence Trends in the Department of Defense, 2002-2012: A Retrospective Analysis. 2014.

The bulk of the increase in use and costs coincided with the introduction of Androgel 1.62% in 2011. While this study could not conclude that direct-to-consumer advertising caused the overall increase in testosterone use, the fact remains that Androgel comprised 70% of all testosterone spending in the DoD which represented a dominant market share in 2012.[88]

From June 1, 2011 through May 31, 2012, incident testosterone users had a persistence rate of 45% without a 30-day gap, 65% without a 60-day gap, and 33% without a gap equal to 1.5 times the previous fill's day supply. The mean number of days to discontinuation in incident users was 81 days. In addition, 26% of all patients received only one prescription during the study period.[88]

Following this increasing trend in testosterone use, on March 1, 2013, the DoD

implemented PA and ST for testosterone products (not including implants and injectables) in order to encourage safe, appropriate use of testosterone while simultaneously controlling costs. The DoD Pharmacy and Therapeutics (P&T) Committee developed the guidelines for use at their August 2012 meeting.[90] According to meeting minutes, a budget impact analysis indicated the most cost-effective situation was to recommend Fortesta (testosterone gel by Endo) as the first-line agent. Patients impacted by the formulary change were notified of the change by a letter. The letter is available in Appendix B.

Ultimately three separate processes were implemented. First, PA criteria were established for any use of testosterone. Second, ST guidelines positioned Fortesta as the first-line agent. MN criteria were established for patients wishing to use any non-preferred agent. Finally, for topical forms of testosterone, a screening process was established to detect potential safety issues due to product transfer to household contacts.[90] All three forms are in Appendix C: Department of Defense Forms.

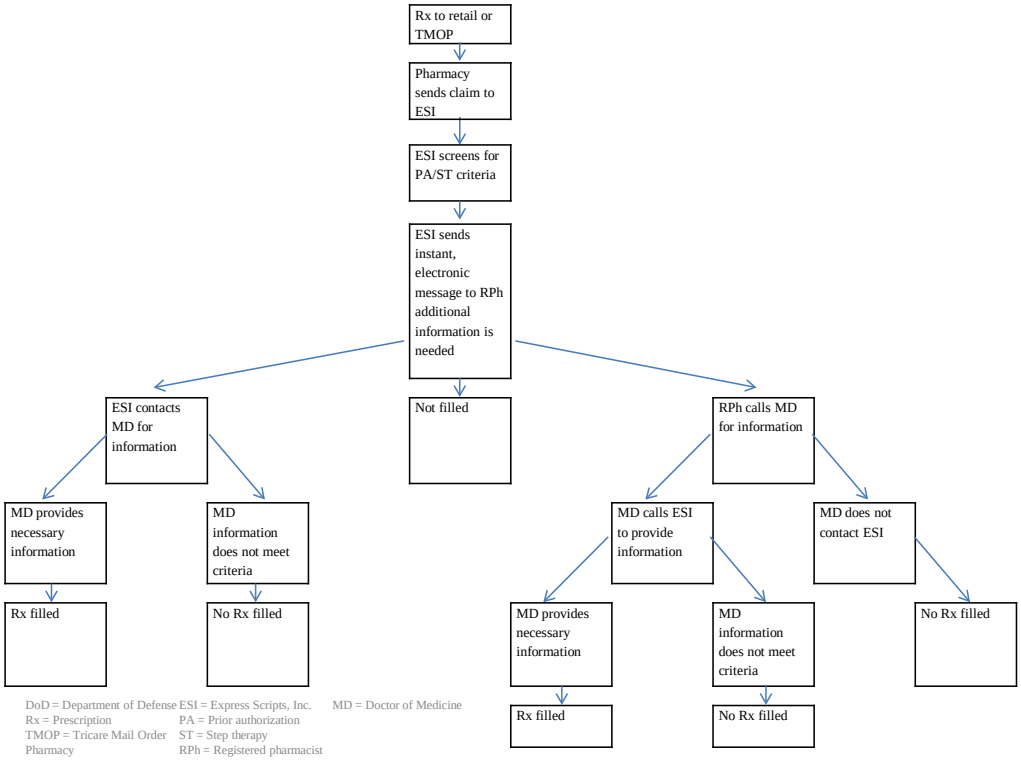
For males, the PA criteria for testosterone use are a history of two or more morning testosterone levels below 300 ng/dL and hypogonadism symptoms. These criteria are consistent with the Endocrine Society treatment guidelines for hypogonadism. According to the ST guidelines, all patients, new or established on testosterone, must fail Fortesta before qualifying for all other non-injectable forms of testosterone. Due to concerns of contact transfer of topical testosterone, patients must have a low risk of hazardous skin transfer to family members in order to receive a topical product. Patients could not be “grandfathered” for testosterone treatment. In other words, all testosterone

patients, new and established, would have to go through the PA and ST process.[90] The "no grandfathering" policy was atypical for a DoD PA.[84] Motheral found that programs that do not grandfather patients through ST requirements have larger cost savings compared to those that grandfather.[62]

All three pharmacy points of service (POS) are responsible for following DoD formulary guidelines.[91] The process at the MTF differs from retail and TMOP. Figure 2.3 shows the PA process for the DoD at a retail and a TMOP pharmacy POS. Figure 2.4 shows the PA process at MTF pharmacies. The DoD pharmacy benefit at retail and TMOP has been administered by Express Scripts, Incorporated (ESI) since 2003. The contract with ESI was renewed in 2014 for an additional seven years. ESI is responsible for ensuring that PA and ST guidelines established by the DoD P&T are executed accurately at the retail and TMOP points of service.[92]

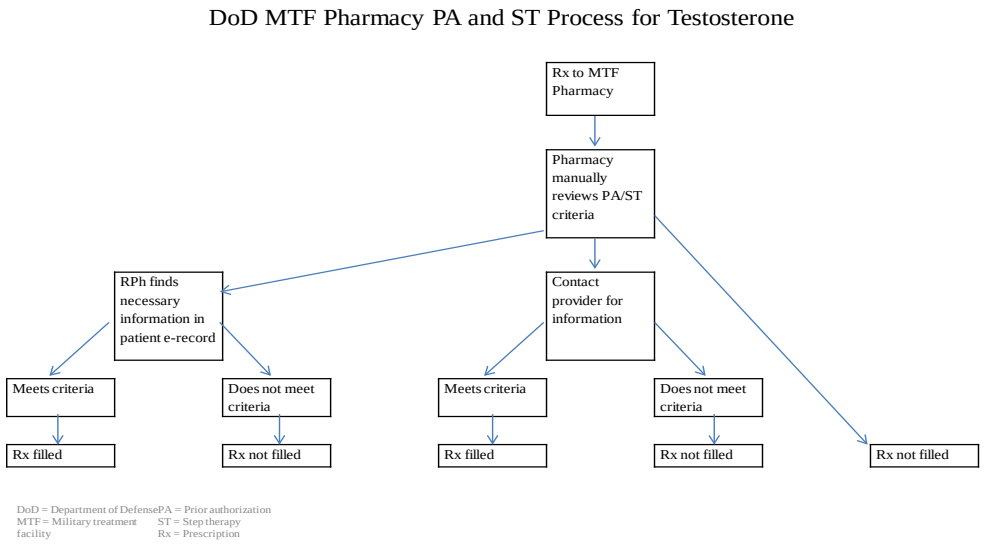
Figure 2.3: DoD Retail and Mail Order Pharmacy PA and ST Process for Testosterone

DoD Retail and Mail Order Pharmacy PA and ST Process for Testosterone



At the MTF, the pharmacy personnel are responsible for ensuring that the PA or ST guidelines are enforced. In MTFs with in-house military providers, prescriptions are submitted to the pharmacy via physician order entry (POE) or written, faxed, or e-prescribed prescriptions from civilian providers. The pharmacy claim is generated in the Pharmacy Data Transaction Service (PDTS) as soon as the prescription is processed at the MTF. If a patient does not meet PA or ST guidelines, the claim should be reversed and the prescription should not be dispensed.

Figure 2.4: DoD MTF Pharmacy PA and ST Process for Testosterone



The results of the DoD study regarding implementation of PA and ST programs for testosterone have not been published. The implementation of the DoD PA/ST criteria for testosterone provides an opportunity to add to the literature on testosterone use, PA, ST, and how they influence persistence, adherence, and other behaviors using a population and setting well suited for this type of study. The following section describes this proposed study in further detail.

RATIONALE AND OBJECTIVES FOR THE STUDY

MCOs and the DoD responded to increased testosterone utilization by putting PA and ST programs in place in order to ensure safe, appropriate use of testosterone and to contain costs. At the same time, there is evidence that patients are inconsistent in TRT

use but the reasons for this behavior are not clear. Previous studies have failed to account for the widespread use of PA and ST programs for testosterone products. These programs restrict access to testosterone possibly contributing to low persistence or adherence rates, switching, restarting, and cycling behavior. Additionally, the extent to which testosterone PA or ST have influenced testosterone utilization and medication costs is unknown.

The DoD PA and ST programs are unique because all patients, even established testosterone users, were required to complete the PA and ST process. Therefore, this particular situation allows for comparison of patient behavior before and after the PA and ST. In addition, a "no-grandfathering" policy for PA and ST programs is atypical for the DoD, and review of the results of this deviation from normal operations may impact future policy decisions. Finally, greater understanding of switching, restarting, and cycling behaviors is needed. This study expands the understanding of testosterone use behaviors that previously may have been considered non-persistent. A retrospective evaluation of utilization, costs, and medication use behaviors in testosterone therapy is warranted and will contribute significantly to the growing literature on testosterone and the impacts of formulary management tools on medication use behaviors.

The purpose of the following study is to evaluate changes in testosterone costs, utilization, and medication use behavior before and after implementation of DoD PA and ST programs on March 1, 2013 as well as measure testosterone use behaviors. The study objectives are listed below and the hypotheses for each objective are available in Table 4.18.

1. Describe medication costs, number of new users, number of 30-day equivalent prescriptions, proportion of prescriptions by pharmacy POS, proportion of prescriptions by product, mean patient age, and mean daily dose before and after PA and ST program initiation in the DoD.
2. Compare adherence and persistence before and after implementation of the PA/ST program.
3. Compare adherence behaviors in testosterone users before and after PA and ST program initiation in the DoD while controlling for covariates (starting dose, overall average daily dose, age, copay, point of service, and product type).
4. Compare persistence behaviors in testosterone users before and after PA and ST program initiation in the DoD while controlling for covariates (starting dose, overall average daily dose, age, copay, point of service, and product type).
5. Determine switching, restarting, and cycling patterns post PA/ST, by product type, overall average daily dose, point of service, and age group.
6. Compare mean gap days between the last prescription in pre-period and the first prescription in the post-period to average gap days overall.

Chapter 3: Methods

This chapter describes the methods of this study. First, the study design and data source, including inclusion criteria and data collection, are presented. Second, independent and dependent variables of interest are defined. Third, the statistical analysis for each hypothesis is concludes this chapter.

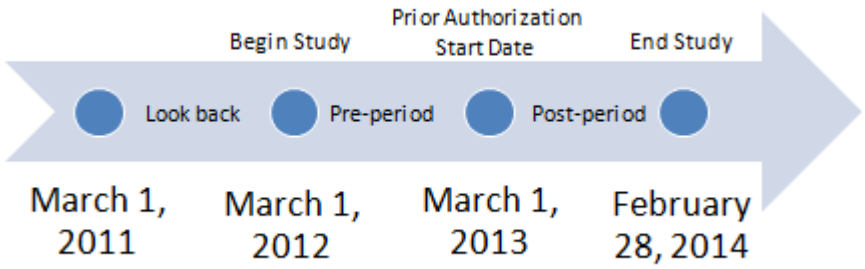
INSTITUTIONAL REVIEW BOARD SUBMISSION

This study was reviewed by The University of Texas at Austin Institutional Review Board. This protocol was determined to be non-human subjects research due to the secondary use of a de-identified data set. In addition, this protocol was approved by The Defense Health Agency (DHA) Privacy and Civil Liberties Office and executed under an approved Data Sharing Agreement (DSA).

STUDY DESIGN

This was a retrospective, secondary database analysis of prescription claims. Specific inclusion and exclusion criteria are listed under inclusion and exclusion criteria. In general, the claims in this study include adult men, 18 years of age or older, from the Department of Defense (DoD) Military Health System (MHS) who received testosterone (other than injectable or implant) anytime from March 1, 2012 through February 28, 2014. The intervention date for the study is March 1, 2013, the day the DoD prior authorization (PA) and step therapy (ST) programs were implemented. Figure 3.1 presents a timeline of the study.

Figure 3.1: Study Timeline



The look-back period, March 1, 2011 through February 28, 2012, was used to determine if patients received a testosterone prescription in the year preceding the beginning of the study on March 1, 2012. In order to be included in the overall group of patients, patients must have had at least one prescription in the time period from March 1, 2012 to February 28, 2014. The paired group of subjects, a subset of the overall group of study subjects, was used for pre-PA and post-PA inferential comparisons. In order to be included in the paired group, patients must have had at least one prescription during the pre-PA period from March 1, 2012 to February 28, 2013 and at least one prescription during the post-PA period from March 1, 2013 to February 28, 2014. The index study prescription was the first prescription claim for each patient occurring on or after March 1, 2012.

Inclusion Criteria

The following inclusion criteria were used: men enrolled in Tricare For Life or Tricare Prime; 18 years old or greater, and received a prescription for Androgel, Testim, Axiron, Androderm, Testoderm, Fortesta, Striant, Vogelxo, or a generic topical testosterone product during the time period March 1, 2012 through February 28, 2014.

The paired group will then be limited to those patients with one prescription in the pre-PA period and one prescription in the post-PA period. Appendix A: Included Testosterone Forms provides a summary of products included in this study. A nasal gel was approved in May 2014, but at the time of study design was not commercially available and therefore not included.[93] Paid prescription claims were included in the analyses.

Exclusion Criteria

Patients using injectable and implantable forms of testosterone were not included. These claims are not consistently processed as pharmacy claims. Rather, those claims often result from office-based procedures. Patients under the age of 18 years old were not included because these patients would not qualify through the PA/ST process in this study and would instead require a separate process not of interest for this study. Claims made to the Veteran's Health Administration (VHA) and in theater (deployed) were excluded.

