ALABAMA STATE BOARD OF MEDICAL EXAMINERS

Recommended Guidelines for Testosterone Replacement Therapy in Males

- Only symptomatic men with demonstrably abnormal serum testosterone levels below 300ng/dl confirmed on subsequent morning lab evaluations should be considered for testosterone replacement therapy (TRT) after exclusion of other related medical conditions.
    - Valid symptoms in the setting of testosterone less than 300ng/dl include:
        - Persistent fatigue after lifestyle and medical workup
        - Decline in muscle mass
        - Decline in libido
        - Erectile dysfunction
        - Depression
        - Sleep disturbance
        - Idiopathic anemia
        - Osteopenia / osteoporosis
        - Persistent sleep disturbance with ongoing treatment of sleep apnea
    - Subsequent / confirmatory lab evaluation should include fasting early morning serum total testosterone, LH, H/H, prolactin, FSH, and PSA.
        - Potential pituitary abnormalities, such as hyperprolactinemia or the combination of low LH and low testosterone, should be referred to a specialist for evaluation and management.
- All testosterone replacement therapy candidates should be screened for contraindications **prior** to initiating testosterone replacement therapy:
    - Desire to maintain sufficient quality and quantity of sperm production for future fertility
    - Active prostate cancer
    - Uncertain serum PSA status
    - Major cardiac or thromboembolic event within 6 months
    - Cardiac Arrythmia
    - Undiagnosed / Unmanaged Obstructive Sleep Apnea
    - Primary or secondary polycythemia
    - Active liver and/or gallbladder disease
- All testosterone replacement therapy candidates should undergo a physical exam including:
    - Penis

    - Scrotum
    - Testes
    - Prostate
    - Breasts
    - General body habitus
- All testosterone replacement therapy candidates should be counseled on the evidence-based risks of TRT; including, but not limited to:
    - Loss of testicular volume and function – impairment of fertility
    - Small increase in the risk of thrombotic events including cardiac and cerebral
    - Small increase in the risk of cardiac arrythmia
    - Significant risk of secondary polycythemia / erythrocytosis
    - Possible risk of a major cardiac event or thrombotic event if testosterone levels are allowed to elevate past a safe level or if the medicine is abused
    - Significant possibility for elevated estrogen levels and resulting gynecomastia and mood alteration
    - Potential for increase in prostate size and lower urinary tract symptoms
- All testosterone replacement therapy candidates should be counseled on the potential evidence-based benefits of testosterone replacement therapy including improvements in:
    - Libido
    - Erectile function
    - Body composition
    - Insulin sensitivity
    - Mood
    - Bone density, if deficient
- Initial lab evaluations should include two early morning serum testosterone levels.
    - Values below 300ng/dl should be considered “low”
- All men should be evaluated with serum LH, prolactin, Hemoglobin and Hematocrit (H/H), FSH, and PSA levels prior to initiating testosterone replacement therapy.
- Karyotype should be obtained on individuals with physical exam findings and lab findings concerning 47XXY / Klinefelter’s syndrome. Appropriate subspecialty referral(s) or consults should be made if 47XXY / Klinefelter’s syndrome is determined to be present.
- All men should be counseled on the importance of a high-quality diet, exercise, sleep quality, stress management, weight management, avoidance of marijuana and alcohol, and general medical evaluation. Optimizing these variables will often help patients normalize testosterone levels without testosterone replacement therapy.

- After initiation of testosterone replacement therapy, repeat serum testosterone, H/H, and PSA levels should be checked at 3 months by a physician to ensure safety and efficacy of therapy. At this time, the patient should be examined by the physician of record to ascertain benefits derived from therapy. If no benefits are confirmed, the physician should offer discontinuation of therapy at this time.
- When intramuscular testosterone replacement therapy is used, the following guidance should be followed:
    - Serum testosterone levels change daily for men on injectable TRT.
    - Physicians should standardize serum testosterone level testing by checking mid dose interval serum testosterone level. This testing allows the physician to ascertain the approximate peak and trough testosterone levels without overburdening the patient with multiple blood draws.
    - Self-injecting TRT patients should inject on a consistent day allowing lab testing to be accurately arranged and communicated to the patient.
    - Appropriate mid dose interval testosterone levels will vary from patient to patient. However, levels should never be above 700 ng/dl, which would suggest a peak testosterone level above 800ng/dl.

