Daily Dose and Costs of Therapy With Topical Testosterone Agents

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Male hypogonadism (HG), caused by disturbance of the hypothalamic-pituitary-testicular axis, occurs when the testes produce insufficient testosterone and below-normal spermatozoa.[1] Hypogonadism may be attributed to specific diagnoses (eg, Klinefelter's syndrome), nonspecific diagnoses related to low testosterone levels, or a combination of the 2, and is comorbid with a number of chronic conditions including hypertension, hyperlipidemia, diabetes, back/neck pain, decreased bone/muscle mass, sexual dysfunction, and psychiatric disorders.[1-5] Healthcare resource use and costs associated with these comorbidities are often greater than those for HG alone.[5] The estimated prevalence of HG varies widely based on definition and population, but has recently been estimated at 39% in men older than 45 years seeking healthcare in the primary care setting and 24% of men aged 30 to 70 years.[6,7]

To alleviate symptoms and improve well-being in men with classical androgen deficiency syndromes, the Endocrine Society recommends testosterone replacement therapy (TRT).[1] The practice guidelines suggest that TRT should raise serum testosterone levels into a mid normal range.[1] Patient preference, formulation pharmacokinetics, and burden and cost of treatment may be considered when choosing TRT.[1]

Topical testosterone agents (TTAs), applied dermally as gels or solutions, are a commonly prescribed TRT in the United States. With once-daily, noninvasive application, TTAs can produce stable serum testosterone concentrations within the normal range in most patients.[1] To ensure proper TTA dosing, serum testosterone levels should be measured at intervals following treatment initiation, including after 1 to 2 weeks and again 3 months after treatment initiation.[1] The daily TTA dose may be altered, as determined by serum testosterone concentration relative to the normal range.[1]

Clinical trial results indicate that many patients require higher TTA doses to attain and maintain normal testosterone

ABSTRACT

Objective: To compare daily maintenance doses and costs of treatment with topical testosterone agents (TTAs) in commercially insured adult men.

Study Design: Adult males (n = 3470) who initiated TTAs at the recommended starting dose (RSD) from January 1, 2011, to March 31, 2012, were identified in a database of commercially insured beneficiaries. Patients were required to have continuous eligibility and no index therapy use in the year before initiation (baseline).

Methods: Baseline demographic characteristics, comorbidities, and testosterone use were compared using χ^2 and Wilcoxon rank-sum tests. Maintenance dose attainment was determined by comparing mean dose per patient per day (PPPD) in sequential months after initiation. Risk-adjusted maintenance dose and costs PPPD were estimated using generalized linear model regressions. Inverse propensity score weighting was conducted as a sensitivity analysis.

Results: Dose stabilized between months 4 and 5 for all agents and maintenance dose was considered attained at month 4. During month 4, risk-adjusted dose PPPD was 112.0%, 112.2%, 120.4%, and 118.0% of RSD for Axiron, AndroGel 1% (not statistically significant vs Axiron), AndroGel 1.62% (P <.001), and Testim (P = .003), respectively. Risk-adjusted third-party payer costs PPPD were $7.50, $9.48, $9.85, and $9.49 (all P <.001), respectively. Third-party payer costs PPPD as a proportion of RSD cost were similar to those as a proportion of RSD. Sensitivity analysis and subgroup results were consistent with study findings.

Conclusions: Maintenance dose as a proportion of RSD was least among Axiron and AndroGel 1% patients; third-party payer costs were lowest among Axiron patients.

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PRACTICAL IMPLICATIONS

- Topical testosterone agents, a commonly used form of testosterone therapy, frequently require dose titration above the recommended starting dose (RSD) to achieve clinical benefits.
- We utilized real-world claims data to determine the average time to maintenance dose attainment, and estimated doses and costs per patient per day (PPPD) of maintenance therapy among TTA-treated patients.
- Dose titration to levels greater than the RSD PPPD was lowest among patients treated with Axiron and AndroGel 1%, and costs PPPD were lowest among those treated with Axiron.

levels than the recommended starting dose (RSD) noted in prescribing information. In a phase 3 clinical trial by Wang and colleagues, the effective dose 4 months after initiation of Axiron (Eli Lilly and Company, Indianapolis, IN; RSD 60 mg) was 69.3 mg per day (115.5% of RSD).[8] In another phase 3 clinical trial by Wang and colleagues, the effective dose 6 months following initiation of AndroGel 1% (AbbVie Inc, North Chicago, Illinois; RSD 50 mg) was 75 mg per day (150% of RSD).[9] The phase 3 clinical trial to evaluate the safety and efficacy of AndroGel 1.62% (AbbVie Inc, North Chicago, Illinois; RSD 40.5 mg) found that 6 months following initiation, the effective dose was 60.5 mg per day (149.4% of RSD).[10] In phase 3 clinical trials of Fortesta (Endo Pharmaceuticals, Inc, Malvern, Pennsylvania; RSD 40 mg) and Testim (Auxilium Pharmaceuticals, Inc., Malvern, Pennsylvania; RSD 50 mg), the effective doses 2 months after initiation were 49.2 mg per day (123% of RSD) and 85.4 mg per day (170.8% of RSD), respectively.[11,12]

In a retrospective claims database analysis assessing TTA use among men with HG, an increasing proportion of men used higher doses of TTA over time. The number of patients utilizing the higher dose nearly doubled in the first month of therapy. The rate of dose escalation declined after 3 months of therapy.[13]

A prior study investigated the economic burden of treatment for HG: the excess risk-adjusted direct and indirect costs were $4869 for men with HG in the year after initiating treatment compared with the costs for men without HG.[5] Additionally, third-party payer prescription costs in patients with HG increased $1428 in the year following treatment initiation compared with the prior year. These results suggest that a substantial burden of the direct costs for patients with HG are from prescription drugs.