Data Source

The data source for this study is the DoD Pharmacy Data Transaction Service (PDTS). The DoD PDTS contains prescription claim data for all DoD beneficiaries.[94] Each record in the PDTS represents an outpatient prescription claim filled for an MHS beneficiary.[94] The PDTS contains information on the claim, pharmacy, provider, patient, and drug dispensed. The claim section contains information such as whether the claim was for a compounded medication, date dispensed, day supply, whether the claim was for a generic product, reject codes, quantity dispensed, type of pharmacy, costs, and copays.

The provider section contains the address and identification number for the prescriber. The patient section contains information such as age, identification number, patient or sponsor branch of service and beneficiary status (retired, active, reserve, family member). The drug section contains brand name, generic name, American Hospital Formulary Service (AHFS) classification, dosage form, generic code number (GCN), generic name, route of administration, and strength.[95] Only the fields required to conduct this study were requested. PDTS data are not publicly available, but data can be requested through the DHA Civil Liberties Office with a government sponsor.[94]

Data Collection

Fields for data collection were selected from the MHS Mart which lists the field available for multiple systems including PDTS.[95] Specific fields were selected based on the most current listing available at the time of data extraction. Data were de-identified by replacing patient-specific identification numbers with randomly generated patient identifiers. This process was conducted by the staff at the DoD Pharmacoeconomics Center, now known as the Pharmacy Operations Division.

STUDY VARIABLES

The following section defines and explains the dependent and independent variables used in the study.

Dependent Variables

Total medication cost is the sum of the total amount paid by the DoD overall for each prescription included in the observation period. This was reported descriptively.

Rebates and refunds are not included in calculations and were not available for this study. Cost totals were not adjusted for copays.

Patients with "new user status" are incident users. This includes any patient receiving a testosterone prescription who did not receive any other included form of testosterone in the previous year. Claim data from March 1, 2011 through February 29, 2012 were used only for look-back purposes. New user status can occur during the pre-PA or post-PA time period. This variable was designed to establish if there are fewer incident users after the PA and ST are implemented.

The MHS allows prescriptions for up to a 90-day supply; therefore, prescription volume should be standardized to 30-day equivalents for comparisons. The days supply for each claim divided by 30 (days) establishes the 30-day equivalent for each prescription. For example, if a 90-day supply prescription is dispensed, it is worth three, 30-day equivalents (90-day supply divided by 30 equals three). This allows for standardized comparisons across prescriptions of varying day-supplies.

The proportion of prescriptions by pharmacy point of service (POS) is a description of the percentage of the total number of prescriptions filled at each pharmacy POS. The same applies to the proportion of prescriptions by product but that is the percentage of prescriptions filled for each product. Calculations for the mean daily dose are discussed under the Independent Variables section.

Adherence was measured using the medication possession ratio (MPR). It was calculated as the total days supply for the prescriptions during the observation period divided by the refill interval. The refill interval was calculated by adding the days' supply

of the last prescription to the difference between the last prescription date and the first prescription date. MPR calculations for the pre-PA period and post-PA period were calculated using the date range for the pre-PA period and the post-PA period.

The range of MPR was not allowed to exceed “1.00”. A dichotomous measure of adherence was determined by the MPR value. Any patient with an MPR of 0.8 or greater was considered adherent. Any MPR less than 0.8 was considered non-adherent.

MPR was used in this study because patients were not expected to use more than one type of testosterone at any given time. However, if a patient is on more than one type of testosterone simultaneously, both types of testosterone were considered concurrently, and the MPR was capped at “1.00” to account for possible double counting of therapy days.

Persistence was the length of therapy in days (days supplied) from either March 1, 2012 through February 28, 2013 (pre-PA/ST) or March 1, 2013 through February 28, 2014 (post-PA/ST) before an unacceptable gap in therapy or the end of the study period. The first prescription during the March 1, 2012 through February 28, 2013 time period was the index date for the pre-period. The post-period began with their first prescription following the PA/ST implementation on March 1, 2013.

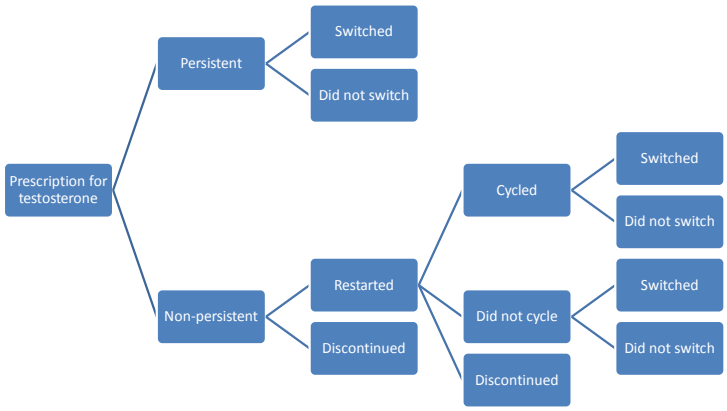
Persistence days, or length of therapy, was a continuous measure of persistence defined as the number of days the patient persisted on therapy before an unacceptable gap or the end of the study period. Unacceptable gaps of 30 days, 60 days, and 1.5 times the previous day’s supply were used for sensitivity analysis. In the event the patient does not

have an unacceptable gap in therapy, the number of days from start of therapy until the end of the observation period was used.

Switching occurred when a patient filled a prescription for any form of testosterone other than the previous product at any time before the end of the study on February 28, 2014. Patients who switched can be adherent or non-adherent, persistent or non-persistent, cyclical or restarting patients. The switch status, a dichotomous variable (switched or did not switch), was established for each paired patient. Product switching in the post-PA period was reported.

Restarting and cycling behaviors occur in patients who are considered non-persistent. Figure 3.2 shows how there are multiple paths for these patients and how persistence, switching, restarting, and cycling occur.

Figure 3.2: Patient Behavior Pathway

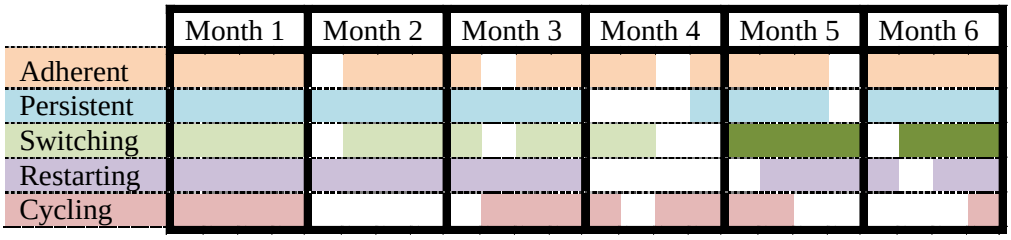


Restarting is considered refilling any testosterone product after a gap in therapy of more than 30 days. Schoenfeld et al. considered patients “restarting” if they went back to their index form of testosterone after a break in therapy of 30 days[5]; however, it is

possible for patients to restart on a different agent, especially after a PA or ST. In this study a restart included restarting any testosterone therapy after a 30-day gap in therapy. The restart status is a dichotomous variable indicating the patient restarted or did not restart.

Cycling occurs when a "restarted" patient has a break in therapy of 30 days or more and then restarts therapy again. These patients "cycle" because they are not continuously adherent or persistent, but have not stopped therapy all together. Patients may repeat this cycle of a gap in therapy of more than 30 days and then filling a prescription multiple times. Figure 3.3 compares each of these behaviors. Each row represents a different behavior and the colored areas represent a time period that the patient has medication. Each group of four columns represents a month of therapy.

Figure 3.3: Potential Behavior Patterns



"Gap days" are the number of days from the expected end of a prescription (the date dispensed plus the days supply) to the next successful prescription claim date. In this study, the gap days from the expected end of the last prescription in the pre-PA period to the first prescription in the post-PA period were investigated specifically and called the 'PA gap days'.

Independent Variables

The PA/ST status indicates if the prescription occurred before or after the PA/ST implementation. The pre-period is March 1, 2012 to February 28, 2013. The post-period is March 1, 2013 to February 28, 2014.

Variables related to dose must be calculated. First, the quantity of the product dispensed in each claim is multiplied by the strength of the product dispensed in order to determine the total amount in milligrams of testosterone dispensed in that particular prescription. The total amount of testosterone dispensed is then divided by the number of days supplied in that prescription. This results in the average dose (in milligrams) per day for that prescription. In order to standardize doses across various forms of testosterone, the dose per day will be converted into a proportion of the recommended starting dose (PRSD) for each product. Recommended starting doses for each product are available in Appendix A. For example, one bottle of Androgel 1.62% metered dose pump contains 1,215 mg of testosterone. The recommended starting dose is 40.5 mg daily. Therefore, in this case, at the recommended starting dose, one bottle of Androgel 1.62% metered dose pump is a 30-day supply of medication. This prescription is 1.00 of the PRSD. If the patient increases to two bottles every 30 days, the dose per day changes to 81 mg per day. Therefore, the new PRSD is 2.00. The starting or initiating dose is the PRSD for the index prescription for each patient. Overall average daily dose is the average PRSD for all of the prescriptions for each patient.

Age, copay amount, and POS are all reported in each prescription claim. Age is the age at index. POS is the type of pharmacy used: retail, mail order, or MTF at index.

Product type is a categorical list of each product included in the study. Product brand is a categorical list of each product brand included in the study. Appendix A is a list of the included products.

STATISTICAL ANALYSIS

Statistical analysis was performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago) and IBM SPSS Statistics for Windows, Version 23.0 (Amonk, NY: IBM Corporation).[96,97] All inferential statistics used two-tailed tests and a significance cut-off of 0.01. Paired t-tests, multivariate regressions, and logistic regressions were used to test hypotheses. All power analyses were conducted using G*Power 3.1.9.2 for Windows.[98,99]

Paired T-test

A paired t-test is used to test for a difference of means between paired observations that differ on the independent variable. The assumptions for a paired t-test are normality and homogeneity of variance.

Several studies inform an estimate of effect size for each t-test. The PA/ST program in this study did not allow grandfathering. A meta-analysis of ST programs indicated that programs that do not grandfather have the largest savings.[62] Delate et al. and Smalley et al. found 50% (SD not given) and 53% (SD = 17.96) reductions respectively in drug expenditures after implementing ST programs with no grandfathering.[100,101] This suggests the effect size for reduction in expenditures could be as high as 0.65. For PA/ST programs that do grandfather, the effect size is likely much lower.[62] Therefore, effect sizes ranging from 0.1 to 0.65 were used for power analysis.

Due to the potential for a large population in this study, power was set at 95% and the lower limit of effect size was assumed to be as conservative as possible (0.1). Therefore, an estimated total n of 1,785 was needed.

Multiple Regression

Multiple regression is used to predict a dependent variable from a set of predictors. Objectives three and four use multiple regression to predict MPR in the post-PA period or persistence days in the post-PA period using the pre-PA MPR or persistence days, respectively, while controlling for covariates. Each objective has one predictor variable of interest.The following assumptions must be met: 1) there is a linear relationship between the dependent and independent variables; 2) lack of multicollinearity (or correlation between independent variables); 3) independence of observations; 4) homoscedasticity of variance; and 5) normal distribution of residuals. The regression model is as follows:

$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \ldots + \beta_nX_n$
Y = dependent variable
β_0 = Intercept
β_1 to β_n = regression coefficients
X_1 to X_n = independent variables

Due to the potential for a large population in this study, power was set at 0.95 and the lower limit of effect size was assumed to be as conservative as possible (0.1). Therefore, an estimated total n of 292 was needed.

Logistic Regression

Logistic regression uses independent variables to predict a dichotomous dependent variable. Observations must be independent in order to meet logistic

regression assumptions. Objective five uses several independent variables to predict switching, restarting, and cycling patterns. The regression model is as follows:

$\text{Logit} [\theta (x)] = \log [\theta (x) / 1 - \theta (x)] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots + \beta_n X_n$
$\theta (x)$ = probability of success
$1 - \theta (x)$ = probability of failure
β_0 = constant of equation
β_1 to β_n = regression coefficients
X_1 to X_n = independent variables

For the power analysis, odds ratios for switching, restarting, and cycling patterns were estimated from existing literature. According to Schoenfeld et al., the probability of switching was 5%. This yields an odds ratio of switching to not switching of 0.0027. The odds of not switching are 361 times higher than switching. Restarting, however, occurred in 33% of patients which results in an odds ratio of 0.25. The odds of not restarting were four times higher than restarting.[5] According to Donatucci et al., 59% of patients had at least one episode of cycling.[7] This corresponds to an odds ratio of 2.07. The odds of cycling are twice the odds of not cycling. These literature-based odds ratios were used to calculate the required sample size. In addition, R-squared was varied from 0.1 to 0.3.

These sample size calculations are summarized in Tables 3.1 – 3.3. For switching, at least 9,406 subjects are needed. For restarting, at least 6,771 subjects are needed. For cycling, at least 4,584 subjects are needed. The highest sample size needed is 9,406.

Table 3.1: Logistic Regression Power Calculations – Switching

Odds ratio	0.0027	0.01	0.05	0.1
Pr(Y=1 | X=1)H_0[a]	0.03	0.03	0.03	0.03
R-squared[b]	0.1	0.1	0.1	0.1
n required	7316	3437	1812	1623
Odds ratio	0.0027	0.01	0.05	0.1
Pr(Y=1 | X=1)H_0[a]	0.03	0.03	0.03	0.03
R-squared[b]	0.2	0.2	0.2	0.2
n required	8230	3866	2039	1825
Odds ratio	0.0027	0.01	0.05	0.1
Pr(Y=1 | X=1)H_0[a]	0.03	0.03	0.03	0.03
R-squared[b]	0.3	0.3	0.3	0.3
n required	9406	4418	2330	2086

Y = dependent variable; X = independent variables; $\alpha = 0.01$ (two-tailed); $\beta = 0.05$(power = 95%); assumes a Poisson distribution for the independent variable of interest

[a] Probability of an event under H_0. The modeled event was switching.

