Testosterone Therapy: Review of Clinical Applications

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Testosterone therapy is increasingly common in the United States, and many of these prescriptions are written by primary care physicians. There is conflicting evidence on the benefit of male testosterone therapy for age-related declines in testosterone. Physicians should not measure testosterone levels unless a patient has signs and symptoms of hypogonadism, such as loss of body hair, sexual dysfunction, hot flashes, or gynecomastia. Depressed mood, fatigue, decreased strength, and a decreased sense of vitality are less specific to male hypogonadism. Testosterone therapy should be initiated only after two morning total serum testosterone measurements show decreased levels, and all patients should be counseled on the potential risks and benefits before starting therapy. Potential benefits of therapy include increased libido, improved sexual function, improved mood and well-being, and increased muscle mass and bone density; however, there is little or mixed evidence confirming clinically significant benefits. The U.S. Food and Drug Administration warns that testosterone therapy may increase the risk of cardiovascular complications. Other possible risks include rising prostate-specific antigen levels, worsening lower urinary tract symptoms, polycythemia, and increased risk of venous thromboembolism. Patients receiving testosterone therapy should be monitored to ensure testosterone levels rise appropriately, clinical improvement occurs, and no complications develop. Testosterone therapy may also be used to treat hypoactive sexual desire disorder in postmenopausal women and to produce physical male sex characteristics in female-to-male transgender patients. (*Am Fam Physician*. 2017;96(7):441-449. Copyright © 2017 American Academy of Family Physicians.)

▶ **See related editorial on page 428.**

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The use of testosterone therapy is increasingly common in the United States, with an estimated 2.3 million American men receiving the therapy in 2013.[1] More than one-half of testosterone prescriptions are written by primary care physicians.[2] Most of these prescriptions are for middle-aged and older men with age-related declines in testosterone,[1] despite inconclusive data on testosterone therapy's safety and effectiveness for this indication.

Physiology of Testosterone and Causes of Hypogonadism in Males

Testosterone is produced by Leydig cells in the testes, in response to luteinizing hormone produced by the pituitary gland. Decreased production of testosterone by testes in men is categorized as hypogonadism, which is classified as primary, secondary, or mixed. Primary hypogonadism is the failure of the testes to produce sufficient testosterone, whereas secondary hypogonadism is caused by decreased production of luteinizing hormone.[3] Hypogonadism may also be classified by timing of onset (i.e., pre- or postpubertal). *Table 1* lists the most common causes of hypogonadism.[4,5]

Testosterone levels begin to decline around 40 years of age. By 80 years of age, more than 50% of men will have testosterone levels in the low range (using a reference range defined by nonobese, healthy men younger than 40 years).[3] Several common medical conditions (e.g., obesity, type 2 diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, human immunodeficiency virus infection) and opioid dependence have been associated with low testosterone levels.[6,7]

WHAT IS NEW ON THIS TOPIC: TESTOSTERONE THERAPY

- Male hypogonadism should be diagnosed only if there are signs or symptoms of hypogonadism and total serum testosterone levels are low on at least two occasions.
- The U.S. Food and Drug Administration clarified in 2015 that prescribing testosterone for low testosterone levels due to aging constitutes off-label use.

Table 1. Causes of Hypogonadism in Men

Type	*Laboratory values*	*Origin*	*Possible causes*
Primary	Decreased total serum testosterone, increased LH and FSH	Congenital	Chromosomal abnormalities, cryptorchidism, FSH/LH receptor gene mutations, Klinefelter syndrome, myotonic dystrophy
		Acquired	Chemotherapy, hypothyroidism, orchitis/epididymo-orchitis (from mumps, gonorrhea, or chlamydia), radiation/trauma to testes, testicular torsion
Secondary	Decreased total serum testosterone, normal or decreased LH and FSH	Congenital	Kallmann syndrome, Prader-Willi syndrome, other genetic abnormalities
		Acquired	Chronic opioid use, hyperprolactinemia, pituitary tumors, sellar radiation, sleep deprivation, surgery, trauma
Mixed primary and secondary	Decreased total serum testosterone, variable LH and FSH	Acquired	Aging, cancer, chronic glucocorticoid use, chronic kidney disease, chronic obstructive pulmonary disease, cirrhosis, diabetes mellitus, hemochromatosis, human immunodeficiency virus infection, obesity

FSH = follicle-stimulating hormone; LH = luteinizing hormone.