Given the prevalence and substantial per patient economic burden of HG and its comorbidities, in particular the burden of prescription drugs, it is necessary to understand the impact of dose titration on maintenance TRT costs to third-party payers. To date, no such studies have been published. The objective of this study was to assess the maintenance dose of TTAs per patient per day (PPPD), dose as a proportion of RSD, costs to third-party payers (hereafter, costs), and costs as a proportion of RSD cost in a real-world setting.

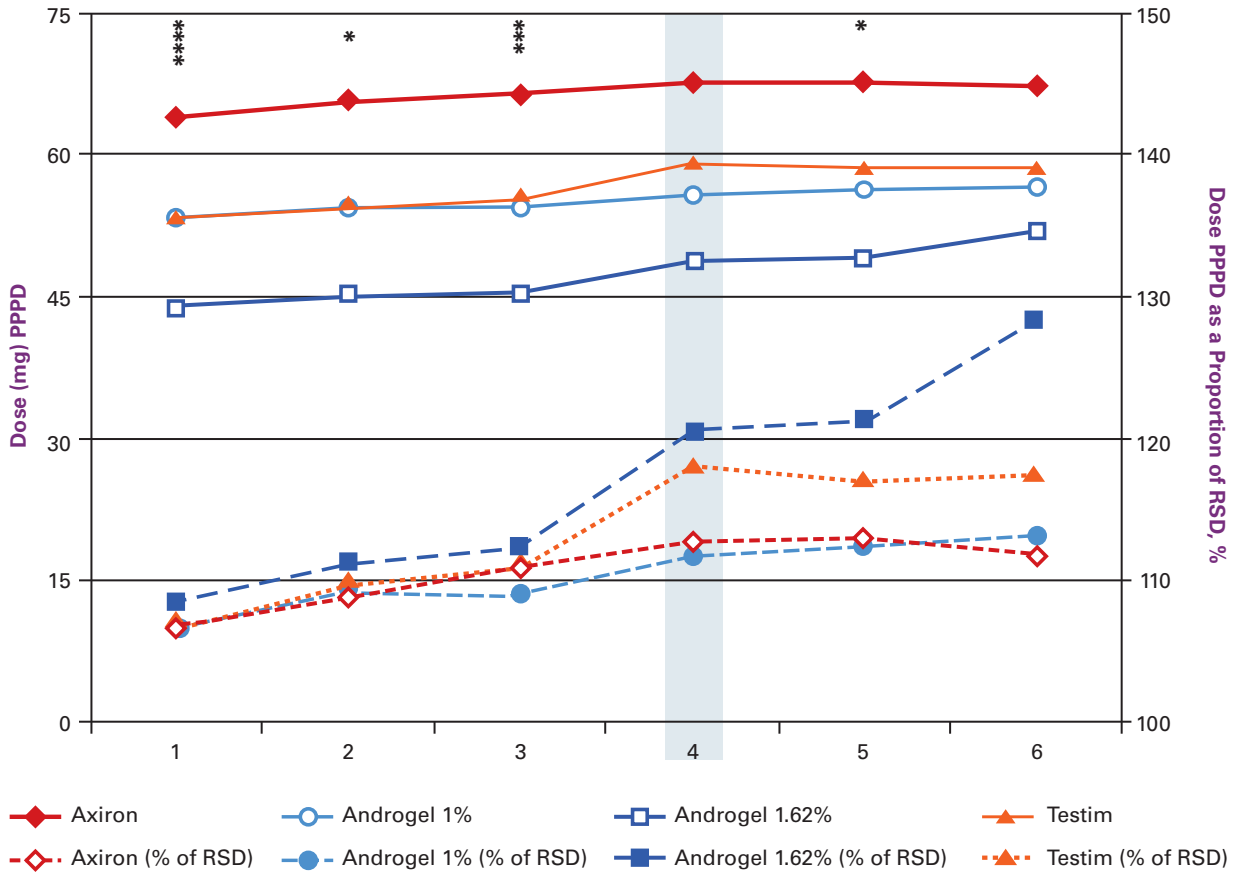
METHODS

This study utilized a de-identified data set (OptumHealth Reporting and Insights, formerly Ingenix Employer Solutions) that covers approximately 15.5 million privately insured lives from 60 US-based companies in a broad array of industries with numerous insurer plans.

The study included patients with at least 1 prescription drug claim for a TTA (Axiron [n = 1601], AndroGel 1% [n = 17,454], AndroGel 1.62% [n = 4861], Fortesta [n = 803], or Testim [n = 6581]) between January 1, 2011, and March 31, 2012. Fortesta was excluded from further analysis because of insufficient sample size, limiting selection to patients initiating therapy with the other TTAs. The study index date was defined as the earliest prescription drug claim with a TTA. However, to maximize sample size for patients who received Axiron, the index date was defined as the earliest claim for Axiron because of its recent market entry. Patients were required to be male, aged 18 years or older, have continuous health plan eligibility, and have no claim for the same TTA in the 12 months preceding the index date (the baseline period; n = 12,047). Other forms of TRT during the baseline period were permitted. Additionally, the index date prescription was required to be for the treatment RSD (n = 9995) to assess dose titration (**eAppendix A** available at **www.ajmc.com**). Because physicians do not always record an HG diagnosis during billing, there was no requirement to have an HG diagnosis for this analysis.