[b] When independent variable of interest is regressed on the other independent variables or covariates in the regression

Table 3.2: Logistic Regression Power Calculations – Restarting

Odds ratio	0.25	0.4	0.5	0.6
Pr(Y=1 | X=1)H_0[a]	0.03	0.03	0.03	0.03
R-squared[b]	0.1	0.1	0.1	0.1
n required	1874	2628	3565	5266
Odds ratio	0.25	0.4	0.5	0.6
Pr(Y=1 | X=1)H_0[a]	0.03	0.03	0.03	0.03
R-squared[b]	0.2	0.2	0.2	0.2
n required	2109	2957	4011	5924
Odds ratio	0.25	0.4	0.5	0.6
Pr(Y=1 | X=1)H_0[a]	0.03	0.03	0.03	0.03
R-squared[b]	0.3	0.3	0.3	0.3
n required	2410	3379	4584	6771

Y = dependent variable; X = independent variables; $\alpha = 0.01$ (two-tailed); $\beta = 0.05$(power = 95%); assumes a Poisson distribution for the independent variable of interest

[a] Probability of an event under H_0. The modeled event was restarting.

[b] When independent variable of interest is regressed on the other independent variables or covariates in the regression

Table 3.3: Logistic Regression Power Calculations – Cycling

Odds ratio	0.5	1.5	2.0	2.5
Pr(Y=1 | X=1) H_0[a]	0.03	0.03	0.03	0.03
R-squared[b]	0.1	0.1	0.1	0.1
n required	3565	2203	526	255
Odds ratio	0.5	1.5	2.0	2.5
Pr(Y=1 | X=1) H_0[a]	0.03	0.03	0.03	0.03
R-squared[b]	0.2	0.2	0.2	0.2
n required	4011	2479	592	287
Odds ratio	0.5	1.5	2.0	2.5
Pr(Y=1 | X=1) H_0[a]	0.03	0.03	0.03	0.03
R-squared[b]	0.3	0.3	0.3	0.3
n required	4584	2833	676	327

Y = dependent variable; X = independent variables; $\alpha = 0.01$ (two-tailed); $\beta =$ 0.05(power = 95%); assumes a Poisson distribution for the independent variable of interest

[a] Probability of an event under H_0. The modeled event was cycling.

[b] When independent variable of interest is regressed on the other independent variables or covariates in the regression

SUMMARY

This study aims to fill a gap in knowledge that impacts the health of millions of men. As utilization management measures become more widely used, it is important to investigate all the outcomes of these actions. It is clear that the outcomes of utilization management not traditionally evaluated may be, in fact, just as important as medication costs and utilization. Simultaneously evaluating utilization management measures with medication use behaviors will ultimately shape the way policy is designed and evaluated in order to ensure the best patient outcomes.

Chapter 4: Results

OVERVIEW

This chapter presents the results of this study. First, there is a description of the data extraction. The next section contains descriptive information about the study subjects. The final section presents the results of each objective.

DATA EXTRACTION

From March 1, 2012 to February 28, 2014, 78,623 patients were identified as having at least one prescription for Androgel, Testoderm, Fortesta, Axiron, Androderm, Fortesta, Striant, Vogelxo, or a generic topical testosterone product. There were 423,336 prescriptions that met the inclusion criteria. This group represents the overall cohort of subjects with at least one qualifying prescription.

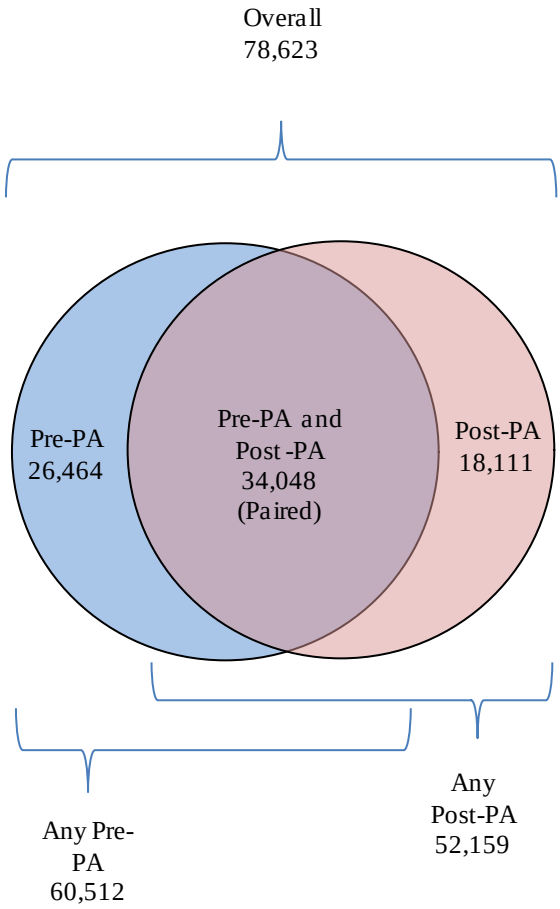
The date of the implementation of the prior authorization (PA) and step therapy (ST) was March 1, 2013. Of the 78,623 patients identified, 26,464 (33.6%) patients only had prescriptions prior to the PA implementation and 18,111 (23.0%) only had prescriptions after the PA implementation. Patients with only one qualifying prescription from March 1, 2012 to February 28, 2014 made up 21.2% (16,646) of the overall cohort. Additionally, 11 patients had prescription claims for Testoderm, a product which was not available during the study period and therefore, those prescriptions were excluded as they may have been inappropriately labeled claims. Table 4.1 lists the results of the application of the exclusion criteria and Figure 4.1 depicts the patient groups.

Table 4.1 Patient and Prescription Exclusion

	Patients Remaining N (%)	Prescriptions Remaining N (%)
Patients with any qualifying prescription from March 1, 2012 to February 28, 2014	78,634 (100%)	423,486 (100%)
Remove Testoderm prescriptions	78,623 (99.9%)	423,336 (99.9%)
Remove patients with only one prescription	61,977 (78.8%)	406,695 (96.0%)
Remove patients without both pre-PA and post-PA prescriptions	34,048 (43.3%)	302,534(71.4%)

As seen in Figure 4.1, of the 78,623 overall patients identified, 34,048 had at least one prescription before March 1, 2013 and at least one prescription on or after March 1, 2013. These subjects represent the paired group with at least one pre-PA and one post-PA prescription. Of the 60,512 patients with claims before the implementation of the PA, 56.3% met the PA criteria and had a successful claim for an included product after PA implementation. Those 60,512 patients represent 77.0% of the overall 78,623 study subjects. Overall, 52,159 (66%) of the 78,623 patients successfully had claims after PA implementation.

Figure 4.1 Number of Patients by Category



Quantity, cost, and days supply claim fields contained outlying values. An algorithm comparing quantity, cost, and days supply of reasonable and frequently occurring claims to those outliers generated adjusted values that were used in data analysis. For example, there were 12,946 (3.1%) claims with a quantity of one. A new variable was created to adjust the quantity of these claims to the appropriate package size corresponding to the product in the claim. A claim with a quantity of "one" for Fortesta was adjusted to a quantity of 60 grams for analysis. Overall, 21,779 quantity adjustments

were made. Of those adjustments, 99.1% occurred in claims from a military treatment facility (MTF).

DESCRIPTIVE RESULTS

Demographics

Overall Group

The overall group (at least one prescription pre-PA or post-PA) consisted of 78,623 patients. Retirees made up 82.6% of this group followed by active duty service members (11.9%). Active duty family members, guard and reserve members and their families, retired family members, and unknown categories make up the remaining 5.5% of patients.

The mean age at index in the overall group was 59.1 (SD 12.9) years. Half of these patients (50.0%) were 45 to 64 years old at index. The next largest age group was patients age 65 and over accounting for 36.7% of the overall subjects. Patients aged 18 to 34 years made up 3.9% of the subjects and those 35 to 44 years old made up 9.4% of the subjects.

Paired Groups

In the 34,048 paired subset (at least one prescription pre-PA and post-PA), retirees made up 86.1% of this group followed by active duty service members (9.4%). Active duty family members, guard and reserve members and their families, and unknown categories made up the remaining 4.5% of patients.

The mean age at index in the paired subset group was 60.2 (SD 12.0) years. Just over half of these patients (51.8%) were 45 to 64 years old at index. The next largest age group was patients age 65 and over, accounting for 38.6% of the subjects. Patients age 18 to 34 made up 2.1% of the subjects and those 35 to 44 years old made up 7.4% of the subjects. Table 4.2 summarizes the demographics of the overall and paired groups.

Table 4.2 Descriptive Comparison of Overall and Paired Groups Demographics

	Overall Group (N=78,623)	Paired Group (N = 34,048)
Beneficiary category		
Retirees	82.6%	86.1%
Active duty service members	11.9%	9.4%
Other	5.5%	4.5%
Mean age at index	59.1 (SD 12.9)	60.2 (SD 12.0)

Clinical Characteristics

Overall Group

This section discusses the clinical characteristics of the 78,623 patients in the overall group. From March 1, 2012 to February 28, 2014, 53.6% of patients had an index prescription for an Androgel product. Specifically, 23.3% of index prescriptions were for Androgel 1.62% metered dose pump. Fortesta represented 19.1% of index prescriptions. Testim represented 11.4%, Androderm represented 8.0%, Axiron represented 7.8%, and Striant represented 0.2% of index prescriptions. A comparison of index products before and after the PA is discussed under ‘Objective One’ results.

The number of prescriptions per patient ranged from one to 39 with a mean of 5.38 (4.77) prescriptions. There were 16,646 patients with one prescription, 11,604 patients with two prescriptions, 8,555 patients with three prescriptions, 7,132 patients with four prescriptions, and 5,737 patients with five prescriptions. Patients with five or fewer prescriptions made up 63.2% of the subjects. All of the patients with 24 or more prescriptions had prescriptions in the pre-PA and post-PA periods.

The mean number of products used per patient was 1.483 (SD = 0.664). Most patients (60.3%) used only one product. Of the 25,135 (32.0%) of patients that used two products, the most common combination (88.0%) was Androgel 1.62% metered dose pump and Fortesta.

Most patients (82.9%) in the overall group used only one pharmacy point of service (POS). The most common POS by prescription claim volume was retail which accounted for 242,795 (57.4%) of claims followed by military treatment facilities (MTF) (28.7%), and mail order (14.0%). Retail claims accounted for 70.2% ($90,401,927) of total costs and 48.1% of 30-day equivalents dispensed.

Each testosterone product delivers testosterone in a unique way. In order to compare doses of testosterone between products, a proportion of the recommended starting dose (PRSD) for each product was calculated for each prescription. The index PRSD for each patient and mean PRSD for each patient was calculated. The mean PRSD for the index prescriptions was 0.9993 (0.5294). The mean overall PRSD for all prescriptions was 1.0091 (0.4377). The recommended starting dose for each product is listed in Appendix A. Table 4.3 summarizes the descriptive clinical characteristics of the

overall group. Tables 4.4 and 4.5 present select characteristics of the 52,159 patients with a successful prescription following PA implementation.

Table 4.3 Clinical Characteristics of the Overall Group

	Overall Group (N = 78,623)
Index product	Androgel (53.6%)
Mean prescriptions per patient	5.38 (SD 4.77)
Number of patients with one prescription	16,646
Number of products per patient	1.483 (0.664)
Proportion of prescription claim volume by point of service	
Retail	57.4%
Military treatment facilities	28.7%
Mail order	14.0%
Mean index proportion of the recommended starting dose	0.993 (SD 0.529)
Mean proportion of the recommended starting dose	1.009 (SD 0.438)

Table 4.4 Frequency and Percentage of Product Brand, Point of Service, and Beneficiary Category in Successful Prior Authorization Patients

		N	%
Brand of Product (Index)	ANDRODERM	3,922	7.5%
	ANDROGEL	25,484	48.9%
	AXIRON	3,208	6.2%
	FORTESTA	14,025	26.9%
	STRIANT	69	0.1%
	TESTIM	5,451	10.5%
	Total	52,159	100.0%
Point of Service	Mail Order	7,061	13.5%
	Military Treatment Facility	15,814	30.3%
	Retail	29,284	56.1%
	Total	52,159	100.0%
Beneficiary Group	Active duty family	462	0.9%
	Active duty service member	6,298	12.1%
	Non-active duty family	77	0.1%
	Non-active service member	1,063	2.0%
	Retiree	43,219	82.9%
	Retiree family	1,014	1.9%
	Unknown	26	0.0%
	Total	52,159	100.0%

Table 4.5 Mean Age and Mean Dose of Patients with Successful Prior Authorization Prescriptions

	Prior Authorization Success N = 52,159	
	Mean	Standard Deviation
Age at index	59	13
Index recommended starting dose	0.99	0.51

OBJECTIVE RESULTS

This section contains the results of the hypotheses tested by each objective. Table 4.18 summarizes the study objectives, hypotheses, and results and can be found at the end of this chapter.

Objective One

The first objective is to describe medication costs, number of new users, number of 30-day equivalent prescriptions, proportion of prescriptions by pharmacy POS, proportion of prescriptions by product, mean patient age, and mean daily dose before and after PA and ST program initiation in the Department of Defense (DoD). The results are presented in Tables 4.6 through 4.11.

Table 4.6 Summary Comparison of Pre- and Post-Prior Authorization Costs and Utilization

	Pre-Prior Authorization	Post-Prior Authorization	Change
Total Medication Costs	$ 78,186,289	$ 50,672,238	$-27,514,051
Number of New Users	26,757	18,111	-8,646
Number of 30-Day Equivalent Prescriptions	311,391	287,063	-24,328
Number of Prescriptions	222,288	201,048	-21,240

The following results are reported in terms of overall prescription volume rather than by patient. Prior to the PA implementation, the majority of prescriptions (65.0%) pe-PA were filled at retail pharmacies. After the PA implementation, the plurality of prescriptions (48.9%) were filled at retail pharmacies, however, the proportion of prescriptions filled at retail pharmacies decreased pre to post. MTF pharmacy utilization increased from 22.1% of pre-prescriptions to 35.9% of prescriptions after PA implementation. Mail order increased as well from 12.9% to 15.2%. As a proportion of all 423,336 prescriptions, these trends remain. Retail pharmacy decreased from 34.1% to 23.2%. MTF pharmacy increased from 11.6% to 17.1%. Mail order pharmacy increased from 6.8% to 7.2%. Table 4.7 summarizes prescription volume by prescription POS and Table 4.8 summarizes total prescription volume by POS.