Information from references 4 and 5.

Diagnosis of Male Hypogonadism

According to guidelines from the Endocrine Society, male hypogonadism should be diagnosed only if there are signs or symptoms of hypogonadism *(Table 2[3,8,9])* and total serum testosterone levels are low on at least two occasions.[9] When diagnosing hypogonadism, physicians should not rely solely on questionnaires such as Androgen Deficiency in Aging Males or Aging Males' Symptoms because of their low sensitivity and specificity.[9,10] Two editorials published previously in *American Family Physician* discuss the pros and cons of screening for testosterone deficiency (http://www.aafp.org/afp/2015/0215/p220.html and http://www.aafp.org/afp/2015/0215/p226.html).

Table 2. Signs and Symptoms of Hypogonadism in Men

Anemia (normocytic, normochromic)*
Breast discomfort, gynecomastia
Depressed mood*
Diminished bone density, low-trauma fractures
Diminished energy, sense of vitality, or sense of well-being*
Diminished muscle mass and strength*
Diminished physical or work performance*
Hot flashes, sweats
Impaired cognition*
Incomplete or delayed sexual development (in cases of prepubertal onset)
Increased body fat, body mass index*
Increased fatigue*
Infertility
Loss of body hair
Sexual symptoms (decreased libido, decreased spontaneous erection)
Very small testes

**—Less specific; may be associated with other conditions.*

Information from references 3, 8, and 9.

Because of circadian variations in testosterone levels, serum testosterone measurement should occur in the morning, or within two hours of awakening in shift workers *(Figure 1[9])*. Although there is no universal laboratory definition of hypogonadism, in most laboratory reference ranges, the lower limit of normal is between 250 and 350 ng per dL (8.7 to 12.2 nmol per L). In men with borderline total testosterone levels, measurement of free testosterone and sex hormone–binding globulin levels should be considered, especially in the presence of conditions that affect sex hormone–binding globulin levels (most commonly, aging, obesity, and diabetes). If low testosterone is confirmed, luteinizing hormone and follicle-stimulating hormone levels should be measured to categorize the deficiency as primary or secondary.[9,11] A prolactin measurement should be considered to rule out pituitary adenoma, especially if luteinizing hormone and follicle-stimulating hormone levels are low.

Benefits of Testosterone Replacement Therapy

LIBIDO AND ERECTILE FUNCTION

A common indication for testosterone therapy is treatment of decreased sexual desire or erectile dysfunction. A systematic review found 23 randomized trials of testosterone therapy's effects on libido; 13 trials showed some benefit, eight showed no benefit, and two had mixed results.[12]

Although evidence regarding erectile dysfunction is mixed, young men with hypogonadism and erectile dysfunction appear to benefit from testosterone therapy.[13] Some studies have shown improvement in erectile dysfunction in older men and men with comorbid conditions,[14,15] whereas others have not.[12,16,17] Moreover, even in positive studies, the effect of testosterone has

been smaller than the effect traditionally reported with phosphodiesterase-5 inhibitors,[14] suggesting that testosterone should not be first-line treatment for erectile dysfunction. There is some evidence supporting the use of testosterone therapy as second-line therapy in men with low testosterone when phosphodiesterase-5 inhibitors are ineffective.[18,19] There is no evidence that testosterone improves erectile function in men with normal testosterone levels. As part of the Choosing Wisely campaign, the American Urological Association says physicians should not prescribe testosterone therapy for men with erectile dysfunction and normal testosterone levels.[20]