Dose PPPD of the TTAs was calculated in each of the 6 months following the index date among patients who remained continuously eligible and who had at least 1 day of supply of the index TTA in a given month and did not receive any other form of TRT (eg, nonindex TTA or testosterone injection). Patient-level mean daily dose was calculated as the total number of milligrams of testosterone prescribed divided by days of prescription supply. In months with fewer days of supply than calendar days, mean dose was the total milligrams of testosterone prescribed for that month divided by the number of days of supply observed in that month. The dose PPPD was calculated as an average of the mean doses for all patients in the

Figure 1. Monthly Mean Dose per Patient per Day Following Treatment Initiation[a]



PPPD indicates per patient per day; RSD, recommended starting dose.
*Number of cohorts in which there is no difference in dose between current and following month, $P < .05$.
[a]Dose in month 5 is not statistically different from that in month 4 in any cohort.

cohort, weighted by the days of supply for each patient in each month.

Dose PPPD was compared sequentially from month 1 to month 6 within each cohort, using a generalized estimating equation regression of month on mean dose PPPD (log link and gamma distribution). Between the fourth and fifth months, no statistically significant difference was observed for any cohort, thus indicating that patients had achieved a stable maintenance dose (**Figure 1**). Therefore, all maintenance dose and cost comparisons between TTAs were conducted in the fourth month.

For patients with continuous eligibility coverage for at least 4 months following the index date and at least 1 day of supply for the index TTA in the fourth month (n = 3470), baseline demographic characteristics, Charlson Comorbidity Index[14] (CCI), and individual comorbidities were described. All comparisons were between the Axiron cohort and each of the other TTA cohorts. Chi-square and Wilcoxon rank-sum tests were used for comparisons of categorical and continuous measures, respectively.

In the fourth month after treatment initiation, mean dose PPPD, dose PPPD as a proportion of RSD, and third-party payer costs PPPD (amount reimbursed by payer) were calculated. Third-party payer costs as a proportion of RSD cost (defined as the month 4 daily cost divided by cost per day of the index claim) were also calculated. To avoid estimation bias driven by outliers (with costs for the index claim close to zero leading to very small denominators), the top percentile of observations for this measure was removed from this analysis. To control for case mix, generalized linear model regressions (log link and gamma distribution) were used to estimate dose as a proportion of RSD PPPD, third-party payer cost PPPD, and third-party payer costs as a proportion of RSD cost. Each regression controlled for TTA cohort,

Table 1. Baseline Patient Demographic Characteristics, Comorbidities, and Prior Testosterone Use

Baseline Characteristics	Cohort				*P*[a]		
	Axiron (n = 345) (A)	AndroGel 1% (n = 1552) (B)	AndroGel 1.62% (n = 523) (C)	Testim (n = 1050) (D)	A vs B	A vs C	A vs D
Demographic characteristics							
Age,[b] mean (SD), y	53.7 (10.4)	54.9 (10.9)	53.3 (10.4)	54.7 (10.4)	.013	.652	.069
Insurance type,[c] n (%)							
HMO	26 (7.5)	187 (12.0)	72 (13.8)	104 (9.9)	.016	.005	.189
PPO	221 (64.1)	858 (55.3)	314 (60.0)	453 (43.1)	.003	.233	<.001
POS	52 (15.1)	200 (12.9)	73 (14.0)	226 (21.5)	.279	.647	.009
Other/unknown	46 (13.3)	307 (19.8)	64 (12.2)	267 (25.4)	.005	.635	<.001
HG and other conditions of low T,[d] n (%)	209 (60.6)	614 (39.6)	235 (44.9)	558 (53.1)	<.001	<.001	.016
CCI, mean (SD)	0.6 (1.1)	1.2 (2.5)	0.8 (1.8)	1.1 (2.1)	.004	.346	.013
Select comorbidities included in the CCI, n (%)							
Cerebrovascular disease	11 (3.2)	101 (6.5)	16 (3.1)	48 (4.6)	.018	.915	.268
Mild liver disease	2 (0.6)	38 (2.4)	13 (2.5)	16 (1.5)	.029	.035	.271
Renal disease	6 (1.7)	70 (4.5)	19 (3.6)	43 (4.1)	.018	.103	.039
Metastatic solid tumor	0 (0.0)	31 (2.0)	11 (2.1)	5 (0.5)	.008	.004	.341
HIV/AIDS	1 (0.3)	34 (2.2)	4 (0.8)	41 (3.9)	.018	.653	.001
Any testosterone use during baseline,[e] n (%)	146 (42.3)	225 (14.5)	74 (14.1)	386 (36.8)	<.001	<.001	.065
Injection	49 (14.2)	102 (6.6)	37 (7.1)	63 (6.0)	<.001	.001	<.001
Injection in 30 days before the index date	12 (3.5)	38 (2.4)	18 (3.4)	24 (2.3)	.280	.977	.226
Topical	101 (29.3)	49 (3.2)	15 (2.9)	299 (28.5)	<.001	<.001	.776
Patch	7 (2.0)	74 (4.8)	16 (3.1)	28 (2.7)	.023	.355	.511
Implant	2 (0.6)	1 (0.1)	3 (0.6)	5 (0.5)	.087	1.000	.685
Other	3 (0.9)	8 (0.5)	4 (0.8)	6 (0.6)	.432	1.000	.698

AIDS indicates acquired immunodeficiency syndrome; CCI, Charlson Comorbidity Index; HG, hypogonadism; HIV, human immunodeficiency virus; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; T, testosterone.

[a]Chi-square tests were used for comparisons of categorical variables. Wilcoxon rank-sum tests were used for comparisons of continuous variables.

[b]Age on the index date.

[c]Insurance types differ in structure, and can impact resource utilization and costs. HMOs deliver and cover health services within a closed network; PPOs and POS plans provide more flexibility in selecting providers, but costs may be higher for out of network providers.

[d]HG and other conditions of low-T defined by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 257.1-257.9, 253.2, 253.4, 253.7, 259.0, 608.3, 758.7, 752.89, and E932.1.