Table 4.7 Number and Percentage of Prescription Volume before and After Prior Authorization by Point of Service

	Pre-Prior Authorization		Post-Prior Authorization		Total	
	Number of Prescriptions	%	Number of Prescriptions	%	Number of Prescriptions	% All Prescriptions
Mail Order	28,603	12.9%	30,477	15.2%	59,080	14.0%
Military Treatment Facility	49,189	22.1%	72,272	35.9%	121,461	28.7%
Retail	144,496	65.0%	98,299	48.9%	242,795	57.4%
Total	222,288	100.0%	201,048	100.0%	423,336	100.0%

Table 4.8 Number and Percentage of Total Prescription Volume before and After Prior Authorization by Point of Service

	Pre-PA		Post-PA		Total	
	Number of Prescriptions	%	Number of Prescriptions	%	Number of Prescriptions	% All Prescriptions
Mail Order	28,603	6.76%	30,477	7.20%	59,080	13.96%
Military Treatment Facility	49,189	11.62%	72,272	17.07%	121,461	28.69%
Retail	144,496	34.13%	98,299	23.22%	242,795	57.35%
Total	222,288	52.51%	201,048	47.49%	423,336	100.00%

The market share for each product by prescription volume changed after PA implementation. The proportion of each product dispensed changed from pre-PA to post-PA. The largest change was the proportion of Fortesta prescriptions. Pre-PA prescriptions for Fortesta represented 2.31% of the total 423,336 prescriptions. After PA, Fortesta represented 30.82% of the total 423,336 prescriptions. All Androgel products combined represented the largest proportion of prescriptions (35.1%) prior to the PA. After the PA, however, Androgel products represented 8.9% of total prescription volume and Fortesta had the largest proportion (30.8%). After PA implementation, the utilization of all agents

other than Fortesta decreased compared to prior to the PA. Table 4.9 summarizes the proportion of specific products dispensed before and after PA implementation. Table 4.10 summarizes the brand of products dispensed before and after PA implementation.

Table 4.9 Number and Percentage of Prescription Volume Before and After Prior Authorization by Product and Strength

	Pre-Prior Authorization		Post-Prior Authorization		Total	
	# Prescriptions	% All Prescriptions	# Prescriptions	% All Prescriptions	# Prescriptions	% All Prescriptions
ANDRODERM 2 MG/24 HR PATCH TD24	3,152	0.74%	2,847	0.67%	5,999	1.42%
ANDRODERM 2.5MG/24 HR PATCH TD24	11,906	2.81%	9,471	2.24%	21,377	5.05%
ANDRODERM 5 MG/24 HR PATCH TD24	366	0.09%	16	0.00%	382	0.09%
ANDROGEL 1.25G (1%) GEL MD PMP	33,219	7.85%	5,382	1.27%	38,601	9.12%
ANDROGEL 1.25G-1.62 GEL PACKET	23	0.01%	222	0.05%	245	0.06%
ANDROGEL 2.5G-1.62 GEL PACKET	26	0.01%	390	0.09%	416	0.10%
ANDROGEL 20.25/1.25 GEL MD PMP	66,154	15.63%	21,845	5.16%	87,999	20.79%
ANDROGEL 25MG(1%) GEL PACKET	7,064	1.67%	1,445	0.34%	8,509	2.01%
ANDROGEL 50 MG (1%) GEL PACKET	42,392	10.01%	8,396	1.98%	50,788	12.00%
AXIRON 30MG/1.5ML SOL MD PMP	17,871	4.22%	6,522	1.54%	24,393	5.76%
FORTESTA 10 MG (2%) GEL MD PMP	9,786	2.31%	130,479	30.82%	140,265	33.13%
STRIANT 30 MG MUC ER	334	0.08%	275	0.06%	609	0.14%
TESTIM 50 MG (1%) GEL (GRAM)	29,995	7.09%	13,758	3.25%	43,753	10.34%
Total	222,288	52.51%	201,048	47.49%	423,336	100.00%

Table 4.10 Number and Percentage of Prescription Volume Before and After Prior Authorization by Product

	Pre-Prior Authorization		Post-Prior Authorization		Total	
	# Rxs[1]	% Total Rxs[1]	# Rxs[1]	% Total Rxs[1]	# Rxs[1]	% Total Rxs[1]
ANDRODERM	15,424	3.64%	12,334	2.91%	27,758	6.56%
ANDROGEL	148,878	35.17%	37,680	8.90%	186,558	44.07%
AXIRON	17,871	4.22%	6,522	1.54%	24,393	5.76%
FORTESTA	9,786	2.31%	130,479	30.82%	140,265	33.13%
STRIANT	334	0.08%	275	0.06%	609	0.14%
TESTIM	29,995	7.09%	13,758	3.25%	43,753	10.34%
Total	222,288	52.51%	201,048	47.49%	423,336	100.00%

[1] Rxs = Prescriptions

The following results are reported in terms of the 78,623 overall qualifying patients, rather than by prescriptions. Table 4.11 summarizes key characteristics comparing the pre-PA patients and post-PA pateints. The mean index age for patients with their index prescription occurring in the pre-PA period was 60 years (SD = 13, N = 60,512). The mean age in patients with their index prescription occurring in the post-PA period was 56 years (SD = 13, N = 18,111).

The mean PRSD in the pre-PA index patients was 1.03 (SD = 0.43, N = 60,512). In the post-PA period the mean PRSD was 0.92 (SD = 0.44, N = 18,111). The index PRSD in the pre-PA index patients was 1.03 (SD = 0.53, N = 60,512). In the post-PA period the index PRSD was 0.91 (SD = 0.53, N = 18,111).

Table 4.11 Patient Level Comparison Before and After Prior Authorization

	Pre-Prior Authorization	Post-Prior Authorization
Number of Patients	60,512	18,111
Mean Index Age (SD)	60 (13)	56 (13)
Mean Daily Proportion of Recommended Starting Dose (SD)	1.03 (0.43)	0.92 (0.44)
Mean Index Proportion of Recommended Starting Dose (SD)	1.03 (0.53)	0.91 (0.53)
Most Common Index Product	Androgel 1.62% metered dose pump (27.3%)	Fortesta (69.6%)
Most Common Index Brand	Androgel (65.2%)	Fortesta (69.6%)

Objective Two

Objective two compares adherence and persistence before and after the implementation of the PA and ST criteria. The patients in this objective are the 34,048 patients with at least one prescription in the pre-PA period and at least one prescription in the post-PA period. These patients are the paired patient group.

The first hypothesis (Ho_{2a}) is that there is no significant difference in adherence before and after PA/ST implementation. Adherence was measured using MPR. In the 34,048 paired patients, 4,715 patients did not have two prescriptions in the pre-PA period. In the post-PA period, 5,160 did not have two prescriptions. Therefore, 1,435 patients did not have two pre-PA prescriptions or two post-PA prescriptions and both pre-PA and post-PA MPR could not be calculated. A total of 8,442 patients did not meet MPR criteria (at least two prescriptions) in the pre-PA and post-PA time periods. Therefore, the t-test included 25,606 of the 34,048 patients.

In the pre-PA period, 55.22% of patients achieved an MPR of 0.80 or greater. In the post-PA period, 53.46% of patient achieved an MPR of 0.80 or greater. A paired t-test showed that the mean MPR before the PA (0.7865, SD = 0.195) was slightly (but statistically significantly) higher than the mean MPR after the PA (0.7784, SD = 0.200) ($t = 5.798$; $df = 25{,}605$; $p < 0.01$). Therefore, the hypothesis is rejected. Table 4.12 summarizes the results of this test.

Table 4.12 Adherence Before and After Prior Authorization (N= 25,606)

N = 25,606	Pre- Prior Authorization	Post-Prior Authorization
MPR Mean (SD)	0.7865 (0.195)	0.7784 (0.200)
MPR ≥ 0.80 N (%)	14,140 (55.22%)	13,689 (53.46%)

The second hypothesis (Ho_{2b}) is that there is no significant difference in persistence when comparing before and after PA/ST implementation. Persistence was measured using persistence days. Three acceptable gaps were used to determine persistence. Acceptable gaps of 30 days, 60 days, and 1.5 times the previous days supply were tested. Table 4.13 summarizes the results.

Table 4.13 Comparison of Persistence Before and After Prior Authorization

N = 34,048	Pre-Prior Authorization Proportion of Persistent Patients N = 34,048	Mean Persistence Days (SD)	Post-Prior Authorization Proportion of Persistent Patients	Mean Persistence Days (SD)	Significance
30 day gap	64%	117.7 (96.8)	63%	115.3 (96.3)	t = 4.049; df = 34,047; p < 0.01
60 day gap	75%	148.2 (104.6)	74%	147.8 (105.9)	t = 0.686; df = 34,047; p = 0.493
Gap 1.5 times previous days supply	58%	98.8 (88.6)	56%	97.6 (87.9)	t = 2.253; df = 34,047; p = 0.024

A paired t-test showed that the mean persistence days before the PA (117.7, SD = 96.8) was slightly (but statistically significantly) higher than the mean persistence days after the PA (115.3, SD = 96.3) (t = 4.049; df = 34,047; p < 0.01) when an acceptable gap of 30 days was used. Therefore, this hypothesis was rejected.

A paired t-test showed no significant difference in mean persistence days before the PA (148.2, SD = 104.6) and mean persistence days after the PA (147.8, SD = 105.9) (t = 0.686; df = 34,047; p = 0.493) when an acceptable gap of 60 days was used. Therefore, this hypothesis failed to be rejected.

A paired t-test showed no significant difference in mean persistence days before the PA (98.8, SD = 88.6) and mean persistence days after the PA (97.6, SD = 87.9) (t = 2.253; df = 34,047; p = 0.024) when an acceptable gap of 1.5 times the previous prescriptions' days supply was used. Therefore, this hypothesis failed to be rejected.

Objective Three

Multiple regression was used to test whether adherence measured by MPR in the pre-PA time period is a predictor of MPR in the post-PA time period while controlling for covariates (starting dose (index PRSD), mean dose (PRSD), age, mean copay, point of service, and brand of product). The dependent variable was MPR in the post-PA period. The independent variable was MPR in the pre-PA period.

The variable entry method was used. Covariates were placed in block one and the independent variable in block two. Assumptions of constant variance, normality of residuals, and multicollinearity were checked. There is no pattern in the plot of the residuals versus the predicted values of the DV indicating constant variance. The plot of the residuals appears reasonably normal. Multicollinearity diagnostics indicate tolerance is not less than 0.1 for any IV and therefore multicollinearity is not present.

Model one includes only the covariates and indicates at least one of the covariate predictors is significantly related to the MPR in the post-PA time period ($R^2 = 0.051$, $R^2_{adj} = 0.051$, $F(11,25594) = 125.81$, $p < 0.001$). This model, overall, is able to explain 5.1% of the variability in MPR post-PA.

Model two contains the covariates and MPR pre-PA as the predictor and indicates at least one of the predictors is significantly related to the MPR in the post-PA time period ($R^2 = 0.16$, $R^2_{adj} = 0.159$, $F(12,25593) = 405.77$, $p<0.001$). This model, overall, is able to explain 15.9% of the variability in MPR post-PA. MPR in the pre-PA time period was a significant positive predictor of post-PA MPR ($B = 0.348$, $\beta = 0.338$, $t(25,593) = 57.5$, $p < 0.001$. This means for every increase in the pre-PA MPR by 1, the post-PA

MPR increases by 0.348. Therefore, the hypothesis is rejected. There is a significant difference in adherence before and after PA/ST implementation while controlling for covariates.

Objective Four

Multiple regression was used to test whether persistence measured by persistence days in the pre-PA time period is a positive predictor of persistence in the post-PA time period while controlling for covariates (starting dose (index PRSD), mean dose (PRSD), age, mean copay, point of service, and brand of product). The dependent variable was persistence days in the post-PA period. The independent variable was persistence days in the pre-PA period. Persistence days associated with a gap of 30 days are reported.

The variable entry method was used. Covariates were placed in block one and the independent variable in block two. Assumptions of constant variance, normality of residuals, and multicollinearity were checked. There is no pattern in the plot of the residuals versus the predicted values of the DV indicating constant variance. The plot of the residuals appears somewhat normal. Multicollinearity diagnostics indicate tolerance is not less than 0.1 for any IV and therefore multicollinearity is not present.

Model one includes only the covariates and indicates at least one of the covariate predictors is significantly related to persistence days in the post-PA time period (R^2= 0.009, R^2_{adj} = 0.009, $F(11,34036) = 28.27$, $p < 0.001$) when using a 30 day gap. This model, overall, is able to explain 0.9% of the variability in persistence days post-PA. The results of model one were robust to changes in the allowable gap (30 days, 60 days, and 1.5 times the previous prescriptions' days supply).

Model two contains the covariates and persistence days pre-PA as the predictor and indicates at least one of the predictors is significantly related to the MPR in the post-PA time period ($R^2 = 0.129$, $R^2_{adj} = 0.129$, $F(12,34045) = 419.53$, $p < 0.001$). This model, overall, is able to explain 12.9% of the variability in persistence post-PA. Persistence days in the pre-PA time period was a significant positive predictor of post-PA persistence days ($B = 0.348$, $\beta = 0.350$, $t(34,045) = 68.42$, $p < 0.001$. This means for every increase in pre-PA persistence days by one, the post-PA persistence days increase by 0.348. The results of model one were robust to changes in the allowable gap (30 days, 60 days, and 1.5 times the previous prescriptions' days supply). Therefore, the hypothesis is rejected. There is a significant difference in persistenc before and after PA/ST implementation while controlling for covariates.

Objective Five

In the post-PA period, 19.1% of the 34,048 patients switched products at least once from their index post-period product. Restarting behaviors occurred in 23.4% of the 34,048 paired patients. Cycling occurred in 18.6% of paired patients. The goal of objective five is to predict the likelihood of switching, restarting, and cycling patterns post PA/ST, by product type, overall average daily dose, point of service, and age group using logistic regression. Table 4.17 summarizes the results of the logistic regression. Tables 4.14, 4.15, and 4.16 summarize the results of the logistic regression for switching, restarting, and cycling respectively.

