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Class Update: Topical Androgens

Month/Year of Review: July 2014
PDL Class: Topical Androgens
Literature Search End Date: June 2014

Date of Last Review: September, 2013
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred agents: Testosterone (Androgel®), testosterone gel (Testim®), testosterone cypionate injection and testosterone enathate injection.
- Non-preferred agents: Testosterone transdermal gel (Fortesta®), testosterone transdermal solution (Axiron®), testosterone patch (Androderm®).

Previous Conclusions/Recommendations:

- There is no new evidence that there is a difference in efficacy between the different testosterone products.
- Testosterone patches are associated with a higher incidence of adverse reactions related to administration.
- There is new low quality evidence that there is a potential increased risk of cardiovascular related events associated with testosterone therapy, and caution should be used in older men where cardiovascular disease is common.
- There is insufficient evidence that the new formulations (Axiron® , Androgel® 1.62%, and Fortesta®) have improved efficacy or safety than other available agents.
- No further review or research needed at this time.
- Evaluate comparative costs in executive session.

PA Criteria: A prior authorization criterion is currently in place for transdermal androgens to cover only for covered diagnosis and for medically appropriate conditions (Appendix 1). Use for body building and sexual dysfunction is not covered.

Conclusions:

- There is no new evidence that there is a difference in efficacy or safety between the different testosterone products.
- There is insufficient evidence that new depot formulation of testosterone (Aveed®) has improved efficacy or safety than other available agents. The new depot formulation of testosterone (Aveed®) offers less frequent dosing schedule, but at risk of serious pulmonary oil microembolism reactions and anaphylaxis.[1]

- The most recent FDA safety alert on potential risk of stroke, heart attack, and death in men taking testosterone supplementation was based on low quality evidence (2 observational trials).[2,3] There remains insufficient long term evidence assessing the long-term benefits and risk of testosterone therapy in men and further randomized controlled trials are needed.
- There is insufficient evidence to support androgen therapy as part of hormone therapy for the treatment of primary ovarian insufficiency.[4]

Recommendations:

- Re-evaluate safety of testosterone therapy once FDA concludes its review.
- Remove ovarian failure from list of covered diagnoses in PA criteria.
- Evaluate comparative costs in executive session; designate Aveed as non-preferred with no grandfathering.

Methods:

A MEDLINE OVID search was conducted using the following search terms: testosterone, testosterone, steroids, anabolic agents, androgens, hypogonadism, weight gain, and osteoporosis. The search is limited to randomized controlled trials (RCTs) and meta-analysis, English language, and conducted in humans from July 2013 to first week of May 2014.

The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New drugs:

None.

New Formulations/ Indications:

In March 2014, the FDA approved testosterone undecanoate (Aveed®), an injectable depot formulation, for use in men with hypogonadism who require testosterone replacement therapy.[1] The recommended dosage is 750 mg injected intramuscularly at 0 and 4 weeks, and then every 10 weeks thereafter.[1] An unpublished 84-week trial of testosterone undecanoate therapy in 130 hypogonadal men (mean age 54 years), found that 94% of those who participated in the study through week 24 maintained average serum testosterone concentrations in the normal range after the third injection of the drug. The average maximum testosterone concentration at steady state was 891 ng/dL and the average minimum was 324 ng/dL. The percentage of patients with maximum concentrations >1500 ng/dL was 7.7%.[1]

In clinical trials, the most common adverse effects of testosterone undecanoate injections that occurred in about 5% of patients included acne, injection site pain, and an increase in prostate specific antigen levels above 4 ng/mL. Postmarketing surveillance of testosterone undecanoate products approved in other countries found that some patients developed pulmonary oil microembolism (POME) reactions that have included cough, dyspnea, throat tightening, chest pain, dizziness, and syncope occurring during or immediately after injection of the drug. Some of these episodes lasted several hours, and some required

hospitalization. Life-threatening anaphylactic reactions have also been reported. As a result, the FDA labeling includes boxed warning requiring that patients be observed for 30 minutes after injections of Aveed®, and use of the drug is restricted to healthcare providers and settings certified through a Risk Evaluation and Mitigation Strategy (REMS) program.[1] This new depot formulation of testosterone offers less frequent dosing schedule, but at risk of serious pulmonary oil microembolism reactions and anaphylaxis.