[e]Baseline period was defined as the 1 year before the index date.

demographics, CCI, and comorbidities with statistically significant differences at baseline (hypogonadism and other conditions associated with low testosterone, cerebrovascular disease, mild liver disease, renal disease, metastatic solid tumors, and human immunodeficiency virus/acquired immunodeficiency syndrome).

To confirm the results of the multivariate analysis with an alternate approach to address confounding, a sensitivity analysis using inverse propensity score weighting was conducted. For each patient, the propensity for treatment with Axiron was estimated with multinomial logistic regression on index therapy, controlling for patient baseline demographics and comorbidities. Baseline characteristics and all PPPD measures in the fourth month were weighted by the inverse of the propensity score, and compared descriptively.

To assess the potential impact on the results due to the inclusion of patients without a diagnosis of HG, the generalized linear model analysis was repeated on a subgroup of patients with a diagnosis of HG or other conditions associated with low testosterone (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 257.1-257.9, 253.2, 253.4, 253.7, 259.0, 608.3, 758.7, 752.89, E932.1; see **eAppendix B** available at **www.ajmc.com** for corresponding diagnoses) in the year prior to index date (n = 1752).

SAS version 9.3 (SAS Institute, Cary, North Carolina) was used for all analyses. Statistical significance was defined as $P \leq .05$.

Table 2. Mean Dose and Costs per Patient per Day in the Fourth Month After Topical Testosterone Agent Initiation

	Cohort, Mean (SD)			
PPPD Measure in the Fourth Month[a]	Axiron (n = 345)	AndroGel 1% (n = 1552)	AndroGel 1.62% (n = 523)	Testim (n = 1050)
Dose, mg	67.62 (19.04)	55.94 (18.39)	48.85 (24.23)	59.04 (29.49)
Dose as a proportion of RSD	112.7% (32%)	111.9% (37%)	120.6% (60%)	118.1% (59%)
Third-party payer costs	$7.53 ($3.08)	$9.48 ($3.73)	$9.83 ($5.56)	$9.50 ($5.46)
Cost PPPD as a proportion of RSD cost[b]	110.6% (41%)	115.3% (45%)	119.4% (46%)	118.3% (52%)

PPPD indicates per patient per day; RSD, recommended starting dose; TTA, topical testosterone agent.
[a]Results are weighted by the proportion of days of TTA supply per patient to the mean days of TTA supply within the cohort.
[b]The daily cost in month 4 divided by the daily cost for the index claim. After the removal of the top percentile outliers, 345 Axiron, 1536 AndroGel 1%, 519 AndroGel 1.62%, and 1036 Testim patients were included in the analysis.

RESULTS

Baseline Characteristics

The final study cohorts consisted of 345 patients with Axiron, 1552 with AndroGel 1%, 523 with AndroGel 1.62% and 1050 with Testim therapy (**Table 1**).

Axiron patients were slightly younger than AndroGel 1% patients and of similar age to AndroGel 1.62% and Testim patients (53.7 vs 54.9 [P = .01], 53.3, and 54.7 years [both P >.05], respectively). Axiron patients were more likely to be enrolled in a preferred provider organization than AndroGel 1% and Testim patients (64.1% vs 55.3% and 43.1%, respectively; all $P \leq .05$), more likely to have a diagnosis of HG or other low-testosterone conditions than the other cohorts (60.6% vs 39.6%, 44.9%, and 53.1%, respectively; all $P \leq .05$), and had higher rates of other testosterone use during baseline than both AndroGel 1% and AndroGel 1.62% patients (42.3% vs 14.5% and 14.1%, respectively; both P <.001). Mean CCI was lower for Axiron patients than AndroGel 1% and Testim patients (0.6 vs 1.2 and 1.1, respectively; both $P \leq .05$).

Maintenance Dose and Cost PPPD

In the first month after index date, the mean dose PPPD for patients receiving Axiron, AndroGel 1%, AndroGel 1.62% and Testim was 64.86 mg, 54.49 mg, 44.66 mg, and 54.25 mg, respectively. The mean dose PPPD in the fourth month following treatment initiation was 67.62 mg, 55.94 mg, 48.85 mg, and 59.04 mg, respectively (**Table 2**). This amounted to 112.7%, 111.9%, 120.6%, and 118.1% of RSD, respectively.

Mean unadjusted third-party payer costs were lowest amongst Axiron patients: $7.53 PPPD compared with $9.48, $9.83, and $9.50 for AndroGel 1%, AndroGel 1.62%, and Testim, respectively. Mean third-party payer costs PPPD as a proportion of RSD costs were also lowest among Axiron patients.

Adjusting for case mix and treatment selection, the estimated dose PPPD as a proportion of RSD was 112% for Axiron patients versus 112.2% (P = .918), 120.4% ($P \leq .05$), and 118.0% ($P \leq .05$) for patients treated with AndroGel 1%, AndroGel 1.62%, and Testim, respectively (**Figure 2**).

In the risk-adjusted analysis of third-party payer costs, patients treated with Axiron had lower third-party payer costs PPPD than patients treated with AndroGel 1%, AndroGel 1.62%, and Testim ($7.50 vs $9.48, $9.85, and $9.49, respectively; all $P \leq .05$). Results for risk-adjusted third-party payer costs as a proportion of RSD cost were consistent with results for dose as a proportion of RSD, and were significantly lower for Axiron than for AndroGel 1.62% and Testim (Figure 2).