    - Serum estradiol may be checked for patients with breast complaints, paradoxically decreased libido and/or erectile dysfunction, or at the discretion of the physician and consider that referral to appropriate specialist may be indicated.
- Repeat safety labs (mid dose interval serum testosterone and H/H) every 6 months while on therapy.
    - Serum Total Testosterone above 800 ng/dl should be considered excessive.
    - Physicians should not refill testosterone prescriptions without safety screening labs on file within the past 6 months.
- Physicians should adhere to the philosophy of "lowest effective dose" when prescribing testosterone replacement therapy.
- After initial evaluation, patients should undergo a 3-month visit with lab studies (Serum testosterone, H/H, PSA) and must be seen <u>in person</u> annually by a physician.
    - Telehealth is <u>not</u> an acceptable visit to qualify as a managing physician visit.
    - PSA should be checked at least annually. Physicians should consider checking PSA every 6 months in men with a father or brother with a prostate cancer history or a personal history of prostate cancer in durable remission.
- Prescribers should consider checking the PDMP at initiation and thereafter to identify potential testosterone replacement therapy prescription abuse.
- Physicians should offer to refer the patient to a qualified urologist or endocrinologist for any challenging treatment situation.

The above guidelines were approved by the Alabama Board of Medical Examiners on February 20, 2025. More resources on testosterone replacement therapy can be found on the Board's website: www.albme.gov.

ALABAMA STATE BOARD OF MEDICAL EXAMINERS

Recommended Guidelines for Testosterone Replacement Therapy in Females

- **Introduction:** The following recommendations for testosterone use in women are based primarily on the American Endocrine Society's clinical guidelines[i] and the Global Consensus Position Statement on the Use of Testosterone Therapy for Women.[ii]

- **Indications**:
  - ***Recommended:***
  - Current data supports the short-term efficacy and safety of <u>low dose</u> testosterone therapy to achieve high levels in the normal/premenopausal range in postmenopausal women with sexual dysfunction due to hypoactive sexual desire disorder (HSDD), after a formal biopsychosocial approach has excluded other causes such as relationship, psychological, and medication related (e.g. SSRIs/SNRIs).[iii]
  - Limited data also supports the use in late reproductive age premenopausal women for the treatment of HSDD, after a complete evaluation has excluded other causes and the individual's circulating testosterone levels are not mid to high normal.[iv]
  - Combined hormonal and psychosexual approaches may be beneficial in some cases with mixed etiologies.[v]
  - The diagnosis of HSDD is made:
    - Following an evaluation that includes the use of the validated self-report screening and diagnostic instrument (e.g., the Decreased Sexual Desire Screener), that enables the diagnosis of generalized acquired HSDD and associated biopsychosocial factors, following the International Society for the Study of Women's Sexual Health (ISSWSH) Process of Care guidelines for assessment of low sexual desire.[vi][1]
  - Total testosterone levels should be measured <u>*before*</u> initiating therapy to exclude women with mid- to high-range basal testosterone concentrations, who would not need additional supplementation.[vii] However, in women

[1] Please note that the criteria for the definition of disordered sexual desire may have changed from that used in prior clinical trials, which could impact the recorded response to therapy (Wierman et al, 2014).

whose total testosterone levels are in the upper end of the physiologic range and not experiencing improvement of HSDD symptoms with other modalities, obtaining a free testosterone might provide insight to the lack of response to therapy. Total testosterone should be measured by tandem mass spectrometry and free testosterone by equilibrium dialysis, and not by direct immunoassays.[viii][2]