Table 4.14 Logistic Regression Results for Objective Five - Switching

Product Type – Androgel Reference				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Androderm	0.850	0.739-0.978	8.899	0.003
Axiron	0.703	0.608-0.814	38.473	< 0.01
Fortesta	0.264	0.199-0.349	149.557	< 0.01
Striant	0.355	0.092-1.366	3.921	0.048
Testim	0.804	0.721-0.895	27.183	< 0.01
Product Type – Fortesta Reference				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Androgel	3.225	2.370-4.389	95.803	< 0.01
Androderm	3.794	2.865-5.024	149.557	< 0.01
Axiron	2.668	1.955-3.641	66.084	< 0.01
Striant	1.347	0.341-5.326	0.311	0.577
Testim	3.049	2.270-4.095	94.781	< 0.01
Overall Average Daily Dose				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Overall Average Daily Dose	0.899	0.823-0.981	9.917	0.002
Point of Service – Retail Reference				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Mail Order	0.852	0.763-0.951	13.988	< 0.01
Military Treatment Facility	2.203	2.034-2.385	654.235	< 0.01
Age				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Age	0.989	00.986-0.992	91.029	< 0.01

Hypothesis H_{5oa} states there is no significant difference in the likelihood of switching by product type. The first iteration of this test Androgel is the reference product. In the second iteration, Fortesta is the reference product. In the first iteration, the product type variable was dummy coded with Androgel as the reference product. The Hosmer-Lemeshow test of fit is not significant ($\chi^2 = 0.000$; df = 2, p = 1.000) indicating good model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the primary independent variable, product type, is significant ($\chi^2 = 263.595$; df = 5, $p < 0.01$). This suggests at least one predictor is related to switching status.

The reference product is Androgel. Androderm (OR= 0.850; 99% CI= 0.39 – 0.978; p=0.003), Axiron (OR= 0.703; 99% CI= 0.608 – 0.814; p<0.001), Fortesta (OR= 0.264; 99% CI= 0.199 – 0.349; p<0.001), and Testim (OR= 0.804; 99% CI= 0.721 – 0.895; p<0.001) were significant predictors. Striant was not significant (OR= 0.355; 99% CI= 0.092 – 1.366; p=0.048). Compared to Androgel, the chances of switching decrease by 15% for Androderm, 30% for Axiron, 74% for Fortesta, and 20% for Testim, therefore, the hypothesis is rejected for Androderm, Axiron, Fortesta, and Testim.

In the second iteration, the product type variable was dummy coded with Fortesta as the reference product. The Hosmer-Lemeshow test of fit is not significant ($\chi^2 = 0.000$; df = 2, p = 1.000) indicating good model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the primary independent variable, product type, is significant ($\chi^2 = 263.595$; df = 5, $p < 0.01$). This suggests at least one predictor is related to switching status.

The reference product is Fortesta. Androderm (OR= 3.794; 99% CI= 2.865 – 5.024; p<0.001), Androgel (OR= 3.225; 99% CI= 2.370 – 4.389; p<0.001), Axiron (OR= 2.668; 99% CI= 1.955 – 3.641; p<0.001), and Testim (OR= 3.049; 99% CI= 2.270 – 4.095; p<0.001) were significant predictors. Striant was not significant (OR= 1.347; 99% CI= 0.341 – 5.326; p=0.577). Compared to Fortesta, the chances of switching increase by 279.4% for Androderm, 222.5% compared to Androgel, 166.8% for Axiron, and 204.9% for Testim. Therefore, the hypothesis is rejected for Androderm, Androgel, Axiron, and Testim.

Hypothesis H_{o5b} states there is no significant difference in the likelihood of switching by average daily dose. The Hosmer-Lemeshow test of fit is significant (χ^2 = 420.512; df = 6, p < 0.01) indicating a poor model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the primary independent variable, mean daily dose, is significant (χ^2 = 10.002; df = 1, p < 0.01). This suggests mean daily dose is related to switching status. The odds of switching decrease as mean dose increases, however, these results should be interpreted with caution as there is a violation of assumptions.

Hypothesis H_{o5c} states there is no significant difference in the likelihood of switching by point of service. The Hosmer-Lemeshow test of fit is not significant (χ^2 = 0.000; df = 1, p = 1.000) indicating good model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the primary independent variable, point of service, is significant (χ^2 = 749.19; df = 2, p <0.01). This suggests at least one predictor is related to switching status. The

reference POS is retail. Mail order (OR=0.852; 99% CI=0.763 – 0.951; p<0.001) and MTF (OR= 2.203; 99% CI= 2.034 – 2.385; p<0.001) were significant predictors. Compared to retail, the chances of switching decrease by 14.8% at mail order and increase by 10.3% at the MTF. Therefore, the hypothesis is rejected for mail order and MTF.

Hypothesis H_{o5d} states there is no significant difference in the likelihood of switching by age. The Hosmer-Lemeshow test of fit is significant ($\chi^2 = 19.926$; df = 8, p = 0.011) indicating a poor model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the primary independent variable, age, is significant ($\chi^2 = 90.931$; df = 1, $p < 0.01$). This suggests age is related to switching status. The odds of switching decrease as age increases, however, these results should be interpreted with caution as there is a violation of assumptions.

Table 4.15 Logistic Regression Results for Objective Five - Restarting

Product Type – Androgel Reference				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Androderm	1.016	0.883-1.169	0.087	0.768
Axiron	0.970	0.843-1.115	0.317	0.573
Fortesta	1.298	1.086-1.550	14.271	< 0.01
Striant	1.239	0.479-3.207	0.338	0.561
Testim	0.901	0.811-1.002	6.418	0.011
Overall Average Daily Dose				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Overall Average Daily Dose	0.930	0.852-1.015	4.621	0.032
Point of Service – Retail Reference				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Mail Order	0.733	0.659-0.815	57.045	< 0.01
Military Treatment Facility	1.204	1.107-1.310	32.280	< 0.01
Age				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Age	0.995	0.992-0.998	21.602	< 0.01

Hypothesis H_{o5e} states there is no significant difference in the likelihood of restarting by product type. The product type variable was dummy coded with Androgel as the reference product. The Hosmer-Lemeshow test of fit is not significant ($\chi^2 = 0.000$; df = 2, p = 1.000) indicating good model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the

primary independent variable, product type, is significant ($\chi^2 = 23.333$; df = 5, $p < 0.01$). This suggests at least one predictor is related to restarting status.

The reference product is Androgel. Fortesta (OR= 1.298; 99% CI =1.086 – 1.550; p<0.001), was a significant predictor. Androderm (OR=1.016; 99% CI=0.883 – 1.169; p=0.768), Axiron (OR= 0.970; 99% CI=0.843 – 1.115; p=0.573), Straint (OR=1.239; 99% CI =0.479 – 3.207; p=0.561), and Testim (OR=0.901; 99% CI=0.811 – 1.002; p=0.011) were not significant predictors. Compared to Androgel, the chances of restarting increase by 29.8% for Fortesta. The hypothesis is rejected for Fortesta.

Hypothesis H_{o5f} states there is no significant difference in the likelihood of restarting by average daily dose. The Hosmer-Lemeshow test of fit is significant ($\chi^2 = 19.258$; df = 6, p = 0.04) indicating a poor model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the primary independent variable, mean daily dose, is not significant (OR=0.930; 99% CI=0.852 – 1.015; p=0.032). This suggests mean daily dose is not related to restarting status and failure to reject the hypothesis.

Hypothesis H_{o5g} states there is no significant difference in the likelihood of restarting by point of service. The Hosmer-Lemeshow test of fit is not significant ($\chi^2 = 0.000$; df = 1, p = 1.000) indicating good model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the primary independent variable, point of service, is significant ($\chi^2 = 118.163$; df = 2, p <0.01). This suggests at least one predictor is related to switching status. The reference POS is retail. Mail order (OR=0.733; 99% CI =0.659 – 0.815; p<0.001) and

MTF (OR=1.204; 99% CI=1.107 – 1.310; p<0.001) were significant predictors. Compared to retail, the chances of switching decrease by 26.7% at mail order and increase by 20.4% at MTF and therefore, the hypothesis is rejected.

Hypothesis H_{o5h} states there is no significant difference in the likelihood of restarting by age. Hypothesis H_{5b} states there is no difference in restart status by average daily dose. The Hosmer-Lemeshow test of fit is significant ($\chi^2 = 19.926$; df = 8, p = 0.011) indicating a poor model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the primary independent variable, age, is significant (OR=0.995; 99% CI=0.992 – 0.998; p<0.001). This suggests age is related to restarting status. The odds of restarting decrease as age increases; however, these results should be interpreted with caution as there is a violation of assumptions.

Table 4.16 Logistic Regression Results for Objective Five - Cycling

Product Type – Androgel Reference				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Androderm	1.010	0.870-1.174	0.031	0.861
Axiron	1.215	1.053-1.402	12.250	< 0.01
Fortesta	1.324	1.099-1.594	15.081	< 0.01
Striant	0.659	0.204-2.129	0.838	0.360
Testim	0.885	0.789-0.992	7.584	0.006
Overall Average Daily Dose				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Overall Average Daily Dose	0.946	0.862-1.039	2.333	0.127
Point of Service – Retail Reference				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Mail Order	0.564	0.550-0.636	150.129	< 0.01
Military Treatment Facility	1.053	0.963-1.151	2.188	0.139
Age				
	Odds Ratio	99% Confidence Interval	Wald χ^2	p-value
Age	0.995	0.992-0.998	16.433	< 0.01

Hypothesis H_{o5i} states there is no significant difference in the likelihood of cycling by product type. The product type variable was dummy coded with Androgel as the reference product. The Hosmer-Lemeshow test of fit is not significant ($\chi^2 = 0.000$; df = 2, p = 1.000) indicating good model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the

primary independent variable, product type, is significant ($\chi^2 = 38.552$; df = 5, $p < 0.01$). This suggests at least one predictor is related to cycling status.

The reference product is Androgel. Axiron (OR=1.215; 99% CI=1.053 – 1.402; p<0.001), Fortesta (OR=1.324; 99% CI=1.099 – 1.594; p<0.001), and Testim (OR=0.885; 99% CI=0.789 – 0.992; p=0.006) are significant. Androderm (OR=1.010; 99% CI=0.870 – 1.174; p=0.861) and Striant (OR=0.659; 99% CI=0.204 – 2.129; p=0.360) are not significant. Compared to Androgel, the chances of cycling increase 21.5% with Axiron, increase 32.4% with Fortesta, and decrease 11.5% with Testim. The hypothesis is rejected for Axiron, Fortesta, and Testim.

Hypothesis H_{o5j} states there is no significant difference in the likelihood of cycling by average daily dose. The Hosmer-Lemeshow test of fit is significant ($\chi^2 = 13.643$; df = 6, p = 0.34) indicating a poor model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the primary independent variable, mean daily dose, is not significant (OR=0.946; 99% CI=0.862 – 1.039; p=0.127). This suggests mean daily dose is not related to cycling status and failure to reject the hypothesis.

Hypothesis H_{o5k} states there is no significant difference in the likelihood of cycling by point of service. The Hosmer-Lemeshow test of fit is not significant ($\chi^2 = 0.000$; df = 1, p = 1.000) indicating good model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the primary independent variable, point of service, is significant ($\chi^2 = 183.055$; df = 2, $p < 0.01$). This suggests at least one predictor is related to cycling status. The

reference POS is retail. Mail order (OR=0.564; 99% CI=0.550 – 0.636; p<0.001) was a significant predictor. MTF (OR=1.053; 99% CI=0.963 – 1.151; p=0.139) was not a significant predictor. Compared to retail, the chances of cycling decrease by 43.6% at mail order, therefore the hypothesis is rejected for retail.

Hypothesis H_{o5l} states there is no significant difference in the likelihood of cycling by age. The Hosmer-Lemeshow test of fit is not significant ($\chi^2 = 9.384$; df = 8, p = 0.311) indicating good model fit. The enter variable method was used. The chi-square test of the difference in fit between the null model and the model including the primary independent variable, age, is significant ($\chi^2 = 16.425$; df = 1, $p < 0.01$). This suggests age is related to cycling status. Age (OR=0.995; 99% CI=0.992 – 0.998; p<0.001) was a significant predictor. The odds of cycling decrease by 0.2% for each additional year of age and therefore the hypothesis is rejected.

Table 4.17 Summary of Logistic Regression Results

	Switch	Restart	Cycle
Product type			
Androgel reference	Yes – Compared to Androgel, the chance of switching decreases by 74% for Fortesta. (OR= 0.264; 99% CI= 0.199-0.349;p=<0.01)	Yes – Fortesta users had a 29.8% higher chance of restarting compared to Androgel. (OR= 1.298; 99% CI=1.086-1.550;p= <0.01)	Yes – Compared to Androgel, Fortesta (32.4%) had higher chances of cycling (OR=1.324; 99% CI=;1.099-1.594, p= <0.01)
Fortesta reference	Compared to Fortesta, the chance of switching increases by 222.5% for Androgel. (OR= 3.225; 99% CI= 2.370-4.389;p=<0.01)	N/A	N/A
Overall average daily dose	No	No	No
Point of service	Compared to retail, the chance of switching decreases by 14.8% at mail order (OR= 0.852; 99% CI=0.763-0.951;p= <0.01)and increases by 120.3% at MTF. (OR= 2.203; 99% CI=2.034-2.385;p= <0.01)	Compared to retail, the chance of restarting decreases by 26.7% at mail order (OR= 0.733; 99% CI=0.659-0.815; p= <0.01) and increases by 20.4% at military treatment facility. (OR= 1.204; 99% CI=1.107-1.310;p= <0.01)	Compared to retail, the chance of cycling decreases by 43.6% at mail order. (OR= 0.564; 99% CI=0.500-0.636;p= <0.01)
Age	No	No	The chance of cycling decreases 0.5% for each additional year of age. (OR= 0.995; 99% CI=0.992-0.998;p= <0.01)

Objective Six

Objective six aims to compare the number of days from the expected end of the last prescription in the pre-PA period to the index prescription in the post-PA period (PA gap days) to the mean number of days for all the gap periods (other than the PA gap) in the paired group of patients. A paired-groups t-test showed that the mean number of PA gap days (94.0, SD = 100.5) was significantly higher than the mean gap period days (46.6, SD = 68.8) ($t = 124$; $df = 34{,}047$; $p < 0.001$) and therefore the hypothesis is rejected.