Sensitivity Analysis: Inverse Propensity Score Weighting

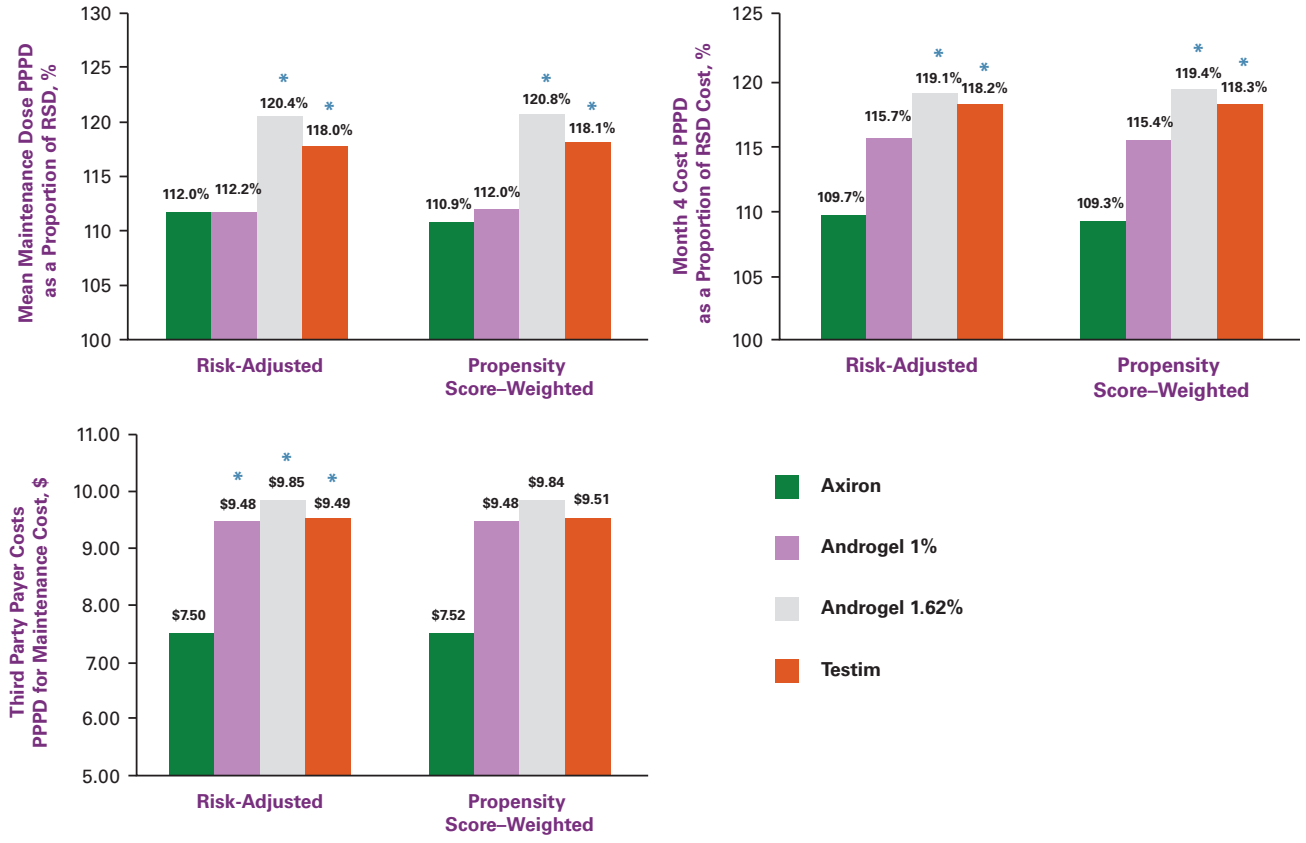
Using the inverse propensity of being treated with Axiron to reweight the cohorts, we observed few statistically significant differences between the reweighted cohorts. Reweighted PPPD measures of dose, dose as a proportion of RSD, costs, and costs as a proportion of RSD cost were similar to the risk-adjusted estimates in the main analysis (Figure 2).

Subgroup Analysis: Patients With a Diagnosis of HG or an Associated Condition

Among patients with a diagnosis of HG or a condition associated with low testosterone during the baseline period, there were 209, 614, 235, and 558 patients treated with Axiron, AndroGel 1%, AndroGel 1.62%, and Testim, respectively. Trends in baseline characteristics for this subgroup were similar to the overall sample (**eAppendix C**, available at **www.ajmc.com**). The subgroup used more TRT during the baseline period compared with the overall sample.

In the fourth month after TTA initiation, Axiron patients received 68.45 mg PPPD (114.1% of RSD), AndroGel 1% patients received 56.68 mg PPPD (113.4% of

Figure 2. Risk-Adjusted[a] and Inverse Propensity Score–Weighted Dose and Costs per Patient per Day in the Fourth Month After Topical Testosterone Agent Initiation



HIV indicates human immunodeficiency virus; PPPD, per patient per day; RSD, recommended starting dose; TTA, topical testosterone agent.
[a]Generalized linear models with log link and gamma distribution controlled for cohort, age, region, health plan, testosterone use during baseline, and comorbidities, including hypogonadism and associated conditions, cerebrovascular disease, mild liver disease, renal disease, metastatic solid tumors, HIV/AIDS, and Charlson Comorbidity Index. Estimation was weighted by the proportion of days of TTA use per patient to the average days of TTA use within the cohort.
*Statistically significant (P <.05) in risk-adjusted analysis. No statistical testing was done on propensity score–weighted measures.