BONE DENSITY, BODY COMPOSITION, AND MUSCLE STRENGTH

Low testosterone levels (less than 200 ng per dL [7.0 nmol per L]) are associated with decreased bone density and unfavorable body composition changes.[21] Testosterone therapy increases bone density at the lumbar spine but not at the hip in middle-aged men with testosterone deficiency.[22] In older men, testosterone therapy increases bone density in the spine and hip.[23,24] There is no evidence that testosterone therapy leads to decreased fractures or falls. Testosterone therapy consistently increases lean mass and decreases fat mass,[25-27] but the effect sizes are small and studies have generally failed to demonstrate improvement in strength or physical function.[22,23,25,26]

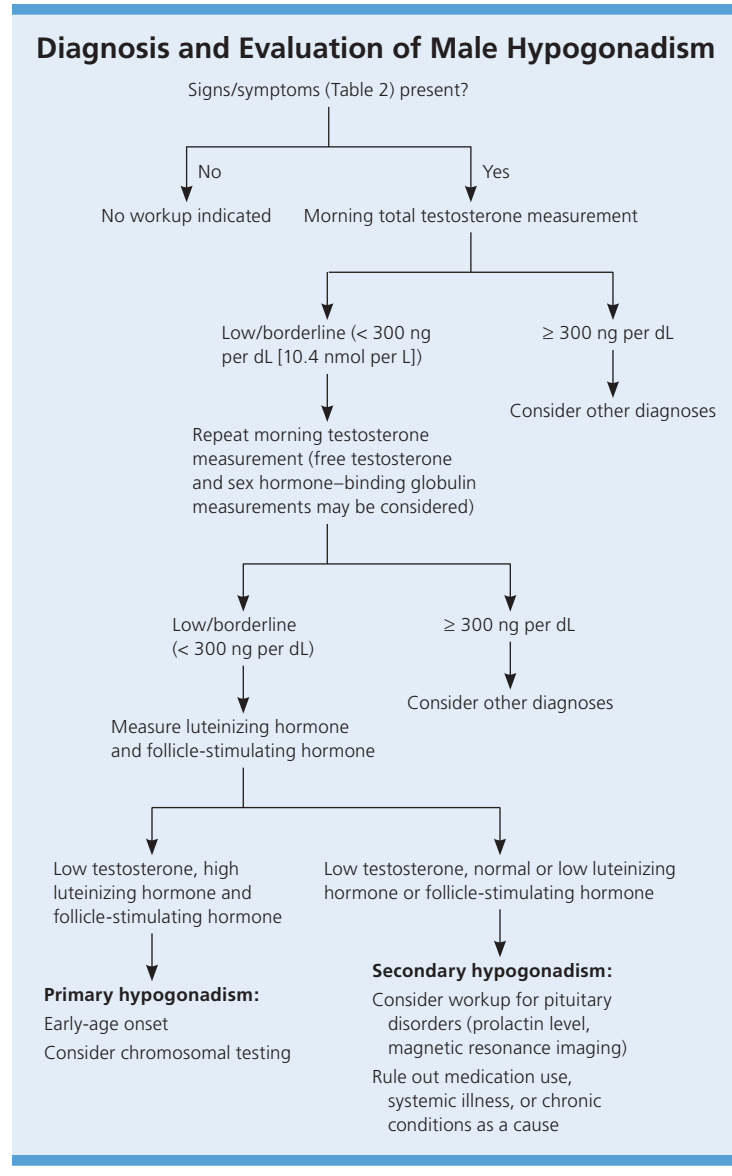

Figure 1. Algorithm for the diagnosis and evaluation of male hypogonadism.

Information from reference 9.

DEPRESSION, MOOD, COGNITION, WELL-BEING, VITALITY

The few studies of testosterone therapy for depressed mood had mixed results.[28-31] Testosterone therapy does not improve cognitive function in men with or without preexisting cognitive impairment.[32-34] There is also mixed evidence for prescribing testosterone to improve vitality, general quality of life, and male "symptoms of aging," with some studies demonstrating improvement with therapy,[35,36] and other studies finding no change.[10,37]

