Testosterone Replacement Therapy (TRT) in Adult Men
Criteria for Use
March 2019

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive TRT.*

- ☐ Adverse reaction to a specific injectable or topical testosterone product (consider use of a different testosterone product)
- ☐ Active prostate cancer
- ☐ Active breast cancer
- ☐ Hematocrit >48% at baseline
- ☐ Thrombophilia or history of unprovoked venous thromboembolism

Exclusion Unless Further Evaluation and Justification: *see Appendix*

- ☐ Severe untreated Obstructive Sleep Apnea (OSA) S*ee Appendix*
- ☐ Unevaluated PSA >4.0 ng/mL or a PSA >3.0 ng/mL in individuals with risk factors for prostate cancer such as African-Americans, or those with first-degree relative with prostate cancer or a history of Agent Orange Exposure, or an unevaluated prostate nodule or induration.
- ☐ Severe lower urinary tract symptoms (AUA International Prostate Symptom Score [IPSS] >19) S*ee Appendix*
- ☐ Inadequately controlled congestive heart failure
- ☐ Severe liver disease or renal failure *See Appendix*
- ☐ Men desiring fertility
- ☐ History of anabolic steroid abuse or dependence
- ☐ **Transgender FtM patients only:** Pregnancy/suspected pregnancy (FDA Pregnancy Category X) or breast feeding

Inclusion Criteria

Reminder: Prior to initiating TRT therapy, the potential risks and benefits should be discussed with the patient and the discussion documented in the medical record. Document that other potential treatable causes of symptoms of low testosterone levels and their suspected etiologies have been addressed.

One of the following:

- ☐ **Men with hypogonadism diagnosed by one clinical sign consistent with androgen deficiency** (*See Appendix*)**.** *If patient is diagnosed outside of VHA without appropriate documentation of diagnosis, consider stopping testosterone therapy for 2-6 weeks (6 weeks if using injectable form) and retest for hypogonadism.*
- ☐ Status post bilateral orchiectomy or unilateral orchiectomy (with documented atrophy or irradiation of second testicle)
- ☐ HIV-infected men with low testosterone levels and weight loss (See *Appendix*)
- ☐ Men receiving high doses of glucocorticoids who have low testosterone levels (daily dose greater than 5-7.5 mg of prednisone or equivalent for at least 6 months) or chronic opioid therapy (especially long-acting opioids)
- ☐ Klinefelter Syndrome, Kallmann Syndrome, or Pan-hypopituitarism and symptoms and signs of hypogonadism
- ☐ **Female-To-Male Transgender** (must meet safety criteria in addition to Transgender Cross Sex Hormone Therapy FtM)

AND Baseline evaluation (except for transgender patients) within the past 12 months prior to initiation of TRT

- ☐ Two baseline serum total testosterone levels, at least one week apart, drawn fasting, between 8AM and 10AM of <264 ng/dL (See *Appendix*)
  - Levels were not checked during acute illness, or until off transdermal TRT for ≥2 weeks or intramuscular TRT for ≥ 6 weeks.
  - If both serum testosterone levels are near or below lower limit of normal, measure serum LH and FSH to determine if primary or secondary hypogonadism are present (may be measured concurrently with second testosterone level);
  - Free (or bioavailable) testosterone levels are acceptable alternatives to total testosterone.
- ☐ PSA (for patients who choose prostate screening and monitoring),
- ☐ Hemoglobin and Hematocrit

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AND

☐ Shared decision-making regarding prostate cancer screening and monitoring has occurred:
- For males 55-69 and life expectancy > 10 years, or
- For males 40-69 years old at high-risk for prostate cancer (African-American, 1st- degree relative with prostate cancer, or Agent Orange exposure).

☐ **Biologic females of childbearing potential who are transgender FtM:** Pregnancy must be excluded prior to receiving testosterone. Patient must be provided contraceptive counseling on potential risk vs. benefit of taking testosterone if patient were to become pregnant.