CONCLUSION

This concludes the reporting of the study results. The next chapter, the discussion, will provide additional context, meaning, and interpretation of the reported results.

Table 4.18 Study Objectives, Hypotheses, and Results

Objective 1: Describe medication costs, number of new users, number of 30-day equivalent prescriptions, proportion of prescriptions by pharmacy point of service, proportion of prescriptions by product, mean patient age, and mean daily dose before and after PA and ST program initiation in the DoD.						
Objective 2: Compare adherence and persistence before and after PA/ST.						
Objectives/ hypotheses	**Dependent variables**	**Measurement level**	**Independent variables**	**Measurement level**	**Statistical analysis**	**Result**
$Ho_{2a:}$ There is no significant difference in mean adherence before and after PA/ST implementation.	MPR	Continuous	PA/ST status	Dichotomous	Paired t-test	Reject
$Ho_{2b:}$ There is no significant difference in mean persistence before and after PA/ST implementation.	Persistence days	Continuous	PA/ST status	Dichotomous	Paired t-test	30 day gap: Reject 60 day gap: Fail to reject 1.5 times previous day supplys gap: Fail to reject
Objective 3: Compare adherence before and after PA/ST while controlling for covariates (starting dose, overall average daily dose, age, copay, point of service, and product type).						
$Ho_{3:}$ There is no significant difference in adherence before and after PA/ST implementation while controlling for covariates.	MPR	Continuous	PA/ST status Covariates	Dichotomous	Multiple regression	Reject
Objective 4: Compare persistence before and after PA/ST while controlling for covariates (starting dose, overall average daily dose, age, copay, point of service, and product type).						
$Ho_{4:}$ There is no significant difference in persistence before and after PA/ST implementation controlling for covariates.	Persistence days	Continuous	PA/ST status Covariates	Dichotomous	Multiple regression	Reject

Table 4.18 Continued

Objective 5: To compare switching, restarting, and cycling patterns post PA/ST, by product type, overall average daily dose, point of service, and age.

Objectives/ hypotheses	Dependent variables	Measurement level	Independent variables	Measurement level	Statistical analysis	Result
Ho_{5a}: There is no significant difference in the likelihood of switching by product type.	Switch status	Dichotomous	Product type	Categorical	Logistic regression	Reject
$Ho_{5b:}$ There is no significant difference in the likelihood of switching by average daily dose.	Switch status	Dichotomous	Overall average daily dose	Continuous	Logistic regression	Fail to reject
Ho_{5c}: There is no significant difference in the likelihood of switching by point of service.	Switch status	Dichotomous	Point of service	Categorical	Logistic regression	Reject
Ho_{5d}: There is no significant difference in the likelihood of switching by age.	Switch status	Dichotomous	Age	Continuous	Logistic regression	Fail to reject
Ho_{5e}: There is no significant difference in the likelihood of restarting by product type.	Restart status	Dichotomous	Product type	Categorical	Logistic regression	Reject

Table 4.18 Continued						
Objective 5: To determine switching, restarting, and cycling patterns post PA/ST, by product type, overall average daily dose, point of service, and age.						
Objectives/ hypotheses	**Dependent variables**	**Measurement level**	**Independent variables**	**Measurement level**	**Statistical analysis**	**Result**
$Ho_{5f:}$ There is no significant difference in the likelihood of restarting by average daily dose.	Restart status	Dichotomous	Overall average daily dose	Continuous	Logistic regression	Fail to reject
$Ho_{5g:}$ There is no significant difference in the likelihood of restarting by POS.	Restart status	Dichotomous	Point of service	Categorical	Logistic regression	Reject
$Ho_{5h:}$ There is no significant difference in the likelihood of restarting by age.	Restart status	Dichotomous	Age	Continuous	Logistic regression	Fail to reject
Ho_{5i}: There is no significant difference in the likelihood of cycling by product type.	Cycling status	Dichotomous	Product type	Categorical	Logistic regression	Reject
$Ho_{5j:}$ There is no significant difference in the likelihood of cycling by average daily dose.	Cycling status	Dichotomous	Overall average daily dose	Continuous	Logistic regression	Fail to reject

Table 4.18 Continued

Objectives/ hypotheses	**Dependent variables**	**Measurement level**	**Independent variables**	**Measurement level**	**Statistical analysis**	**Result**
Objective 5: To determine switching, restarting, and cycling patterns post PA/ST, by product type, overall average daily dose, point of service, and age.						
$H_{5k:}$ There is no significant difference in the likelihood of cycling by point of service.	Cycling status	Dichotomous	Point of service	Categorical	Logistic regression	Reject
$H_{5l:}$ There is no significant difference in the likelihood of cycling by age.	Cycling status	Dichotomous	Age	Continuous	Logistic regression	Reject
Objective 6: Compare mean gap days between the last prescription in pre-period and the first prescription in the post-period to average gap days overall.						
$H_{6:}$ There is no significant difference in gap days during PA/ST implementation and overall mean gap days.	Gap days during PA/ST implementation	Continuous	Mean gap days	Continuous	Paired t-test	Reject

DoD = Department of Defense
PA = prior authorization
ST = step therapy
MPR = medication possession ratio
TBD = to be determined

Chapter 5: Discussion and Conclusions

INTRODUCTION

This is the first known study to examine the Department of Defense (DoD) prior authorization (PA) and step therapy (ST) programs for testosterone products. Results show a decrease in testosterone utilization and costs, as well as possible impacts on testosterone use behaviors. The results chapter presented the overall findings and specific objective findings of this study. This chapter, aims to provide context and meaning to those results. First, the findings of this study will be interpreted. Second, there is a discussion of study limitations and a conclusion including recommended future actions and follow-up research.

DISCUSSION OF RESULTS

Overall Results

Prior to the implementation of the PA program, testosterone use in the DoD was steadily increasing, which is consistent with studies in other populations.[53,87,88] The implementation of the PA for testosterone in the DoD was designed to ensure safe and appropriate use of testosterone products. Of the 60,512 patients with claims before the implementation of the PA, 56.3% met the PA criteria and had a successful claim for an included product after PA implementation. Those 60,512 patients represent 77.0% of the overall 78,623 study subjects. Overall, 52,159 (66%) of the 78,623 patients had successful claims after PA implementation.

In general these results are consistent with other studies evaluating the impacts of PA and ST. One study in Canada found that government-imposed restrictions on

testosterone use led to a 27.9% decrease in testosterone utilization rates in the first six months of prescribing restrictions.[102] Despite these restrictions, within a year, rates of testosterone use returned to historically high levels, primarily driven by topical products.[102] In the year following implementation of the DoD PA and ST programs, utilization of testosterone did decrease, but the trend following the implementation year is not known. Sustained management of testosterone utilization over time is key to the effectiveness of the PA and ST programs, and warrants further investigation.

Demographics

In this study, 50% of patients were 45 to 64 years old at index which is consistent with a previous study showing that in men using topical testosterone, 54% of the patients were age 50-64.[5] The prevalence of low testosterone increases with age; however, in this and other studies the majority of the patients are younger than 65 years old.[5,10,88]

Clinical

Other studies have examined product mix, dose, and duration of therapy in testosterone therapy. Baillargeon et al. found that the majority of testosterone patients were using a topical product.[53] In another study, Androgel was the initiating product in 75% of patients in 2009.[5] From 2010 to 2012, 51% of all testosterone patients in Ontario, Canada used a topical agent.[102] In this study, Androgel was the index product for 53.6% of patients. In this and other studies, Androgel dominated product market share.

Index testosterone dose was, on average, proportionate to the recommended starting dose according to manufacturers in this study and tended to not escalate. Previous studies found that 78.6% of patients initiated at the standard dose and in general tended to

not experience dose escalation. In patients that remained on therapy over time, the proportion of patients on escalated doses did increase.[5] Lack of dose titration is a possible contributor to discontinuation of therapy as patients may not be reaching a dose that is adequate to address symptoms. Additionally, it is known that testosterone levels decline with age, and studies have shown that age may independently be linked to the symptoms of low testosterone, not just the testosterone levels themselves. Therefore, disease escalation may also play a role in therapy failure.[103]

Previous studies found a large number of patients receiving only one prescription. In this study, in the overall group, 21% of patients received only one prescription. Other studies found 18.63% had only one prescription and that only approximately 33% of patients continued therapy longer than two months.[5,53]

Results of Objectives

Here, the results of each of the six objectives are discussed.

Objective One

The first objective is to describe the overall effects of the PA and ST. The PA and ST for were successful at decreasing costs and utilization of testosterone. The process was successful at shifting patients to the preferred agent and eliminating potentially inappropriate use by patients that did not meet treatment criteria. The overall number of utilizers decreased, and additionally the number of new users decreased. The number of utilizers may not have decreased as drastically as it did had there not been no-grandfathering conditions. This is important for future implementation of formulary

decisions. It is important to note that this type of restriction is still not routinely utilized by the DoD in formulary management.

A decrease in the proportion of the recommended starting dose (PRSD) from 1.03 to 0.92 does not represent a clinically relevant decrease in dose, but indicates a trend that after the PA and ST patients did not use as high of a dose as in the pre-period. Doses are adjusted by increments of 50-100% of the PRSD, and therefore a larger change would be needed to be clinically relevant. The utilization of mail order increased in both volume and proportion of prescriptions. Retail utilization decreased and MTF utilization increased. The lowest copays are available at the military treatment facility (MTF) and through mail order.

Objective Two

Objective two compares adherence and persistence before and after the implementation of the PA and ST criteria. Medication possession ratio (MPR) and persistence with a 30 day gap were significantly different before and after implementation. While MPR was higher before implementation, the decrease in MPR was small (0.0081). The proportion of patients with an MPR greater than 0.80 decreased by 1.76%, which is also a small change. Therefore, while MPR was statistically significantly different, these differences are not relevant clinically. Previous studies also found low adherence rates. In one study, the overall average MPR was 56% over six months.[5] In this study the adherence rate ranged from 53.46% to 55.22%.

Persistence days were statistically significantly lower after the implementation with a 30 day gap, but the difference is not clinically relevant. The difference was only

2.4 days. The sensitivity analyses were not statistically significant. This shows that it is important in persistence studies to perform sensitivity analysis for the length of the gap used. Previous studies found the length of therapy ranged from 137 to 146 days.[5] These results are similar to this study, which depending on gap tested, length of therapy ranged from 97.6 to 148.2 days. Use of a shorter, unacceptable gap (30 days) led to higher non-persistent rates and shorter average length of therapy.

The patients that successfully received prior authorization and continued testosterone therapy did not have clinically relevant changes in MPR and persistence overall. There were, however, other persistence related findings which are discussed later in this section.

Objective Three

Objective three examines whether or not MPR in the pre-PA time period can predict MPR in the post-PA time period while controlling for other variables (starting dose (index PRSD), mean dose (PRSD), age, mean copay, point of service, and brand of product). The pre-period MPR and other variables were able to predict 15.9% of the variability in the post-period MPR, and pre-MPR was a significant positive predictor of the post-MPR. The addition of pre-MPR to the model improved the amount of variability explained by 10.8% beyond the other variables. While objective two found that the MPRs were significantly different in the two time periods (but not clinically significant), this objective shows how previous behavior could predict behavior following the PA implementation.

Objective Four

Objective three examines whether or not persistence days in the pre-PA time period can predict persistence days in the post-PA time period while controlling for other variables (starting dose (index PRSD), mean dose (PRSD), age, mean copay, point of service, and brand of product). The pre-PA period persistence days and other variables were able to predict 12.9% of the variability in the post-PA period persistence days, and pre-PA period persistence days were a significant positive predictor of the post-PA period persistence days. The addition of pre-persistence days to the model improved the amount of variability explained by 12.0% beyond the other variables. Objective two found that the persistence days were significantly different in the two time periods (but not clinically significant). This is important because it quantifies what efforts to improve persistence may be able to influence. For every one additional persistence day in the pre-period, there are 0.348 additional days in the future time period.

Objective Five

Objective five examines switching, restarting, and cycling behaviors after the PA and ST implementation by product type, overall average daily dose, point of service, and age. In a previous study, 66.4% of patients discontinued therapy after two months and then 50% of those patients restarted. Only 5% of men who restarted switched to another product.[5] In another study, at three months after initiation, 54% of topical patients and 37% of injectable patients were still using a testosterone product. The majority (60%) of patients using topical therapy had cyclical behavior. There were no meaningful differences between cyclical users by age, physician specialty, copays, diagnosis,

comorbidities, and the use of phosphodiesterase-5 (PDE-5) inhibitors during testosterone therapy. [7]

In this study, the implementation of PA and ST programs shifted patients to Fortesta, the preferred formulary agent. This study specifically isolated the fact that a PA and ST program was implemented, so those switches in product are attributable to a change in benefit design. Fortesta went from 5% of prescription volume to 70% of prescription volume after the PA and ST. After patients successfully navigated the PA and ST therapy, 19.1% had at least one additional therapy switch which was not attributed to the program implementation. Additional research is needed to investigate the characteristics and product mix involved in these switches.

Androgel patient were the most likely to switch products after the PA and ST. Fortesta patients were the least likely to switch products after the PA and ST. This is expected because Fortesta was the preferred product and had the lowest copay and fewest administrative barriers. Additional research is needed to determine clinically if the patients on Fortesta had better outcomes compared to the Androgel patients that may also have contributed to the likelihood of switching. Switching could not be conclusively predicted by dose. Previous studies have shown that as patients discontinue testosterone therapy, the overall average dose increases, indicating that those patients that continue therapy tend to increase their dose over time. Also, escalation of dose was predictive of continuation of therapy.[5] This study was unable to demonstrate a predictive relationship between dose and switching.