Testosterone and Cardiovascular Health

In a 2015 advisory, the U.S. Food and Drug Administration (FDA) warned that testosterone use is possibly associated with increased cardiovascular risk and advised physicians to discuss this risk with patients before initiating testosterone therapy.[38] This warning came after two observational studies[39,40] and a meta-analysis of randomized controlled trials[41] showed an increased cardiovascular risk, and the Testosterone in Older Men with Mobility Limitation (TOM) randomized controlled trial was stopped early because of concerns about a higher incidence of cardiovascular adverse events in the testosterone treatment group.[42] However, other meta-analyses did not find an increased cardiovascular risk,[43,44] and several other observational studies have appeared to demonstrate decreased cardiovascular risk with testosterone therapy.[45-48] Additionally, one of the observational studies that showed increased risk was criticized for its statistical analyses,[40] and many of the adverse events leading to the early stoppage of the TOM trial were of questionable

BEST PRACTICES IN ENDOCRINOLOGY: RECOMMENDATIONS FROM THE CHOOSING WISELY CAMPAIGN

Recommendation	*Sponsoring organization*
Do not prescribe testosterone or testosterone products to men contemplating or attempting to initiate pregnancy.	American Society for Reproductive Medicine
Do not prescribe testosterone to men with erectile dysfunction who have normal testosterone levels.	American Urological Association
Do not prescribe testosterone therapy unless there is laboratory evidence of testosterone deficiency.	American Society for Clinical Pathology
Do not prescribe testosterone therapy unless there is biochemical evidence of testosterone deficiency.	The Endocrine Society/ American Association of Clinical Endocrinologists

Source: For more information on the Choosing Wisely Campaign, see http://www.choosingwisely.org. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see http://www.aafp.org/afp/recommendations/search.htm.

clinical significance. Although the findings of the TOM trial are concerning, this study enrolled a high-risk population, and its findings may not be generalizable to most men being considered for testosterone therapy.

Proponents of testosterone therapy point to a large number of observational studies consistently finding higher cardiovascular morbidity and mortality in men with low baseline testosterone levels and suggest that treating low testosterone should lead to decreased risk,[49] although it is unclear whether low testosterone was a cause of the increased cardiovascular risk or merely a marker of poor overall health. No randomized controlled trial has demonstrated decreased cardiovascular events or mortality with testosterone therapy.

A recent systematic review found some evidence of benefit in congestive heart failure and increased time to ST segment depression in exercise testing. The review found inconsistent effects of testosterone therapy on lipids and no beneficial effect on reported angina.[12]

The effects of testosterone therapy on cardiovascular health remain unclear. The FDA has mandated that testosterone product manufacturers conduct a large-scale randomized controlled trial specifically to determine cardiovascular risk,[38] but results of any such trial would not be available for years. In the meantime, physicians must counsel patients that the cardiovascular risks and benefits of testosterone therapy are uncertain and should engage in shared decision making.[9,11,38]

Risks of Testosterone Therapy and Contraindications

Contraindications to testosterone therapy are listed in *(Table 3)*.[9,11]

PROSTATE CANCER AND LOWER URINARY TRACT SYMPTOMS

Because prostate cancer can be stimulated by testosterone, testosterone therapy is contraindicated in patients with known or suspected prostate cancer. There has long been concern that testosterone therapy may increase the risk of developing prostate cancer and increase the symptoms of benign prostatic hyperplasia. However, several meta-analyses of randomized controlled trials have not shown an increased incidence of prostate cancer.[50-52] Use of testosterone therapy in men with hypogonadism and previously treated (and presumed cured) prostate cancer is controversial, with little data to guide treatment decisions in this group.[53]

Use of supplemental testosterone has been shown to cause a small increase in prostate-specific antigen (PSA) levels,[52] but the significance of this increase is questionable. There also does not appear to be a significant increase in lower urinary tract symptoms with testosterone therapy, although most studies have excluded men with severe lower urinary tract symptoms at baseline.[54]

HEMATOLOGIC CONDITIONS

Testosterone stimulates erythropoiesis, and testosterone therapy (in particular the intramuscular esters)