Monitoring

- **Symptoms** Evaluate symptom response and side effects within 3-12 months after initiation of TRT and then annually.
- **Testosterone level** Evaluate after 3-6 months of initiation of TRT therapy and then annually. For injectable testosterone, measure level midway between injections. **Aim**: serum testosterone level in the mid-normal range for a eugonadal young male (approximately 500 ng/dL to 700 ng/dL). *Note: These are mid-range testosterone levels measured by mass spectrometry. Use the mid-range of normal testosterone levels if other measurement methods are utilized.*
- **Hematocrit:** Re-evaluate HCT within 3-6 months after initiating TRT and then annually. If >54% stop TRT until HCT decreases to <48%, evaluate for other causes of erythrocytosis (e.g. OSA or other conditions associated with hypoxia), then reinitiate therapy at a reduced dose or consider phlebotomy.
- **CBC:** Natal females are especially at risk for increased erythropoiesis. Baseline and ongoing monitoring of CBC is recommended. See Transgender Cross-Sex Hormone Therapy Recommendations
- **PSA** For men who choose monitoring, assess prostate cancer risk at 3-12 months after starting testosterone therapy, then in accordance with guidelines for age and race.
- **Urologic Consultation** Recommended for an increase in PSA absolute value of greater than 1.4 ng/mL from baseline within the first 12 months of therapy, confirmed PSA >4 ng/mL at any time, prostate abnormality on Digital Rectal Examination, or substantial worsening of LUTS.
- **Bone Mineral Density** Measure BMD of lumbar spine and/or femoral neck after 1-2 years of TRT in hypogonadal men with osteoporosis or low trauma fracture consistent with standard of care.

Renewal Criteria

- Adherence assessment
  - Excellent
    - Testosterone injection missed an average of 0-1 time in 3 months
    - Transdermal testosterone applied an average of 6-7 days per week
  - Good
    - Testosterone injection missed an average of 2 times in 3 months
    - Transdermal testosterone applied an average of 5 days per week
  - Fair
    - Testosterone injection missed an average of 3 times in 3 months
    - Transdermal testosterone applied an average of 4 days per week
  - Poor
    - Testosterone injection missed an average of ≥ 4 times in 3 months
    - Transdermal testosterone applied an average of ≤ 3 days or dose was self-decreased (on his own)

- Documentation of improved hypogonadal symptoms
  - Much improved
  - Improved
  - No change
  - Worse
  - Much Worse

Dose adjustment based on testosterone level: (after initial 3-6 months then annually)

- If level remains low but symptoms have improved, no dose change needed
- If no improvement in symptoms and the testosterone level is low (less than 400 ng/dL for topical or less than 500 ng/dL for injectable form), consider dose titration
  - Topical Gel: increase by one pump per day; if at maximum of 4 pumps per day and no symptom improvement, consider changing to injection.
  - Testosterone injection: If testosterone is less than 500 ng/dL midway between injections and symptoms have not improved, increase dose OR decrease the dosing interval to every 10 days.
  - Testosterone patch: If no symptom improvement on 4mg/day patch, increase by adding 2mg/day patch.
  - Testosterone bioadhesive buccal tablet: if T levels are outside of the normal range (300 to 1050 ng/dL) when dosed twice a day, discontinue product.
  - Testosterone subcutaneous pellets: Adjust dose between 150 to 450 mg every 3-6 months adjusting dose to patient response.
  - Testosterone nasal gel: If serum testosterone concentrations are consistently < 300 ng/dL consider an alternative treatment. If consistently > 1050 ng/mL, discontinue therapy.
- If testosterone level is more than 700 ng/dL on topical therapy or midway between injections, decrease the dose.
- If testosterone levels are consistently > 1,000 ng/dL on lowest daily dose, therapy should be discontinued.

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Prepared: February 2016. Contact: Mark C. Geraci, Pharm.D., BCOP VA Pharmacy Benefits Management Services. Updated March 2019. Reviewed by Suzanne Martinez, MD, Alvin Matsumoto, MD, Shannon Kilgore, MD.