Compared to retail patients, patients at the MTF were 120.3% more likely to switch products. This may be attributable to the mix of provider type represented by each point of service (POS), but that information is not known in this study. MTF pharmacies do not have an automated process to implement formulary changes, whereas Express Scripts, Incorporated (ESI) automates the adjudication and approval of PA and ST. MTF pharmacists may have been slower to fully implement the PA and ST, and switches to Fortesta may have occurred after the implementation date leading to a higher likelihood of switching at MTF.

Age was not a reliable predictor of switching. A recent study found that age and testosterone levels are confounding variables in the presence of low testosterone symptoms. Therefore, if testosterone levels are treated adequately and to goal, age is no longer a relevant indicator of disease severity.[103] This study did not include testosterone levels, but follow-up research may show that the actual patient testosterone level would predict medication use behaviors. Dose was also not predictive and appeared to remain stable throughout the study period, which further supports that the appropriateness of therapy for each individual patient and testosterone levels may be driving behaviors.

Restarting behaviors occurred in 23.39% of the 34,048 paired patients. Whether or not the patient restarted represents two concepts. First, that that patient had a break in therapy of greater than 30 days. Second, that patient chose to pursue therapy even after discontinuation. It can be seen as a negative that there is a break in therapy, but the fact that the patient restarted is a positive. This information is usually not captured in persistence studies. The fact that so many patients restarted (23.9%) indicates there is

more to how patients use testosterone than just discontinuation rates. The following section discusses factors that predict restarting behaviors.

Patients on Fortesta were 29.8% more likely to restart compared to patients on Androgel. The other products were not significant predictors of switching. Further research is needed to understand why Fortesta patients were more likely to restart. It may be that patient satisfaction was higher with Androgel and they never had a break in therapy, or patients had breaks but valued therapy enough to return.

Dose was not a significant predictor of restarting, but pharmacy POS was. Mail order was less likely to restart compared to retail, and MTF was more likely to restart compared to retail. Mail order may have been the least likely to restart because the filling procedures are the least immediate. Patients must wait for the medication to arrive. Also, testosterone is a controlled substance, and a new prescription is required every six months. Therefore, additional steps are needed to restart therapy at mail order, and impulsive restarts would be reduced.

As age increases, the odds of restarting decrease. It is known that testosterone levels decrease with age, and patients may become more willing to accept low testosterone symptoms as the natural progression of aging. Additional research is needed in this area to determine if adequate treatment influences restart rate based on age and if these differences are clinically significant.

Cycling occurred in 18.60% of all patients. Cycling patients are important because they are not detected in traditional persistence studies, but they represent a population that has continuous exposure to testosterone which has implications for safety

and behavioral studies. Labeling a single prescription an exposure may not be accurate, and categorizing patients discontinued after one therapy gap lacks inclusion of those patients that cycle.

Product was a significant predictor of cycling. Fortesta patients were 32.4% more likely to cycle compared to Androgel patients. Additional analysis of these patients would reveal whether or not the Fortesta patients are more likely to cycle because they are more likely to have gaps in therapy, or if there is an unknown factor contributing to a intermittent treatment cycle.

Dose was not predictive of cycling behavior. Patients that cycle are exhibiting behavior that indicates they have intermittent need or desire for treatment. Dose is unique to each individual patient's clinical situation. Actual testosterone levels should be evaluated as a potential predictor of cycling behavior.

Compared to retail, the odds of cycling decrease by 43.6% at mail order and MTF is not significantly different from retail. Mail order may be more difficult for patients to obtain a prescription after a break in therapy. A new prescription must be transmitted and the patient has to wait for delivery. This type of service is not conducive to impulsive or intermittent therapy.

Age was a statistically significant predictor of cycling, but age may not be a meaningful predictor. The odds of cycling decrease with each year of age, but only by 0.2%. While the trend is useful, and supports that the odds of restarting also decrease with age, the actual quantification of the odds are small. It is intuitive, however, that

patients would be less likely to cycle because they are also less likely to pursue therapy at all.

Objective Six

The final objective sought to examine the number of days (gap days) from the end of the last pre-PA prescription to the first post-PA prescription. PA gap days were significantly longer than mean gap days. This indicates that on average the longest period between prescriptions occurred immediately following the implementation of the PA and ST. This indicates that the presence of a PA and ST was related to the longest period of time between prescriptions. This information is key for two reasons. First, this signals the need for persistence studies to be informed by the formulary status and changes for each product. Second, PA and ST programs with no grandfathering may have longer gap days than those with grandfathering, and the implications of these differences are not known. Patients spent longer between prescriptions after the PA than the average of their other gaps. This information is needed to understand the actual factors that influence adherence and persistence.

Limitations

The following discussion of limitations provides the framework by which the study results should be interpreted. Retrospective, claims based studies have multiple inherent limitations and there are additional limitations specific to this study.

The data used in this study are comprised of pharmacy claims information in the DoD Pharmacy Data Transaction System (PDTS). These data were not expressly collected for use in this type of study, but with appropriate steps, may be useful. One

major issue with these data is the potential for poor data integrity. For example, individual pharmacies may have erroneously entered incorrect information such as incorrect days supply or quantity. To minimize the effect of outliers or unreliable data, an analysis of outliers was conducted and values that could be reasonably managed were adjusted. The DoD is aware of these data integrity issues from MTF pharmacies and employs extensive efforts to correct and prevent incorrect data submission in the pharmacy claims. Overall, 21,779 quantity adjustments were made. Of those adjustments, 99.1% occurred in claims from MTFs. In general, these adjustments accounted for discrepancies in package sizes.

There are known inaccuracies in the PDTS data for costs. This study does not account for the additional refunds provided by manufacturers at retail pharmacies, and therefore retail costs are relatively correct but not refund-adjusted. There is also potential for cost inaccuracies at the MTFs, however, relative reductions in costs are reliable.

Claims data cannot account for the patient that either used alternative health insurance (non-DoD) payment methods or paid cash for prescriptions. There are multiple potential situations this could occur. First, if patients encountered the PA and ST process and did not pursue the prescription, there is no record of this attempt. Those patients may have received the prescription using other insurance or cash payment.

In addition to the limitations present in claims studies, this study has specific design limitations. First, potentially important information may have been excluded. A longer study period, inclusion of all types of testosterone, and inclusion of other payment

types (other insurance or cash payment) would allow for a broader evaluation of testosterone use patterns.

Second, other events that occurred during the study period may have influenced the results. At the time of the study, there were media reports on safety issues of testosterone use. The Food and Drug Administration (FDA) recommended avoiding testosterone therapy in patients with low testosterone due to aging and also emphasized potential cardiovascular risks in testosterone therapy. At the same time, robust marketing campaigns touted the benefits of treating low testosterone in a general campaign with a wide audience.

During the study period, changes were made to the DoD copay structure. On February 1, 2013, copays for brand name and non-formulary agents increased at both retail and mail order pharmacies. Patients may have chosen to forgo testosterone therapy at the higher copays. After the copay changes, injectable generic testosterone was the least expensive testosterone option.

In terms of generalizability, the DoD population may not be comparable to other populations. Additionally, the 'no grandfathering' aspect of the DoD PA and ST may have created a stricter environment for the PA and ST to be applied that may not occur in other programs. Because even established patients were held to the new criteria, additional patients could have discontinued therapy. Finally, the presence of statistically significant results using large databases may not translate into significant clinical results.

RECOMMENDATIONS

This section presents recommendations resulting from this study. Recommendations for the military health system (MHS) specifically and general recommendations are described.

MHS Recommendations

New Drugs to Market and Potential Cost Threats

When new products were launched prior to August 26, 2013, they were automatically placed on the Uniform Formulary (UF). This means new, brand name drugs were available at the brand copay immediately and usually without restriction. This study shows how this particular policy can have negative financial consequences if utilization and costs are not actively managed. By the time the PA and ST were in place, many patients had already received prescriptions that were possibly inappropriate. The National Defense Authorization Act of 2015 created a program to classify certain newly approved drugs as non-formulary until they can be reviewed by the Pharmacy and Therapeutics (P&T) Committee.[104] This effort will address a portion of the immediate financial risks after a medication launches, however, the results of this program are yet to be seen. Programs that allow for proactive, swift, flexible responses to concerning drugs trends are needed.

Continue to Improve Data Integrity

MTF pharmacies have recognized, extensive issues with data integrity. Multiple programs and efforts are in place to manage these issues. Researchers using DoD data should be aware of these issues and adjust study design and interpretation accordingly.

General Recommendations

Interpret Adherence/Persistence Studies with Caution if Benefit Design Unknown

This study is the only known study to evaluate adherence and persistence for certain testosterone products specifically in the presence of PA and ST programs. Other studies did not include the formulary status of each agent or the presence of potentially restrictive formulary benefit design programs. This study shows that these formulary guidelines and restrictions should be considered in evaluations of adherence and persistence as the actual patient behavior may be caused by changes to benefit design.

Use Caution Interpreting Testosterone "Exposure"

Studies that evaluate the safety of exposure to a medication must make assumptions about what constitutes exposure. In many testosterone studies, patients fail to continue beyond six months. In studies evaluating safety, it would be prudent to examine how long the patient persisted on therapy, as around 20% of patients do not continue beyond one prescription, and that exposure risk is likely not equivalent to those patients that continued on therapy for longer periods of time.

FUTURE RESEARCH

Additional research is needed in the areas of testosterone therapy (TTh) and the policy and impacts of benefit design.

Testosterone

One of the limitations of this study was the length of the study. Further study of testosterone therapy over a longer period of time is recommended. Evaluating dose over time, any product changes over time, and in patients that are essentially committed to

therapy, or continue using it for at least 12 months, the actual length of therapy is important to know. Also, further evaluation of those short term patients, those that filled only one or two prescriptions, and greater understanding of why they initiated and why they discontinued should be pursued.

Patients using concomitant PDE-5s may experience improved sexual symptoms above and beyond improvements attributable to testosterone alone. For this reason, patients using both PDE-5s and testosterone may have different treatment patterns. These patients should be identified and isolated in future studies.

The absence of baseline and follow-up labs in testosterone therapy may signal a lack of follow-up and potentially dose titration in general. Also, no actual labs or evidence of labs were collected. The word of the clinician was accepted to be adequate. Further information is needed to know if patients truly only used testosterone for the FDA indicated conditions.

Lastly, the number of patients using Low-T clinics is unknown. These clinics offer access to injectable testosterone, labs, and management with or without insurance coverage. Little is known about this population of testosterone patients.

Benefit Design

The literature review previously stated that additional studies are needed evaluate the intended and unintended consequences of PA or ST programs. This study found that these processes may have contributed to non-persistence. There were 8,646 patients that did not successfully receive a prescription after the PA implementation that were on therapy prior to the PA implementation. Additional research is needed to evaluate the

unintended consequences of the PA for these patients. These patients discontinued therapy at the point of implementation, but the reason for discontinuation is unknown. Whether PA contributes to non-persistence in other medication classes, in those PA or ST programs that do allow grandfathering, and those outside the DoD system requires further investigation. In addition, it is unknown whether the reductions in utilization and costs are sustained beyond the first year after implementation.

CONCLUSIONS

This study adds to the existing testosterone use literature, specifically how PA and ST programs influence testosterone use behaviors. The effectiveness and impact of testosterone benefit design will inform future DoD formulary decisions and deepen understanding of testosterone use behaviors and how patients are impacted by benefit design. Additional research in this area is needed to explore how testosterone use occurs over time, how no-grandfathering programs differ from grandfathering programs, and enhance understanding of how benefit designs can be incorporated into adherence and persistence studies.

Furthermore, this study examined switching, restarting, and cycling behaviors in the context of formulary management programs. There is evidence these programs influenced all three behaviors. Previous switching studies did not account for benefit design, yet this study found benefit design directly influenced switching behaviors as patients were switched to the preferred formulary agent. Discontinuation, restarting, and cycling were also driven by the implementation of the PA/ST. Of the patients established on testosterone prior to PA/ST, 56.3% successfully continued therapy after the PA/ST

implementation. Without considering benefit design in this study, the discontinuation rate may have been attributed to other variables. Additionally, patients that were successful at meeting PA/ST criteria had the longest break in therapy immediately following PA/ST implementation indicating the benefit design may have triggered restarting behaviors.

Testosterone deficiency is an important health condition that impacts millions of men. Treating testosterone deficiency is costly and controversial. More information is needed on how patients use testosterone and the consequences of treatment. This study uncovers additional factors to be considered and identifies important research initiatives for the future.