Table 3. Contraindications to Starting Testosterone Therapy

Absolute contraindications
Breast cancer
Polycythemia (hematocrit > 54%)
Prostate cancer
Prostate-specific antigen > 4 ng per mL (4 mcg per L) or presence of nodules/induration on digital rectal examination (referral to a urologist is required before considering testosterone therapy)
Relative contraindications
Baseline hematocrit > 50%*
Desire for fertility (testosterone therapy suppresses spermatogenesis)
Severe lower urinary tract symptoms
Uncontrolled congestive heart failure
Untreated obstructive sleep apnea

**—The criterion for discontinuing or decreasing testosterone therapy is a rise to a hematocrit of > 54%. A baseline hematocrit of > 50% predicts a likely rise to > 54% on therapy and is therefore a relative contraindication to starting therapy.*

Information from references 9 and 11.

Table 4. Preparations of Testosterone

Type of testosterone (brand)	*Dosage and frequency*	*Common starting dosage*	*Cost**	*Comments*
Buccal testosterone (Striant)	30 mg twice daily	30 mg twice daily	NA ($620) for 60 tablets	May alter taste or irritate oral mucosa
Injectable/intramuscular				
Testosterone cypionate (Depo-Testosterone)	50 to 400 mg every one to four weeks	100 mg weekly or 200 mg every two weeks	200 mg per mL: $115 ($130) for one 10-mL vial	—
Testosterone enanthate (Delatestryl)	50 to 400 mg every one to four weeks	100 mg weekly or 200 mg every two weeks	200 mg per mL: $80 ($100) for one 5-mL vial	Serum levels tend to have peaks and troughs
Testosterone undecanoate (Aveed)	750-mg initial dose and another 750 mg four weeks later, then 750 mg every 10 weeks	Two doses four weeks apart, then every 10 weeks	NA ($995) per 750-mg dose	Special prescriber registration required because of risk of anaphylaxis and pulmonary oil microembolism
Intranasal gel (Natesto)	33 mg; one actuation (11 mg) in each nostril three times daily	Three times daily	NA ($235) for one inhaler	Adverse effects include headache, nasopharyngeal and upper respiratory symptoms
Pellets (Testopel)	150 to 450 mg every three to six months	150 mg every three months	NA ($950) for 10 75-mg pellets	—
Transdermal gel				
Androgel 1% or 1.62%	50 to 100 mg daily	50 mg daily	1% gel: $310 ($560) for 30 50-mg doses	Possible to transfer from one person to another; risk of virilization of exposed women and children
Fortesta	10 to 70 mg daily	40 mg daily	$350 ($450) for one pump	
Testim 1%	50 to 100 mg daily	50 mg daily	$400 ($600) for 30 50-mg doses	
Transdermal patch (Androderm)	2 to 4 mg daily	2 mg daily	NA ($550) for 30 4-mg patches	Skin rash common; patients should be advised to rotate application sites
Transdermal solution (Axiron)	30 to 120 mg daily	60 mg daily	30 mg: NA ($615) for one bottle	Applied to axillary area similar to deodorant; risk of transfer to others as with gel forms

NA = not available.

**—Estimated retail price based on information obtained at http://www.goodrx.com (accessed March 29, 2017). Generic listed first, brand in parentheses.*

Information from references 59 and 60.

is associated with an increased risk of polycythemia.[50] Preexisting polycythemia (hematocrit of more than 54%) is an absolute contraindication to starting testosterone therapy. Development of polycythemia during treatment should lead to cessation of therapy, lowering of the dose, or switching to a lower-risk formulation to avoid increased risk of myocardial infarction, stroke, and venous thromboembolism. Testosterone therapy has been shown to increase hemoglobin levels and correct anemia in a significant portion of older men with anemia of otherwise unknown etiology. Testosterone measurement should be considered in older men with unexplained anemia.[55]

VENOUS THROMBOEMBOLISM

Based on postmarket reports, in 2014 the FDA required manufacturers of testosterone products to add a warning to the drug label about the risk of venous thromboembolism.[56] Subsequently, a large case-control study and another large retrospective cohort study found no evidence of increased venous thromboembolism risk.[57,58]