In June 2014, the FDA approved another testosterone gel (Vogelxo™) that is available in tube, unit dose packet or meter dose gel pump. It is dosed once daily topically. At time of this review, there is no published RCTs evaluating its efficacy and safety. Based on product prescribing information, the FDA approval was based on one multi-center RC trial in 406 patient for 90 days[5]. The study was double-blind for the doses of testosterone gel and placebo, but open label for the nonscrotal testosterone transdermal system. During the first 60 days, patients were evenly randomized to testosterone gel 50 mg, testosterone gel 100 mg, placebo gel, or testosterone transdermal system. At Day 60, patients receiving testosterone gel were maintained at the same dose, or were titrated up or down within their treatment group, based on 24-hour averaged serum testosterone concentration levels obtained on Day 30. Of 192 hypogonadal men who were appropriately titrated with testosterone gel and who had sufficient data for analysis, 74% achieved an average serum testosterone level within the normal range (300 to 1,000 ng/dL) on treatment day 90[5].

New FDA safety alerts:

January 2014 FDA released a safety alert on the investigation of the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products.[6] This alert was based on the recent publication of two separate observational studies that each suggested an increased risk of cardiovascular events among groups of men prescribed testosterone therapy.[2,3] At this time, FDA has not concluded that FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death. Patients should not stop taking prescribed testosterone products without first discussing any questions or concerns with their health care professionals. FDA encourage weighing the benefits vs. potential risks of treatment before prescribing.

The first study was a retrospective cohort study in the VA system including men with low serum testosterone (<300 ng/dl) who were undergoing coronary angiography, to assess for coronary artery disease. Some of the men received testosterone treatment while others did not and the primary outcome was a composite of all-cause mortality, myocardial infarction (MI), and ischemic stroke. On average, the men who entered the study were about 60 years old, and many had underlying cardiovascular disease (more than 80% had coronary artery disease). This study suggested a 30 percent increased risk of stroke, heart attack, and death in the group that had been prescribed testosterone therapy (HR 1.29; 95% CI 1.05-1.58; p=0.02).[2] The absolute risk differences in events were 1.3% (95% CI -7.1% to 9.7%) at 1 year, 3.1% (95% CI -4.9% to 11.0%) at 2 years, and 5.8% (95%CI -1.4% to 13.1%) at 3 years. There are many limitations to this study, including the retrospective study design and use of ICD-9 codes to determine outcomes.

A second observational cohort study reported an increased risk of MI in older men, as well as in younger men with pre-existing heart disease, who filled a prescription for testosterone therapy.[3] The study reported a two-fold increase in the risk of heart attack among men aged 65 years and older in the first 90 days following the first prescription (RR 2.19; 95% CI 1.27 to 3.77). Among younger men less than 65 years old with a pre-existing history of heart disease, the study reported a two- to three-fold increased risk of MI in the first 90 days following a first prescription. Younger men without a history of heart disease who filled a prescription for testosterone, however, did not have an increased risk of MI (RR 1.17; 95% CI 0.84 to 1.63).

On June 19, 2014, FDA released a general warning on potential venous clots while on testosterone products. The risk of venous blood clots is already included in the labeling of testosterone products as a possible consequence of polycythemia, an abnormal increase in the number of red blood cells that sometimes occurs

with testosterone treatment. Because there have been postmarket reports of venous blood clots unrelated to polycythemia, FDA is requiring a change to drug labeling of all testosterone products to provide a more general warning regarding venous blood clots and to ensure this risk is described consistently in the labeling of all approved testosterone products. Because these clots occur in the veins, this new warning is not related to FDA's ongoing evaluation of the possible risk of stroke, heart attack, and death in patients taking testosterone products[7].