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APPENDIX

- **Baseline Testosterone labs <264 ng/dL:** This is the lower 2.5th percentile threshold of normal testosterone levels measured by mass spectrometry assay that is harmonized and standardized against CDC measurements certified for accuracy. Testosterone levels and lower limits measured by other assay methods (e.g. immunoassay) may differ, and it may be necessary to use the lower limit of normal testosterone levels in the specific assay used as a threshold.
- **Free testosterone levels:** Acceptable methods to measure free testosterone levels include equilibrium dialysis or calculated using the levels of total testosterone, SHBG and albumin. Direct free testosterone measurements by immunoassay are inaccurate and not recommended. Consider evaluation of free testosterone if patient is suspected of having altered Sex Hormone Binding Globulin (SHBG) concentrations, e.g. elderly or with obesity, diabetes, liver or HIV disease, medications (e.g. anticonvulsants, anabolic steroids, or progestins), thyroid disease, etc or if total testosterone is around the lower limit of the normal range.
- **Specific Signs and Symptoms**
  - Incomplete or delayed sexual development
  - Loss of body hair (axillary, pubic, facial)
  - Smaller or shrinking testicles (<6cc)
- **Suggestive Signs and Symptoms**
  - Reduced or low libido
  - Erectile Dysfunction (ED)
  - Gynecomastia, breast discomfort not otherwise explained
  - Inability to father children (testosterone will not treat infertility)
  - Height loss, low-trauma fracture, low BMD
  - Low or zero sperm count
  - Hot flashes/sweats
- **Nonspecific symptoms and signs:** Use of these less-specific signs and symptoms in conjunction with low serum testosterone levels to diagnose hypogonadism should be adjudicated locally:
  - Reduced muscle mass or strength
  - Depressed mood/dysthymia
  - Reduced motivation/initiative/self-confidence
  - Increased body fat, body mass index
- **OSA** Use with caution in patients with severe treated OSA. TRT may increase pressure requirements in some patients although this may occur in a time dependent fashion and returns to baseline by 18 weeks of therapy.[1,2,]
- **LUTS** In men without severe lower urinary tract symptoms, testosterone therapy does not worsen symptoms. Men with severe lower urinary tract symptoms at baseline were excluded from clinical trials.[3]
- **HIV infected men** Short term TRT (generally 3-6 months) associated with gains in body weight, lean body mass, and muscle strength.
- **High dose glucocorticoids** Glucocorticoids for extended periods of time can decrease testosterone production.
- **Opioids** Chronic opioid therapy can decrease testosterone levels.
- **Concomitant spironolactone** TRT should not be used routinely in patients on concomitant spironolactone therapy as spironolactone has anti-androgen effects; however, it is not a contraindication to therapy.
- **Secondary Exposure**: There is a risk for secondary exposure when using topical testosterone gel products. This can be especially harmful to pregnant or breast-feeding women, and children. The application sites should be covered by clothing (e.g. a T shirt) once the product is dry. Patients should wash their hands immediately after product application. Prior to direct skin-to-skin contact, patient should wash application area with soap and water to remove residue.
- **Venous thromboembolic events:** There have been post-marketing reports of venous thromboembolic events (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products primarily in patients with thrombophilia. This association in epidemiologic studies has been inconsistent, showing no increase during Testosterone treatment and one showing an increase, causing the FDA to require a warning on the label for the possibility that testosterone therapy might cause a VTE.[4,5,6] If a venous thromboembolic event is suspected, discontinue treatment and initiate appropriate workup and management.
- **Obesity**: Obesity can lower testosterone serum levels. Advise obese patients on weight loss techniques through diet and exercise.
- **Severe liver disease and severed renal disease**: While not a contraindication for testosterone therapy, either of these conditions puts patients at an increased risk for edema due to testosterone therapy.
- **FtM:** Testosterone therapy for transgender women may result in the continuation or initiation of menses.
  Testosterone is not an effective form of contraception and may not suppress menses. Refer to Transgender Cross Sex Hormone Therapy FtM for more guidance on both issues.
- **Cardiovascular Safety** The literature concerning the risk of adverse cardiovascular events with TRT has been conflicting; if there is a signal it is weak and requires more definitive studies. No studies have been long enough to adequately assess effects of testosterone therapy on major adverse cardiovascular events (MACE). In 2014, the FDA issued a Drug Safety Communication that it was evaluating the risk of stroke, heart attack, and death with FDA-approved testosterone products based on the publication of 2 studies, one in VA patients.[7,8] The association of endogenous Testosterone (T) concentrations with coronary artery disease or cardiovascular events is inconsistent.[9,10 ,11,12] Randomized clinical trials evaluating the effects of T therapy on MACE have been small with varying degrees of limitations in study design. Retrospective analyses using electronic health records have also been inconclusive with similar limitations.[8,13,14,15,16,] Meta-analyses assessing the association of T replacement therapy with cardiovascular events, MACE, and death in randomized clinical trials did not find a statistically significant association.[17,18] Finally, there is some data so suggest that the route of administration of TRT may alter the risk for cardiovascular adverse events, with a greater risk with injections compared to patches and gels.[19] The American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of testosterone therapy and cardiovascular risk concurred with the FDA that the retrospective cohort studies had major design flaws and limitations and the signal for cardiovascular risk is weak. They advise that large-scale prospective randomized controlled trials are needed that focus on cardiovascular benefits and risks of testosterone replacement therapy.[20]