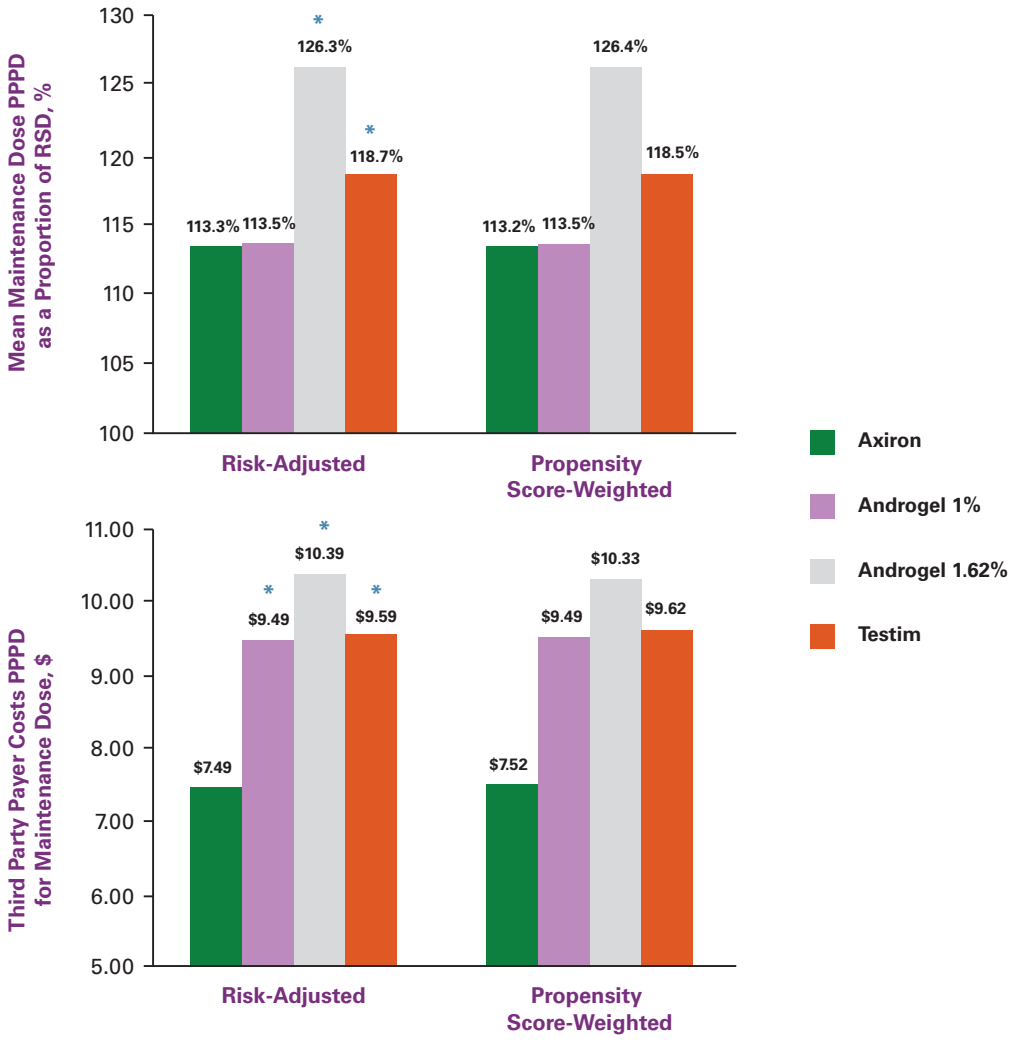
RSD), AndroGel 1.62% patients received 51.18 mg PPPD (126.4% of RSD), and Testim patients received 59.24 mg PPPD (118.5% of RSD). Third-party payer costs PPPD as a proportion of RSD costs were generally consistent with the results for dose as a proportion of RSD (**eAppendix D**).

Adjusting for case mix and treatment selection, the estimated dose PPPD as a proportion of RSD was 113.3% for Axiron patients vs 113.5% (P >.05), 126.3% (P ≤.05), and 118.7% (P ≤.05) for patients treated with AndroGel 1%, AndroGel 1.62%, and Testim, respectively (**Figure 3**). Risk-adjusted costs were also consistent with the overall sample. Patients treated with Axiron had lower third-party payer costs PPPD than patients treated with AndroGel 1%, AndroGel 1.62%, and Testim ($7.49 vs $9.49, $10.39, and $9.59, respectively; all P ≤.05). Trends across cohorts for third-party payer costs PPPD as a proportion of RSD costs were consistent with the results of the main analysis, and results for Axiron were significantly lower than results for AndroGel 1.62%. Inverse propensity score–weighted results were consistent with the risk-adjusted analysis (Figure 3).

DISCUSSION

This study compared daily maintenance doses and costs of TTA treatment in commercially insured adult men, and provides insight on real-world use of TTAs, including who is using them and how they are being used over time. A stable maintenance dose for all studied TTAs was attained within 4 months after treatment initiation. Patients treated with Axiron and AndroGel 1% used the lowest maintenance dose PPPD as a proportion of RSD in the fourth month following treatment initiation, whereas AndroGel 1.62% and Testim patients were titrated to higher maintenance doses relative to RSD. This result suggests variation among TTAs in the amount of titration needed from the RSD (which varies by TTA) to achieve serum testosterone within the normal range.

Figure 3. Risk-Adjusted[a] and Inverse Propensity Score–Weighted Dose and Costs per Patient per Day in the Fourth Month After Topical Testosterone Agent (TTA) Initiation in the Subgroup of Patients With a Diagnosis of Hypogonadism or an Associated Condition During the Baseline Period



HIV indicates human immunodeficiency virus; PPPD, per patient per day; RSD recommended starting dose; TTA topical testosterone agent.
[a]Generalized linear models with log link and gamma distribution controlled for cohort, age, region, health plan, testosterone use during baseline, and comorbidities, including cerebrovascular disease, mild liver disease, renal disease, metastatic solid tumors, HIV/AIDS, and Charlson Comorbidity Index. Estimation was weighted by the proportion of days of TTA use per patient to the average days of TTA use within the cohort.
*Statistically significant (P <.05) in risk-adjusted analysis. No statistical testing was done on propensity score–weighted measures.