- In women being considered for testosterone therapy, sex hormone binding globulin (SHBG) should also be measured (by immunoassay) as women with SHBG levels greater than the normal range are less likely to benefit from testosterone therapy[ix], due to increased binding of the administered testosterone reducing the available free testosterone fraction.
- The National Institute for Health and Care Excellence of the United Kingdom (NICE) Menopause Guidelines (NG23) and the British Medical Society also recommend that a trial of conventional HRT be given before testosterone supplementation is considered.[x]

- ***Not recommended:***
- The general use of testosterone in women for infertility; sexual dysfunction other than HSDD; cognitive, cardiovascular, metabolic, or bone health; depression; or general well-being is not recommended.[xi]
- The use of testosterone to enhance cognitive performance, or to delay cognitive decline, in postmenopausal women is not recommended, as there is insufficient evidence to support use for this indication.[xii]
- The routine prescription of testosterone or dehydroepiandrosterone (DHEA) for the treatment of women with low androgen levels due to hypopituitarism, adrenal insufficiency, surgical menopause, pharmacological glucocorticoid administration, or other conditions associated with low androgen levels is not recommended, as there are limited data supporting improvement in signs and symptoms with therapy and no long-term studies of risk.[xiii]

- **Contraindications:**
  - Hepatic disease and hyperlipidemia are contraindications to testosterone therapy.[xiv]

[2] In all women, total testosterone levels should be measured using high quality, validated and ultrasensitive assays, such as liquid chromatography followed by tandem mass spectrometry (LC-MSMS), and not by direct immunoassays. Likewise, free testosterone, if needed, should be calculated starting with an accurately measured total testosterone and estimated using a highly accurate method, e.g. equilibrium dialysis (Rosner et al, 2007).

- **Treatment:**
  - **Doses and routes:**
    - Dosing should aim to achieve testosterone concentrations in the upper physiologic premenopausal range.[xv][3] [4]
    - Treatment using any male product for women should be initiated using one-tenth of the recommended starting dose for men.[xvi]
    - ***Recommended[xvii]:***
      - Transdermal treatment provides the most physiological form of replacement therapy for women, administered as a gel. Options include:
        - Use of small doses of 1.62% testosterone gel (e.g., approx. 1/5 of a pump actuation of Androgel® (roughly the size of a black-eyed pea) daily).[xviii]
      - The topical preparation should be applied to the skin surface, typically the shoulders, upper arms, or abdomen (stomach).
      - Patients using topical gels should be counseled about potential transference of testosterone from the application site to the skin of individuals or animals with whom they have close contact with and that may potentially be affected (e.g., young children, female partners, pets). Alternatively, the risk of exposure to a male partner is minimal.
      - We should note that at present, physiological testosterone preparations for use in women are not available in many countries, including the United States.[xix]

    - ***Not recommended[xx]***:
      - Testosterone implants, which may result in supraphysiological levels and do not allow for dose titration.
      - Intramuscular (IM) injections and oral preparations are not recommended, owing to the adverse effects related to short-term safety.

[3] In one study of women aged 20–29 years, 30–39 years, and 40–49 years without complaints of sexual dysfunction, testosterone values ranged from 45.5 to 57.5 ng/dl, 27.6 to 39.8 ng/dl, and 27.0 to 38.6 ng/dl, respectively. Guay A, Munarriz R, Jacobson J, et al. Serum androgen levels in healthy premenopausal women with and without sexual dysfunction: part A. Serum androgen levels in women aged 20–49 years with no complaints of sexual dysfunction. Int J Impot Res 2004;16:112–120.

[4] These ranges are approximately 1/10th–1/15th of the testosterone values found in healthy men (range 300–800 ng/dl). Platz EA, Barber JR, Chadid S, et al. Nationally representative estimates of serum testosterone concentration in never-smoking, lean men without aging-associated comorbidities. J Endocr Soc 2019;3:1759–1770.

