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Topical Testosterone Therapy Adherence and Outcomes Among Men With Primary or Secondary Hypogonadism

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ABSTRACT

Background: Men with primary or secondary hypogonadism (HG) prescribed testosterone therapy (TTh) who terminate treatment early might not obtain the benefit of symptom relief.

Aim: To estimate adherence to topical TTh and to compare baseline characteristics and follow-up outcomes between adherent and non-adherent patients in a population of commercially insured US men with primary or secondary HG.

Methods: A retrospective cohort of adult men with primary or secondary HG and initiating topical TTh from 2007 through 2014, with continuous coverage during 12-month baseline and follow-up periods, was identified from a large US health plan. Clinical conditions were assessed using *International Classification of Diseases, 9th Revision, Clinical Modification* codes. Adherence to initial topical TTh was defined as proportion of days covered of at least 80%. Characteristics and outcomes were compared across adherent and non-adherent patients.

Outcomes: Adherence to topical TTh, occurrence of HG-related clinical outcomes, and total health care costs.

Results: We identified 3,184 topical TTh initiators (mean age = 49 years), of whom 17% (n = 538) were adherent at 12 months. Factors positively associated with adherence included prescribing by specialists, a lower prevalence of certain comorbidities at baseline, residence in the Northeast, and an earlier start year of the topical TTh prescription. Adherence to topical TTh was associated with lower odds of having HG-associated clinical conditions (composite measure) over 12-month follow-up. In the subset of patients with available laboratory results, adherent patients had greater increases in testosterone levels compared with non-adherent patients. Increased pharmacy costs for adherent patients were partly offset by decreases in medical costs.

Clinical Implications: Adherence to topical testosterone is low but associated with positive outcomes, demonstrating the need for future efforts to focus on improving adherence in this population.

Strengths and Limitations: Strengths of this study include the large number of analyzed patients and the routine care (rather than interventional trial) setting, which maximizes generalizability within the source population. Limitations are primarily a result of reliance on medical claims data, which lack clinical context and are subject to potential coding errors. Certain factors of potential importance for adherence, such as patient and provider preferences, were not available in the dataset. The study analyzed commercially insured US patients and our ability to generalize these results to the entire US population or other countries might be limited.

Conclusion: Study findings provide further evidence for suboptimal topical TTh adherence among men treated for primary or secondary HG. Adherence is associated with greater improvement in total testosterone laboratory values and might be associated with a lower likelihood of having certain HG-related conditions. **Grabner M, Hepp Z, Raval A, et al. Topical Testosterone Therapy Adherence and Outcomes Among Men With Primary or Secondary Hypogonadism. J Sex Med 2018;15:148−158.**

Key Words: Testosterone; Hypogonadism; Retrospective Studies; Medication Adherence

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INTRODUCTION

Male hypogonadism (HG) is a clinical syndrome resulting from insufficient levels of serum testosterone. HG can be due to certain medical conditions classified as primary or secondary. Primary HG includes genetic conditions; testicular infection, tumor, or injury; chemotherapy; or toxic damage from alcohol or heavy metals. Secondary HG is caused by inherited conditions or by pituitary disorders, injury, or hypothalamic lesions.[1] Primary and secondary HG can be associated with symptoms such as sexual and erectile dysfunction, fatigue, lethargy, and mood disturbances[2,3] and with increased chronic comorbidities and health care costs.[4,5] Careful diagnosis can distinguish HG due to known diseases from age-related decline in testosterone levels, but the prevalence of primary and secondary HG is not known.[6]

For primary or secondary HG, repeated measures of below-normal morning testosterone with characteristic signs and symptoms are indicative of HG, and testosterone therapy (TTh) can be considered to normalize testosterone levels.[2] Currently, different TTh preparations are available such as buccal, oral, intramuscular, and injectable testosterone, subcutaneous implants, and transdermal gels and patches.[7] Topical TTh is commonly prescribed in the United States, with testosterone gels showing the highest rate of overall use.[8]

TTh can be highly effective in treating the symptoms of HG, improving body composition, sexual function, quality of life, and symptom scores compared with placebo in randomized trials.[3,9–11] Although the optimal duration of TTh therapy is unknown, different symptoms decrease or resolve at different times that range from 3 weeks to longer than 12 months.[12] Hence, continuous therapy over a longer period might be necessary to derive the complete benefits of TTh. However, the limited evidence available suggests adherence to TTh for HG varies widely. The proportion of men still taking TTh at 12 months after initiation of treatment has ranged from 82% down to 14%, less than 1 in 7 of those starting therapy.[13–17] These studies used data from 2009 and earlier, leaving recent trends unassessed. Also, no previously published adherence studies have focused on the primary and secondary HG population. Little is known about the effectiveness of current TTh options for HG in the context of observed low compliance with prescribed therapy or how clinical conditions, testosterone levels, and health care costs are affected by topical TTh adherence outside the setting of a clinical trial.

AIMS

The objectives of the present study were to (i) describe demographic and clinical characteristics and treatment adherence and persistence of patients with primary or secondary HG initiating topical TTh in a commercially insured population; (ii) identify factors associated with adherence to topical TTh; and (iii) compare selected clinical outcomes and health care costs for patients adherent vs non-adherent to topical TTh.

METHODS

This was a retrospective, observational cohort study based on a longitudinal review of pharmacy and medical claims and laboratory data. A prespecified research plan was prepared, in accordance with best practices for retrospective research.[18,19] The plan established patient selection criteria, defined primary and secondary outcomes, and described the analyses to be conducted.

Data Source

All study data were extracted from the HealthCore Integrated Research Database (Wilmington, DE, USA), a repository of fully adjudicated claims on more than 40 million health plan members from across the United States, with laboratory results available for a subset of patients. Throughout this study, researchers' access was limited to data removed of all identifiers to ensure confidentiality. An institutional review board did not review the study because only data in the format of a limited dataset were accessed and HealthCore maintains data use agreements with the covered entities in compliance with the Health Insurance Portability and Accountability Act of 1996. Dates queried spanned the period from January 1, 2006 through September 30, 2015.

Patient Selection

Patients initiating topical TTh for primary or secondary HG were identified using medical and pharmacy claims. We determined the diagnosis of primary or secondary HG through *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) diagnosis codes (Appendix A). At least 2 medical claims ($\geq$30 days apart) for the specified conditions were required. Then, we selected patients with at least 1 fill of topical TTh from 30 days before to 1 year after the first primary or secondary HG claim; the earliest topical TTh claim was set as the index date. Patients were required to be at least 18 years old at the index date and to have continuous health plan enrollment 12 months before and after the index date (patients who died or lost coverage during the follow-up period were not included in the analysis) and no record of any TTh before the index date.

Analyses

Descriptive statistics included means (with SD) for continuous data and absolute and relative frequencies for categorical data. The proportion of patients who were persistent with TTh over time was analyzed using Kaplan-Meier curves with 95% confidence bands.

Comparisons between adherent and non-adherent patients were conducted using χ^2 tests for categorical variables, t-tests for normally distributed continuous variables, and Wilcoxon-Mann-Whitney tests for non-normally distributed continuous variables using a significance level of 5%. No adjustments for multiple comparisons were made.