Testosterone Replacement for Male Hypogonadism

FDA-INDICATED USES

As part of its 2015 advisory on cardiovascular risk, the FDA also issued a statement clarifying that testosterone

Table 5. Monitoring of Male Patients on Testosterone Therapy

Test/examination	*Frequency*	*Comment*
History and physical examination	Three to six months following initiation of therapy, then annually	—
Total serum testosterone measurement	Baseline; three to six months after initiation of therapy, then annually if stable	Goal is to increase level to midnormal range, although there is no clear target level Endocrine Society recommends levels between 400 and 700 ng per dL (13.9 and 24.3 nmol per L) one week following injection with testosterone cypionate or enanthate, or at any time with other formulations
Complete blood count (hematocrit)	Baseline; three to six months after initiation of therapy, then annually if stable	If hematocrit is > 54%, therapy should be stopped, or dose lowered or changed to different formulation; it can be restarted at a lower dose once levels decrease
PSA and DRE	Baseline; three to six months after initiation of therapy, then discuss risks/benefits of ongoing screening with the patient given the evidence against routine screening	Only men older than 40 years with baseline PSA > 0.6 ng per mL (0.6 mcg per L) should be screened Refer to a urologist if PSA increases by > 1.4 ng per mL (1.4 mcg per L) over 12 months or there is an abnormality on DRE
Bone density	One to two years after initiation of therapy	In men with osteoporosis or low trauma fracture history

DRE = digital rectal examination; PSA = prostate-specific antigen.

Information from reference 9.

therapy is approved specifically for men with low testosterone levels caused by disorders of the testicles, pituitary gland, or brain that cause hypogonadism (i.e., genetic disorders, damage from chemotherapy or infection, or pituitary tumors) and not for men with age-related low testosterone.[38] Physicians should be aware that prescribing testosterone for low testosterone levels due to aging constitutes off-label use.

FORMULATIONS AND PRECAUTIONS

Many testosterone formulations are available *(Table 4*[59,60]*)*, and no formulation has superior clinical effects. The selection of formulation requires discussion about administration route, adverse effects, and cost. Testosterone preparations are FDA Schedule III controlled substances that are subject to diversion and misuse. Completion of a controlled substance contract should be considered before prescribing.

Monitoring of Men on Testosterone Therapy

Men receiving testosterone therapy should be monitored regularly for adverse effects and to ensure normalization of serum testosterone levels *(Table 5*[9]*)*. Before initiation of testosterone therapy, testing should include a complete blood count to measure hematocrit, and a PSA test and digital rectal examination to detect preexisting prostate cancer.[9] Patients should be reevaluated for therapeutic response and adverse effects three to six months after initiation of treatment, including a repeat testosterone measurement, complete blood count, digital rectal examination, and PSA test.[9,11] If laboratory results are stable, reevaluation may be performed annually.[9] An increase in hematocrit to greater than 54% should lead to cessation of treatment, lowering of the dose, or change to a lower-risk formulation. An increase in PSA of greater than 1.4 ng per mL (1.4 mcg per L) over 12 months or an abnormal digital rectal examination result should prompt referral to a urologist.[9]

Of note, there is no consensus on the necessity and timing of repeated PSA testing and digital rectal examination for men on testosterone therapy. Although the Endocrine Society and a multidisciplinary Canadian panel recommend annual PSA and digital rectal examination screening in men 40 years and older,[9,11] the U.S. Preventive Services Task Force recommends against routine PSA screening and does not specify its recommendation on digital rectal examination.[61] Therefore, physicians and patients should engage in shared decision making, weighing the risks and benefits of ongoing prostate cancer screening in the context of testosterone therapy.

Most experts agree that the goal serum testosterone level should be in the midnormal range (i.e., 400 to 700 ng per dL [13.9 to 24.3 nmol per L]); values outside of this range require a dose adjustment.[9] Most importantly, ongoing evaluation of treatment effectiveness is required.