New Systematic Reviews (Appendix 2):
Corona et.al. recently conducted a systematic review and meta-analysis of testosterone replacement therapy's (TRT) outcomes in late-onset hypogonadism (LOH).[8] This review examined the diagnostic criteria for hypogonadism, effects of lifestyle modification and weight loss in LOH and medical treatment of LOH including the effect of androgen supplementation on comorbidities including: type 2 diabetes (T2DM) and metabolic syndrome(MetS), HIV infection, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), osteoporosis, and cardiovascular diseases. Six RTCs specifically evaluated the effect of TRT on MetS enrolling 483 patients and 5 RCTs on T2DM with total 263 patients. The results showed TRT showed a significant reduction of fasting glycemia (mmol/L) (diff. in mean: -0.48; 95% CI -0.78 to -0.19; p = 0.00); triglycerides (nmol/L) (diff. in mean: -0.40; 95% CI -0.66 to -0.14; p = 0.00), and waist circumference (cm) (diff. in mean: -4.09); 95%CI -7.78 to -0.39; p = 0.03) in MetS. Accordingly, an improvement of fasting glycemia (mmol/L) (diff. in mean-1.09; 95% CI -1.84 to -0.35; p = 0.00), HbA1C (%) (diff. in mean: -0.62; 95% CI -1.0 to -0.24; p = 0.00) and triglycerides (nmol/L) (diff. in mean: -0.60; 95% CI -0.83 to -0.37; p = 0.00) was observed in subjects with T2DM. In patients with HIV infection, TRT significantly improved lean mass over placebo (kg) (diff. in mean: 0.91; 95 CI 0.15 to 1.66; p = 0.02) based on 6 RTCs. The studies of TRT in patients with CKD, COPD, CVD and osteoporosis are scarce, information about the benefits and risks of TRT is too limited to draw final conclusions.

In addition to above analysis, there was a clinical review by Su J et.al since last review, that evaluated the effect of TRT on CVDs[9] The review recognized most of the studies examining TRT and CVD were observational, cross sectional, or retrospective studies that cannot demonstrate cause and effect. The more recent control studies pointed toward a potential beneficial effect of TRT on CVD. TRT resulted in positive short- and long-term physiological and biochemical changes in patients with CVD. Favorable effects have been demonstrated on myocardial ischemia, chronic heart failure (CHF) exercise tolerance, and MetS. Clinical trials and meta-analysis investigating the benefits and risks of TRT have not demonstrated significant CV events in acute setting. However, its long term risks were raised in more recent studies. The authors concluded future randomized control studies are needed to better delineate the risks and benefits of TRT in CVD and establish the optimal protocol for TRT while comparing acute versus chronic adverse effects.

Guidelines:
None.

New Trials:
A total of 83 citations resulted from initial literature search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, no relevant head-to-head controlled clinical trials were identified.

Current PA Criteria Evaluation:
Ovarian failure is included as one of diagnoses that can be approved under current PA criteria. Estrogen therapy in combination with a progestin is the gold standard for the treatment in women with primary ovarian insufficiency (premature ovarian failure) with intact uterus.[10] The main purpose of estrogen therapy is to prevent bone loss. Women with primary ovarian insufficiency may have some degree of androgen deficiency when compared with young women without

ovarian insufficiency. However, the clinical consequences of this decrease in ovarian androgens and the possible role of androgen therapy have been extensively studies[10]. Androgen therapy had been reported in uncontrolled studies in the past to be beneficial for vasomotor flushes, cognitive function and mood, and bone mineral density. However, in a Cochrane review and meta-analyses of 54 studies by Somboonporn et al.[4], no evidence of benefit for any of these outcomes was observed in peri-postmenopausal women. The authors concluded there is good evidence that adding testosterone to hormone therapy has a beneficial effect on sexual function in post-menopausal women. However, the combined therapy is associated with a higher incidence of hair growth and acne and a reduction in HDL cholesterol. These adverse events may differ by the different doses and route of testosterone administration. There is insufficient evidence to determine the effect of testosterone in long term use.