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[1] Hoyos CM, et al. Effects of testosterone therapy on sleep and breathing in obese men with severe obstructive sleep apnoea : a randomized placebo-controlled trial. Clin Endocrinology 2012; 77:599-607.

[2] Killick R, et al. The effects of testosterone on ventilatory responses in men with obstructive sleep apnea: a randomized, placebo-controlled trial. J Sleep Res 2013; 22:331-336.

[3] Bhasin S, Brito, JP, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2018; 103:1715-1744.

[4] Martinez C, Suissa S, Rietbrock S, et al. Testosterone treatment and risk of venous thromboembolism: population based case-control study. BMJ 2016;355:i5968.

[5] Baillargeon J, Urban RJ. Morgentaler A, et al. Risk of venous thromboembolism in men receiving testosterone therapy. Mayo Clinic Proc 2015;90:1038-1045.

[6] Glueck CJ, Prince M, Patel N, et al. Thrombophilia in 67 patients with thrombotic events after starting testosterone therapy. Clin Appl Thromb Hemost 2016;22:458-553.

[7] Vigen R, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310:1829-1836.

[8] Finkle W, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLOS One 2014; 9:e85805 doi:10.1371/journal.pone.0085805.

[9] Wu FCW, von Eckardstein A. Androgens and coronary artery disease. Endocrine Reviews 2003;24:183-217.

[10] Ohlsson C, Varrett-Connor E, Bhasin S, et al. High serum testosterone is associated with reduced cardiovascular events in elderly men. The MrOS (Osteoporotic Fractures in Men) study in Sweden. J Am Coll Cardiol 2011;58:1674-81.

[11] Srinath R, Golden SH, Carson KA, Dobs A. Endogenous testosterone and it relationship to preclinical and clinical measures of cardiovascular disease in the atherosclerosis risk in communities study. J Clin Endocrinol Metab 2015;100:1602-1608.

[12] Khazai B, Golden SH, Colangelo LA, et al. Association of endogenous testosterone with subclinical atherosclerosis in men: the multi-ethnic study of atherosclerosis. Clinical Endocrinology 2016;84:700-707.

[13] Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. European Heart Journal 2015; 36:2706-2715.

[14] Anderson JL, May HT, Lappe DL, et al. Impact of testosterone replacement therapy on myocardial infarction, stroke, and death in men with low testosterone concentrations in an integrated health care system. Am J Cardiol 2016;117:794-799.f

[15] Muraleedharan B, Marsh H, Kapoor D, et al. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinology 2013:69:725-733.

[16] Cheettham TC, An JJ, Jacobsen SJ, et al. Association of testosterone replacement with cardiovascular outcomes amone men with androgen deficiency. JAMA Int Med 2017;177:491-499.

[17] Borst SE, Shuster JJ, Zou B, et al. Cardiovascular risks and elevation of DHT vary by route of testosterone administration: a systematic review and meta-analysis. BMC Medicine 2014;12:211-226.

[18] Alexander GC, Iyer G, Lucas E, et al. Cardiovascular risks of exogenous testosterone use among men: a systematic review and meta-analysis. Am J Med 2017;130:293-305.

[19] Layton JB, et al. Comparative safety of testosterone dosage forms. JAMA Internal Med 2015;175:1187-1196.

[20] Goodman N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of testosterone and cardiovascular risk. Endocrine Practice 2015;21:1066-1073.

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