Compared with doses administered at the end of the pivotal clinical trials for each product, maintenance doses described here are uniformly lower. This may be because of trial design; in several clinical trials, some patients initiated therapy at doses up to twice the RSD, and more up-titrations occurred than dose reductions. In this study, patients were required to initiate at the RSD, and the results were consistent with Axiron clinical trial maintenance doses reported by Wang et al.[8] This trial closely matched real-world practice as patients initiated at the RSD and up-titrated as necessary.[8]

Many of the patients here (40%-60% per cohort) did not have a baseline diagnosis of HG; patients included in the sample were not required to have a diagnosis of HG because it frequently remains unrecorded by physicians, even if patients present with the condition. Axiron patients were more likely to have an HG diagnosis, which may be associated with higher rates of testosterone use during baseline. To assess the sensitivity of the results to the inclusion of patients without an HG diagnosis, a sensitivity analysis was conducted, limited to patients with a baseline diagnosis of HG or another condition associated with low

testosterone. No inferences changed, although patients with HG diagnoses typically used slightly higher doses of TTAs compared with the overall sample.

The cost PPPD was lowest in the Axiron cohort, at $7.50 for each day of supply. A previous study estimated that third-party payer costs for prescription testosterone were $617 per patient per year, or about $1.69 PPPD.[5] That analysis included patients receiving testosterone through various routes of administration (eg, injection and patch, many of which may be generic, in addition to TTAs) and included gaps in testosterone utilization, and thus cannot be directly compared with this study. The present analysis is the first effort to quantify the third-party payer costs of TTA doses PPPD, accounting for dose titration. Because dose as a proportion of RSD and cost as a proportion of RSD cost were similar across cohorts, dose escalation appears to be a key driver of costs of testosterone maintenance therapy.

Future research could build on the work presented here by assessing cost sharing and patient attitudes toward therapy and the effects of these factors on adherence and dose titration. Additional work investigating decisions to discontinue or change therapy would improve the understanding of how to maximize treatment benefits. Such studies would provide insight into the patient perspective that is not available in claims data.

LIMITATIONS

This study is subject to typical limitations of claims data analyses, including dependence on accuracy of diagnoses and drug quantities recorded. Further, the cost results are based on TTA prices during the study timeframe; changes in TTA prices may alter inferences. In addition, clinical and laboratory data were unavailable, so it was not possible to assess symptoms, testosterone levels or patient response to TRT. This may be mitigated by the observation of dose titration; if the patient is responding inadequately, the dose may be up-titrated until the desired physiologic response is achieved, at which point the dose stabilizes.

It is well established that cost sharing (eg, co-payments and co-insurance out of patients' pockets) can impact reimbursement rates, utilization, and adherence to prescription drugs.[15,16] Patients paying greater amounts may stretch their prescriptions, refill less often, or switch to cheaper alternatives. Higher patient copayments also reduce costs paid by the third-party payer for each prescription. This study did not assess the impact of cost sharing or variations in health plan structure (eg, plan tiers, formulary coverage, refill limits) on costs or utilization and other measures of adherence, and some unmeasured confounding may exist. However, meaningful differences between cohorts were not observed in the number of days of supply of TTA per patient in the fourth month. Concerns about the effect of cost sharing on adherence may be further mitigated by the large number of available TRT options. A qualitative study developing a tool to assess patient preferences for TRT found that insurance-related issues were problematic for only 4 out of 58 men interviewed, suggesting that cost-sharing may not be a substantial issue.[17]

Finally, because the study assessed only days with TTA coverage, it was not possible to determine the budget impact of differences in third-party payer costs for maintenance dose; however, published literature suggests that adherence and persistence do not vary significantly across TTAs.[18]

The database in the current study involves a commercially insured population from 60 US companies. Results may not be geographically representative, and generalizability to other populations may be limited. In particular, patients over the age of 65 years may not be representative of the majority of Medicare-eligible patients. Third-party payer costs reported are from the perspective of private insurers and may not be generalizable to other coverage.

CONCLUSION

TTAs are important therapy options for men with low testosterone levels. Dose titration above RSD varies by TTA and was lowest among Axiron and AndroGel 1% patients on a PPPD basis. The presented evidence on dose titration through month 4 may help patients and practitioners understand the expected process of TTA initiation and dose titration. Third-party payer costs PPPD for maintenance dose were lowest for Axiron patients over the studied time frame. These results may assist patients, prescribers, and payers in making fully informed decisions in selecting TTAs for use in HG and other conditions associated with low testosterone.

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eAppendices

eAppendix A. Sample selection

	Axiron	AndroGel 1%	AndroGel 1.62%	Testim
Step 0: 1 prescription drug claim for a topical testosterone agent (TTA),	1,601	17,454	4,861	6,581
Step 1: No claims for the same TTA[a] in the 12 months preceding the index date[b]	1,598	7,645	2,819	4,048
Step 2: Male patients	1,598	7,500	2,810	3,936
Step 3: Continuously eligible during the 12 months prior to the index date	1,259	5,533	2,138	3,142
Step 4: Age 18 years or older on the index date	1,256	5,514	2,137	3,140
Step 5: Index TTA claim is for RSD[c]	1,155	4,344	1,698	2,798
Step 6: Eligible patients with > 1 dose in month between index date and end of follow-up				
(a) Month 1	1,155	4,344	1,698	2,798
(b) Month 2	501	2,390	896	1,686
(c) Month 3	460	2,300	782	1,563
(d) month 4[d]	345	1,552	523	1,050
(e) Month 5	282	1,341	397	895
(f) Month 6	186	1,142	283	770

PPPD indicates per patient per day, RSD recommending starting dose;, TTA topical testosterone agent

[a] Patients in the AndroGel 1% and AndroGel 1.62% groups were required to have a 12 month washout of both drugs

[b] The index date was defined as the first Axiron use on or after 1/1/2011. If no Axiron claim was observed, the earliest claim for any other TTA on or after 1/1/2011 was selected