        - Compounded buccal lozenges and troches result in substantial gut absorption through swallowing of saliva as they are held in the mouth and thus should be considered to be equivalent to oral testosterone therapy.[xxi]
    - **Duration[xxii]:**
        - A 3- to 6-month trial of a dose of testosterone resulting in a mid-to high normal premenopausal value in a reference assay in postmenopausal women who request therapy for properly diagnosed HSDD, and in whom therapy is not contraindicated, is suggested.
        - Testosterone therapy for women who have not responded to treatment after 6 months of treatment should be discontinued.
        - Symptoms often recur after discontinuation of therapy, and sexual dysfunction often requires long-term treatment.
    - **Monitoring**:
        - Testosterone levels should be measured at baseline and after 3–6 weeks of initial treatment to assess patient overuse.[xxiii]
        - However, endogenous testosterone levels do not predict response to therapy and the response to therapy does not correlate with levels of testosterone.[xxiv]
        - Measurement of liver function and a fasting lipid profile is recommended before initiating treatment. Liver disease and hyperlipidemia are contraindications to testosterone therapy.[xxv]
- **Safety:**
    - No safety and efficacy data for testosterone therapy is available after 24 months.[xxvi]
    - Long-term effects of testosterone therapy on cardiovascular risk and breast cancer incidence are not known.[xxvii]
    - Any woman receiving testosterone therapy should be monitored every 6 months for signs and symptoms of androgen excess.[xxviii]

[i] Wierman ME, Arlt W, Basson R, Davis SR, Miller KK, Murad MH, Rosner W, Santoro N. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014 Oct; 99(10):3489-510.

[ii] Davis SR, Baber R, Panay N, Bitzer J, Cerdas Perez S, Islam RM, Kaunitz AM, Kingsberg SA, Lambrinoudaki I, Liu J, Parish SJ, Pinkerton J, Rymer J, Simon JA, Vignozzi L, Wierman ME. Global Consensus Position Statement on the Use of Testosterone Therapy for Women. Climacteric. 2019 Oct; 22(5):429-434. Erratum in: Climacteric. 2019 Dec; 22(6):637.

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[iii] Wierman et al, 2014; Davis et al, 2019; Parish et al, 2021.

Panay N. British Menopause Society Tool for clinicians: Testosterone replacement in menopause. Post Reprod Health. 2022 Sep;28(3):158-160.

[iv] Parish et al, 2021.

[v] Panay et al, 2022.

[vi] Davis et al, 2019.

Clayton A, Goldfischer ER, Goldstein I, et al. Validation of the decreased sexual desire screener (DSDS): a brief diagnostic instrument for generalized acquired female hypoactive sexual desire disorder (HSDD). J Sex Med 2009; 6:730–738.

[vii] Wierman et al, 2014; Parish et al, 2021.

[viii] Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. J Clin Endocrinol Metab. 2007 Feb; 92(2):405-13.

[ix] Parish et al, 2021.

Shifren J, Davis S, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 study. Menopause 2006;13:770–779.

[x] Panay et al, 2022.

[xi] Wierman et al, 2014; Parish et al, 2021.

[xii] Davis et al, 2019.

[xiii] Wierman et al, 2014; Davis et al, 2019; Parish et al, 2021.

[xiv] Davis et al, 2019.

[xv] Parish et al, 2019.

[xvi] Park, Amy J; Yauger, Belinda. Compounded bioidentical menopausal hormone therapy. Clinical Consensus No. 6. American College of Obstetricians and Gynecologists. Obstet Gynecol 2023;142:1266-73.

[xvii] Wierman et al, 2014, Parish et al, 2019.

[xviii] Parish et al, 2019.

Nachtigall L, Casson P, Lucas J, et al. Safety and tolerability of testosterone patch therapy for up to 4 years in surgically menopausal women receiving oral or transdermal estrogen. Gynecol Endocrinol 2011;27:39–48.

[xix] Wierman et al, 2014.

[xx] Wierman et al, 2014; Parish et al, 2021.
[xxi] Parish et al, 2021, Park, Amy, et al 2023.
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[xxii] Wierman et al, 2014.
[xxiii] Wierman et al, 2014.
[xxiv] Wierman et al, 2014.
[xxv] Davis et al, 2019.
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