References:

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9. Su JJ, Park SK, Hsieh TM. The Effect of Testosterone on Cardiovascular Disease: A Critical Review of the Literature. *Am J Mens Health*. 2014. doi:10.1177/1557988314522642.

10. Nelson LM et al. Management of spontaneous primary ovarian insufficiency (premature ovarian failure). Available at: http://www-uptodate-com.liboff.ohsu.edu/contents/management-of-spontaneous-primary-ovarian-insufficiency-premature-ovarian-failure?topicKey=ENDO%2F7426&elapsedTimeMs=3&source=see_link&view=print&displayedView=full. Accessed June 14, 2014.

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Appendix 1: Current PA Criteria

Hormones – Testosterone (Androgens)

Goal(s):

- Cover only for covered diagnosis and for medically appropriate conditions.
- Use for body building is not covered.
- Use for sexual dysfunction is not covered.

Length of Authorization: 6 months

Requires PA: All testosterones require PA for coverage verification

Covered Alternatives: Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Does the diagnosis for the medication requested include any of the following? ~~- Ovarian failure (256.31, 256.39)~~ - Testicular Hypofunction (257.2) - Hypopituitarism and related disorders (253.2, 253.4, 253.7, 253.8) - AIDS-related cachexia (253.2)	**Yes**: Go to #3	**No**: Pass to RPh. RPh go to #4

3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. Approve for 6 months.	**No**: Approved for 6 months.
4. RPH only All other indications need to be evaluated to see if they are above the line or below the line.	**If above the line or clinic provides supporting literature:** approve for length of treatment.	**If below the line:** Deny, (Not Covered by the OHP).

P&T / DUR Action: 2/23/12 (TDW), 9/16/10 (KS), 2/23/06, 2/21/01, 9/6/00
Revision(s): 5/14/12, 1/24/12, 1/1/11, 9/1/06
Initiated:

Appendix 2

1. **Corona G, Rastrelli G, Maggi M. Diagnosis and treatment of late-onset hypogonadism: Systematic review and meta-analysis of TRT outcomes. Best Practice & Research Clinical Endocrinology & Metabolism. 2013;27(4):557-579.**

Abstract

Late-onset hypogonadism (LOH) is a relatively common conditions affecting the aging male. The aim of this review is to summarize the available evidence regarding LOH and its interaction with general health. LOH is often comorbid to obesity and several chronic diseases. For this reason lifestyle modifications should be strongly encouraged in LOH subjects with obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) and good treatment balance of chronic diseases. Medical therapy of LOH should be individualized depending on the etiology of the disease and the patient's expectations. Available evidence seems to suggest that testosterone replacement therapy is able to improve central obesity (subjects with MetS) and glycometabolic control (patients with MetS and T2DM), as well as to increase lean body mass (HIV, chronic obstructive pulmonary disease), along with insulin resistance (MetS) and peripheral oxygenation (chronic kidney diseases). However, it should be recognized that the number of studies on benefits of T supplementation is too limited to draw final conclusions. Longer and larger studies are needed to better clarify the role of TRT in such chronic conditions.

2. **Su JJ, Park SK, Hsieh TM. The Effect of Testosterone on Cardiovascular Disease: A Critical Review of the Literature. *Am J Mens Health*. 2014.**

Abstract

Cardiovascular disease is the leading cause of death in the United States. Testosterone is the principal male sex hormone and plays an important role in men's health and well-being. Historically, testosterone was believed to adversely affect cardiovascular function. However, contemporary literature has refuted this traditional thinking; testosterone has been suggested to have a protective effect on cardiovascular function through its effects on the vascular system. Data from modern research indicate that hypogonadism is closely related to the development of various cardiovascular risk factors, including hyperlipidemia and insulin resistance. Several studies have demonstrated beneficial effects of testosterone supplementation therapy on reversing symptoms of hypogonadism and improving cardiovascular disease risk profiles. In this review, we perform a critical analysis on the association between testosterone and cardiovascular disease.