Future and Ongoing Research

In February 2016, the first results from the Testosterone Trials sponsored by the National Institutes of Health were published.[14] This set of seven randomized controlled trials assessing sexual function, vitality,

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Testosterone therapy should be considered for men with low testosterone levels and clinical symptoms of hypogonadism, particularly sexual dysfunction.	B	10, 12-23, 25-37
Before starting treatment, male hypogonadism should be documented with low morning testosterone levels on two occasions.	C	9
Men considering testosterone therapy should be counseled about the uncertainty of the long-term safety of testosterone, including possible cardiovascular harms, and patients and physicians should engage in shared decision making, weighing the risks and benefits of therapy.	C	9, 11, 38
Men receiving testosterone therapy should be monitored regularly for adverse effects and treatment effectiveness, including testosterone measurements, complete blood count to measure hematocrit, and prostate-specific antigen testing.	C	9, 11
Testosterone therapy may be considered for treatment of postmenopausal women with hypoactive sexual desire disorder.	B	65

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.

Table 6. Use of Testosterone Therapy in Postmenopausal Women

Recommended only for treatment of hypoactive sexual desire disorder
Diagnosis is clinical; there is no established cutoff level of testosterone to indicate treatment
There are no formulations readily available in the United States that provide the recommended treatment dosage for women (300 mcg per day), necessitating the use of compounding pharmacies
Adverse effects may include virilization (acne, hirsutism, deepening of the voice) and adverse lipid changes; the effect of testosterone on breast and endometrial tissue is not well studied, although there is currently no evidence of cancer risk
Treatment should begin with a six-month trial period, and continued only if the patient is responding favorably at that time; there are no safety and effectiveness data beyond 24 months

Information from references 64 and 65.

physical function, cognitive function, anemia, bone density, and cardiovascular health represents the largest, most rigorously conducted study of the benefits of testosterone therapy for older men. Results of the trials assessing cognitive function, anemia, bone density, and cardiovascular health are forthcoming. However, the Testosterone Trials were designed to assess only effectiveness and not the risks of testosterone therapy, including prostate cancer or cardiovascular disease.

Testosterone Therapy in Women

In women, testosterone is produced by the ovaries and adrenal glands, and by conversion of proandrogens in peripheral tissues. Levels decrease gradually starting in the 20s or 30s. There is no abrupt decrease during menopause, with the exception of surgical menopause.[62] Testosterone is also converted to estrogen by aromatases in many tissues; therefore, testosterone is an important source of estrogen in postmenopausal women.[63] Testosterone deficiency in women may be associated with problems with sexual function, mood, cognition, and body composition.[64]

A comprehensive meta-analysis of postmenopausal women found improvement in sexual function with testosterone therapy. There was no evidence of improvement in anxiety, mood, body weight or mass, or bone density.[64] Subsequently, a consensus statement released by several major organizations, including the Endocrine Society and American College of Obstetricians and Gynecologists, supported the use of testosterone therapy for hypoactive sexual desire disorder in postmenopausal women but not for any other indication.[65] Of note, there are no FDA-approved products for testosterone therapy in women, and no formulations are readily available in the United States that provide the recommended treatment dosage for women (300 mcg per day), necessitating the use of compounding pharmacies. The use of testosterone therapy in women is summarized in *Table 6*.[64,65]

Testosterone Therapy in Female-to-Male Transgender Patients

Testosterone therapy is used to produce physical male sex characteristics in female-to-male transgender patients. Primary care physicians may be involved in prescribing testosterone for these patients or monitoring their laboratory tests. Although a full discussion of the treatment of gender identity disorder is beyond the scope

of this article, physicians can review the 2009 Endocrine Society guideline on the disorder,[66] or a concise guideline on transgender hormone treatment at http://www.bumc.bu.edu/endo/clinics/transgender-medicine/guidelines.

This article updates a previous article on this topic by Margo and Winn.[67]

Data Sources: PubMed, Essential Evidence Plus, the Cochrane database, and the National Guideline Clearinghouse were searched using the key term testosterone, alone and with cardiovascular, cognition, sexual function, bone density, strength, depression, risk, benefit, and adverse event. Reference lists from the included meta-analyses were reviewed for potential sources. Search dates: November 30, 2015; January 15, 2016; February 10, 2016; and March 17, 2017.

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