[c] Daily RSD of testosterone is: Axiron, 60 mg; AndroGel 1%, 50 mg; AndroGel 1.62%, 40.5 mg; Testim, 50 mg. Patients were selected if the dose provided by the quantity and days of supply in the index date TTA claim(s) was recommended starting dose of the index TTA

[d] month 4 was selected as the month in which dose stabilization occurred; month 4 sample was used to compare maintenance doses and costs PPPD

eAppendix B. Diagnoses corresponding to ICD-9 codes for hypogonadism

ICD-9-CM Code	Corresponding diagnosis
257.2	Other testicular hypofunction
257.1-257.9	Testicular dysfunction (excluding 257.2)
253.2	Panhypopituitarism
253.4	Other anterior pituitary disorders
253.7	Iatrogenic pituitary disorders
259.0	Delay in sexual development and puberty, not elsewhere classified
608.3	Atrophy of testis
758.7	Klinefelter's syndrome
752.89	Other specified anomalies of genital organs
E932.1	Androgens and anabolic congeners

eAppendix C. Baseline patient demographic characteristics, comorbidities, and prior testosterone use among patients with a baseline diagnosis of hypogonadism or another condition associated with low testosterone

	Cohort				P-value[c]		
Baseline characteristics, N (%)	**Axiron n = 209 [A]**	**AndroGel 1% n = 614 [B]**	**AndroGel 1.62% n = 235 [C]**	**Testim n = 558 [D]**	**[A] vs [B]**	**[A] vs [C]**	**[A] vs [D]**
Demographic characteristics							
Age,[a] years, mean (SD)	54.0 (10.0)	54.2 (11.6)	53.4 (10.7)	54.4 (10.9)	.4012	.5916	.4213
Insurance type							
HMO	14 (6.7%)	74 (12.1%)	35 (14.9%)	64 (11.5%)	.0305	.0059	.0516
PPO	133 (63.6%)	364 (59.3%)	137 (58.3%)	219 (39.2%)	.2664	.2501	<.0001
POS	34 (16.3%)	70 (11.4%)	31 (13.2%)	119 (21.3%)	.0674	.3600	.1186
Other/unknown	28 (13.4%)	106 (17.3%)	32 (13.6%)	156 (28.0%)	.1909	.9461	<.0001
CCI, mean (SD)	0.7 (1.2)	1.0 (2.0)	0.8 (1.4)	0.9 (1.9)	.0736	.4415	.3124

Select comorbidities included in the CCI							
Cerebrovascular disease	9 (4.3%)	39 (6.4%)	6 (2.6%)	21 (3.8%)	.2757	.3075	.7299
Mild liver disease	1 (0.5%)	16 (2.6%)	6 (2.6%)	8 (1.4%)	.0872	.1265	.4569
Renal disease	2 (1.0%)	19 (3.1%)	10 (4.3%)	21 (3.8%)	.0905	.0324	.0424
Metastatic solid tumor	0 (0.0%)	8 (1.3%)	4 (1.7%)	3 (0.5%)	.2132	.1259	.5664
HIV/AIDS	0 (0.0%)	12 (2.0%)	1 (0.4%)	12 (2.2%)	.0438	1.0000	.0434
Any testosterone use during baseline[b]	113 (54.1%)	157 (25.6%)	57 (24.3%)	260 (46.6%)	<.0001	<.0001	.0653
Testosterone route of administration							
Injection	42 (20.1%)	85 (13.8%)	31 (13.2%)	56 (10.0%)	.0307	.0501	.0002
Injection in 30 days before the index date	11 (5.3%)	31 (5.0%)	16 (6.8%)	21 (3.8%)	.9032	.4964	.3550
Topical	74 (35.4%)	33 (5.4%)	10 (4.3%)	191 (34.2%)	<.0001	<.0001	.7602
Patch	5 (2.4%)	42 (6.8%)	12 (5.1%)	17 (3.0%)	.0167	.1369	.6289
Implant	1 (0.5%)	1 (0.2%)	3 (1.3%)	5 (0.9%)	.4436	.6259	1.0000
Other	3 (1.4%)	5 (0.8%)	2 (0.9%)	5 (0.9%)	.4258	.6698	.4554

CCI indicates Charlson Comorbidity Index; HG, hypogonadism; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization.

[a] Age was on the index date.

[b] Baseline period was defined as the 1 year prior to the index date.

[c] Chi-square tests were used for comparisons of categorical variables. Wilcoxon rank sum tests were used for comparisons of continuous variables.

eAppendix D. Mean dose and costs per patient per day (PPPD) in the fourth month after topical testosterone agent initiation among patients with a baseline diagnosis of hypogonadism (HG) or another condition associated with low testosterone

	Topical testosterone agent			
Measure in the fourth month,[a] Mean (SD)	**Axiron n = 209**	**AndroGel 1% n = 614**	**AndroGel 1.62% n = 235**	**Testim n = 558**
Dose (mg) PPPD	68.45 (21.53)	56.68 (19.43)	51.18 (27.24)	59.24 (27.16)
Dose PPPD as a proportion of RSD	114.1% (36)	113.4% (39)	126.4% (67)	118.5% (54)
Third-party payer costs PPPD	$7.55 (3.25)	$9.47 (3.7)	$10.35 (6.27)	$9.60 (5.03)
Cost PPPD as a proportion of RSD cost[b]	111.5% (41)	117.2% (47)	123.8% (48)	119.9% (51)

HG indicates hypogonadism; mg, milligrams; PPPD per patient per day; RSD recommended starting dose; SD standard deviation.

a. Results are weighted by the proportion of days of TTA supply per patient to the mean days of TTA supply within the cohort.

b. The daily cost in month 4 divided by the daily cost for the index claim. After the removal of the top percentile outliers, 209 Axiron, 606 AndroGel 1%, 232 AndroGel 1.62%, and 553 Testim patients were included in the analysis.