APPENDICES

APPENDIX A: INCLUDED TESTOSTERONE FORMS

Form	Brand Name	Strength	Starting Dose	Maintenance Dose	How Supplied (NDC and product description)
Gel	Androgel[23]	1% 25 mg in 2.5g packet 50 mg in 5g packet	50 mg (either 2, 25 mg packets or 1, 50 mg packet) applied once in the AM	If testosterone levels are below normal range, increase from 50 to 75 mg or 75 mg to 100 mg as directed by physician. If levels above normal range, decrease dose. If sustained doses of 50 mg are needed, discontinue use.	0051-8425-30 30, 25 mg packets 0051-8450-30 30, 50 mg packets
Gel	Androgel[22]	1.62% 20.25 mg in 1.25g packet 40.5 mg in 2.5g packet	40.5 mg (1 packet) applied once in the AM	Adjusted based on pre-dose testosterone levels: < 350 ng/dL: Add 20.25 mg per day 350 ng/dL to 750 ng/dL: No change > 750 ng/dL: Decrease by 2.25 mg per day	0051-8462-12 Unit dose 20.25 mg packet 0051-8462-31 30, 20.25 mg packets 0051-8462-01 Unit dose 40.5 mg packet 0051-8462-30 30,40.5 mg packets

Form	Brand Name	Strength	Starting Dose	Maintenance Dose	How Supplied (NDC and product description)
Gel	Androgel Pump[23]	1% (12.5 mg/actuation)	50 mg (4 pump actuations) applied once in the AM	If testosterone levels are below normal range, increase from 50 mg to 75 mg or 75 mg to 100 mg as directed by physician. If levels above normal range, decrease dose. If sustained doses of 50mg are needed, discontinue use.	0051-8488-88 2, 75 g pump (each pump dispenses 60 actuations)
Gel	Androgel Pump[22]	1.62% (20.25 mg/actuation)	40.5 mg (2 pump actuations) applied once in the AM	Adjusted based on pre-dose testosterone levels: < 350 ng/dL: Add 20.25 mg per day 350 ng/dL to 750 ng/dL: No change > 750 ng/dL: Decrease by 2.25 mg per day	0051-8462-33 88 g pump (60 actuations)
Gel	Fortesta[27]	10 mg/actuation (1%)	40 mg (4 pump actuations) applied once in the AM	Dose range is 10 mg to 70 mg depending on pre-dose testosterone levels	63471-183-16 1 canister 63481-183-17 2 canisters 63481-183-18 3 canisters
Gel	Testim[25]	50 mg/5g	50 mg (one tube) applied once in the AM	Dose range is 50 mg (one tube) to 100 mg (2 tubes) depending on pre-dose testosterone levels	66887-001-05 30, 50 mg tubes
Gel	Vogelxo[28]	50 mg/5g 50 mg in 1 packet 50 mg in 1 tube	50 mg applied at the same time each day	Dose range is 50 mg to 100 mg depending on pre-dose testosterone levels	0245-0871-05 30, 50 mg tubes 0245-0871-65 1, 50 mg tube 0245-0871-35 30, 50 mg packets 0245-0871-89 1, 50 mg packet

Form	Brand Name	Strength	Starting Dose	Maintenance Dose	How Supplied (NDC and product description)
Gel	Vogelxo Pump[28]	12.5 mg/actuation (75g of 1%)	50 mg (4 pump actuations) applied at the same time each day	Dose range is 50 mg (4 pump actuations) to 100 mg (8 pump actuations) depending on pre-dose testosterone levels	0245-0872-42 2, 75 g pumps (each pump dispenses 60 actuations of 12.5 mg)
Buccal	Striant[30]	30 mg mucoadhesive, buccal system	30 mg every 12 hours applied to gum region above incisor tooth	No adjustment recommended by manufacturer. Recommend discontinuing if testosterone does not reach 300 ng/dL to 1050 ng/dL within four to twelve weeks	52244-030-60 6 blister packs 10 buccal systems per pack Each buccal system delivers 30 mg
Transdermal patch, 24 hours	Androderm[26]	2 mg/24 hours 4 mg/24 hours (previously discontinued strengths of Androderm will also be included)	One 4 mg/day system applied every 24 hours	Recommend dose range of 2 mg/24 hours to 6 mg/24 hours depending on pre-dose testosterone levels	52544-076-60 60, 2 mg systems 52544-077-30 30, 4 mg systems
Transdermal solution	Axiron[69]	30 mg/actuation	60 mg (2 pump actuations) applied once per day	Recommend a dose range of 30 mg to 120 mg depending on pre-dose testosterone levels	0002-1975-90 Pump containing 60 actuations

APPENDIX B: LETTER TO BENEFICIARIES

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
HEALTH AFFAIRS
7700 ARLINGTON BOULEVARD, SUITE 5101
FALLS CHURCH, VIRGINIA 22042-5101

TRICARE MANAGEMENT ACTIVITY

January 2013

20104 201300214 1
JOHN Q PUBLIC
123 STREET NAME
CITY, ST 99999

Dear TRICARE Beneficiary:

Our records indicate you may be taking one or more prescription drugs that will be moving to non-formulary (Tier 3) or require 'prior authorization' as recommended by the Department of Defense Pharmacy and Therapeutics Committee (DoD P&T). The DoD P&T oversees the TRICARE Management Activity drug formulary.

The affected drug(s) and alternatives are listed on the attachment to assist you in making the best decision regarding your pharmacy needs. We recommend you talk to your health care provider about the options prior to the effective date listed on the attachment.

All of the preferred products on the attachment are available through the TRICARE Home Delivery pharmacy, or at a retail network pharmacy with the associated cost share. They may also be available at Military Treatment Facility (MTF) pharmacies in your area. We encourage you to consider TRICARE Home Delivery as a convenient and cost-effective way to receive your regular prescriptions if an MTF is not an option. Learn more about home delivery at www.tricare.mil/homedelivery; and find your nearest participating TRICARE pharmacies at www.express-scripts.com/TRICARE/pharmacy.

Please keep in mind, you will be responsible for the full cost if you do not have an approved prior authorization for a medication that requires prior authorization. The request for prior authorization can be submitted by your physician with a review by Express Scripts.

Express Scripts is contracted by DoD to process retail pharmacy claims and fill TRICARE Home Delivery prescriptions for TRICARE beneficiaries.

For more information on formulary, non-formulary, prior authorization, or additional questions, you or your provider can go to www.tricare.mil/pharmacy or contact the TRICARE Pharmacy Program at (877) 363-1303.

We at TRICARE are proud to serve our nation's military heroes and their families and are committed to providing the best possible health care.

Sincerely,

Mary Kaye Justis
Assistant Deputy Director

Attachment: Formulary Alternatives for Non-formulary or Prior Authorization Medications
1.

Formulary Alternatives for Non-formulary Medications

Cost Share/Prior Authorization Changes Effective 6 February, 2013

Non-Formulary (Tier 3) Medications	**Formulary Medications (Tier 1 & Tier 2)**
Testosterone Replacement Therapies for Male Hypogonadism	
Cost share = $25* **(Upon Approval of Prior Authorization)** AndroGel® (testosterone gel, 1% pump) AndroGel® (testosterone gel, 1.62% pump) AndroGel® (testosterone gel, 2.5 g packet) AndroGel® (testosterone gel, 5 g packet) Axiron® (testosterone topical solution, 30 mg/1.5 mL) Without an approved Prior Authorization: At Retail, 100% patient responsibility (you pay full cost for the medication) At Home Delivery, the medication will be unavailable.	Cost share = $12* at Retail for a up to a 30 day supply; $9* through Home Delivery for up to a 90 day supply Fortesta™ (testosterone gel, 2% pump) Androderm® (testosterone transdermal system) Striant® (testosterone buccal system) Testim® (testosterone gel, 1%)

***Note:** Section 712 of the National Defense Authorization Act for 2013 establishes the cost-sharing rates under the TRICARE pharmacy benefits program as $5 for generic medications, $17 for formulary medications and $44 for non-formulary medications for not more than a 30-day supply obtained through retail pharmacies, and $0 for generic medications, $13 for formulary medications, and $43 for non-formulary medications for not more than a 90-day supply obtained through the TRICARE mail-order pharmacy. These changes are scheduled to take effect 1 February, 2013.

For more information on Prior Authorization, go to:
http://www.tricare.mil/mybenefit/home/Prescriptions/Medications/PriorAuthorizations?

Has your permanent address changed?
If so, please contact DEERS at (800) 538-9552, or *www.tricare.mil/**deers***

APPENDIX C: DEPARTMENT OF DEFENSE FORMS

Prior Authorization Request Form for **Fortesta** (testosterone 2% topical gel)

5692

To be completed and signed by the prescriber. To be used only for prescriptions which are to be filled through the Department of Defense (DoD) TRICARE pharmacy program (TPHARM). Express Scripts is the TPHARM contractor for DoD.

MAIL ORDER and RETAIL	• The provider may **call**: **1-866-684-4488** or the completed form may be **faxed** to: **1-866-684-4477** • The patient may attach the completed form to the prescription and **mail** it to: **Express Scripts, P.O. Box 52150, Phoenix, AZ 85072-9954** or **email** the form only to: **TPharmPA@express-scripts.com**

Prior authorization criteria and a copy of this form are available at: http://pec.ha.osd.mil/forms_criteria.php. This prior authorization has no expiration date.

Step 1 **Please complete patient and physician information** (please print):

Patient Name:		Physician Name:	
Address:		Address:	
Sponsor ID #		Phone #:	
Date of Birth:		Secure Fax #:	

Step 2 **Please complete the clinical assessment:**

1. Is the patient a male who is 17 years of age or older?	☐ Yes Proceed to question 2	☐ No **Coverage not approved**
2. Does the patient have a diagnosis of hypogonadism as evidenced by 2 or more morning total testosterone levels below 300 ng/dl ?	☐ Yes Proceed to question 3	☐ No **Coverage not approved**
3. Is the patient experiencing symptoms usually associated with hypogonadism?	☐ Yes **Sign and date below**	☐ No **Coverage not approved**

Step 3 **I certify the above is true to the best of my knowledge.**
Please sign and date:

Prescriber Signature _____ Date _____

[6 February 2013]

Prior Authorization Request Form for
Androderm, AndroGel, Axiron, Natesto, Striant, Testim, Vogelxo

5693

To be completed and signed by the prescriber. To be used only for prescriptions which are to be filled through the Department of Defense (DoD) TRICARE pharmacy program (TPHARM). Express Scripts is the TPHARM contractor for DoD.

MAIL ORDER and RETAIL	- The provider may call: **1-866-684-4488** or the completed form may be faxed to: **1-866-684-4477** - The patient may attach the completed form to the prescription and mail it to: **Express Scripts, P.O. Box 52150, Phoenix, AZ 85072-9954** or email the form only to: **TPharmPA@express-scripts.com**

Prior authorization criteria and a copy of this form are available at: http://pec.ha.osd.mil/forms_criteria.php. This prior authorization has no expiration date.

Medication requested:

Step 1 **Please complete patient and physician information** (please print):

Patient Name: _____ Physician Name: _____

Address: _____ Address: _____

_____ _____

Sponsor ID # _____ Phone #: _____

Date of Birth: _____ Secure Fax #: _____

Step 2 **Please complete the clinical assessment:**

1. **Is the patient a male who is 17 years of age or older?**	☐ Yes Go to question 2	☐ No **Coverage not approved**
2. **Does the patient have a diagnosis of hypogonadism as evidenced by 2 or more morning total testosterone levels below 300 ng/dl ?**	☐ Yes Go to question 3	☐ No **Coverage not approved**
3. **Is the patient experiencing symptoms usually associated with hypogonadism?**	☐ Yes Go to question 4	☐ No **Coverage not approved**
4. **Has the patient tried Fortesta for a minimum of 90 days AND failed to achieve total testosterone levels above 400 ng/dl (labs drawn 2 hours after Fortesta application) AND without improvement in symptoms?**	☐ Yes **Sign and date below**	☐ No Go to question 5
5. **Does the patient have a contraindication or relative contraindication to Fortesta that does not apply to the requested agent?**	☐ Yes **Sign and date below**	☐ No Go to question 6
6. **Has the patient experienced a clinically significant skin reaction to Fortesta that is not expected to occur with the requested agent?**	☐ Yes **Sign and date below**	☐ No Go to question 7
7. **Is the request for Androderm, Natesto, or Striant?**	☐ Yes Go to question 8	☐ No **Coverage not approved**
8. **Does the patient require a testosterone replacement therapy that has a low risk of skin-to-skin transfer between family members?**	☐ Yes **Sign and date below**	☐ No **Coverage not approved**

Step 3 **I certify the above is true to the best of my knowledge.**
Please sign and date:

_____ _____

Prescriber Signature Date

[02 July 2014]

TRICARE Pharmacy Program Medical Necessity Form for **AndroGel** and **Axiron**

5691

This form applies to the TRICARE Pharmacy Program (TPharm). The medical necessity criteria outlined on this form also apply at Military Treatment Facilities (MTFs). The form must be completed and signed by the prescriber. ***Note:*** *Medications in this class require prior authorization before they will be covered by TRICARE. This form does NOT fulfill prior authorization requirements. Please see: http://pec.ha.osd.mil/forms_criteria.php for more information.*

- **Androderm, Fortesta, Striant, and Testim are the formulary testosterone replacement therapies on the DoD Uniform Formulary. And Fortesta is the preferred agent in this class.** AndroGel 1% and 1.62%, and Axiron are non-formulary, but available to most beneficiaries at the non-formulary cost share. Please note that prior authorization (PA) requirements also apply to all products in this class. PA forms are available on the TRICARE Pharmacy website at: http://pec.ha.osd.mil/forms_criteria.php. This Medical Necessity form may **NOT** be used to meet PA requirements.
- You do NOT need to complete this form in order for non-Active duty beneficiaries (spouses, dependents, and retirees) to obtain non-formulary medications at the non-formulary cost share. The purpose of this form is to provide information that will be used to determine if the use of a non-formulary medication is medically necessary. If a non-formulary medication is determined to be medically necessary, non-Active duty beneficiaries may obtain it at the formulary cost share.
- Active duty service members may not fill prescriptions for a non-formulary medication unless it is determined to be medically necessary. There is no cost share for active duty service members at any DoD pharmacy point of service.

MAIL ORDER and RETAIL	- The provider may call: **1-866-684-4488** or the completed form may be faxed to: **1-866-684-4477** - The patient may attach the completed form to the prescription and mail it to: **Express Scripts, P.O. Box 52150, Phoenix, AZ 85072-9954** or email the form only to: **TPharmPA@express-scripts.com**	MTF	- Non-formulary medications are available at MTFs only if **both** of the following are met: o The prescription is written by a military provider or, at the discretion of the MTF, a civilian provider to whom the patient was referred by the MTF. o The non-formulary medication is determined to be medically necessary. - Please contact your local MTF for more information. There are no cost shares at MTFs.

Step 1 **Please complete patient and physician information** (please print):

Patient Name: _____ Physician Name: _____

Address: _____ Address: _____

_____ _____

Sponsor ID #: _____ Phone #: _____

Date of Birth: _____ Secure Fax #: _____

Step 2 **Please explain why the patient could not be treated with ALL of the formulary medications. Circle a reason code if applicable. You MUST supply a specific written clinical explanation as to why each of the formulary medications would be unacceptable.**

Formulary Medication	Reason	Clinical Explanation
Androderm transdermal patch	1 2 3	
Fortesta transdermal gel	1 2 3	
Striant buccal tablet	1 2 3	
Testim transdermal gel	1 2 3	

Clinical reason for not using the formulary medication:

1. Use of the formulary medication is contraindicated.
2. The patient has experienced a significant adverse effect from the formulary medication.
3. Use of the formulary medication resulted in therapeutic failure.

Step 3 **I certify the above is true to the best of my knowledge.** Please sign and date:

_____ _____

Prescriber Signature Date

[6 Feb 2013]

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