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Drug Class Update: Androgens for Hypogonadism

Date of Review: October 2024

Date of Last Review: July 2014
Dates of Literature Search: 8/1/2014 – 7/1/2024

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To perform a comprehensive literature search and evaluation on the comparative efficacy and safety of androgens (i.e. testosterone preparations) in the treatment of adult male hypogonadism based on evidence published since the last update in 2014. The scope of the update will not include evidence for gender affirming care which has been previously reviewed by the Pharmacy and Therapeutics (P &T) Committee.

Plain Language Summary:
- This review looks at recent evidence on testosterone products to decide if current policy should be changed.
- Testosterone is a hormone made by the body. Larger amounts of testosterone are present in males compared to females. As men age, their testosterone levels may decrease. Men with low testosterone levels can develop symptoms including decreased sexual interest, decreased muscle mass, increased stomach fat, thin bones that break easily, low energy, and low red blood cell count. Doctors may decide to start people on testosterone replacement if their testosterone levels are lower than normal, causing troubling symptoms. There is limited evidence that testosterone therapy will improve quality of life, bone health, or other symptoms.
- The possible harms of testosterone medicines have been studied and the evidence is mixed. When used between 3 to 12 months, there is likely no difference between testosterone therapy and placebo in risk of dying due to heart problems, prostate-related events, urinary tract symptoms, or in stopping treatment due to side effects.
- Testosterone comes in many forms: it can be injected into a muscle or under the skin, rubbed on the skin as a gel, worn as a patch, inserted under the skin, or taken by mouth. The Food and Drug Administration (FDA) recently approved 3 new testosterone medicines that can be taken by mouth (Jatenzo, Tlando, and Kyzatrex) and 1 new medicine that is injected under the skin (Xyosted). All forms of testosterone are only available with a prescription.
- The FDA has given warnings about health risks when using any form of testosterone as a prescription medicine. These warnings include possible increases in blood pressure that can lead to a major heart attack or stroke. The long-term effects of testosterone therapy are not well understood.
- Some people take testosterone in large amounts to improve strength, muscle mass, and sports performance. Testosterone should only be used when prescribed by a medical provider. The Food and Drug Administration (FDA) warns that testosterone misuse can lead to serious heart and mental health problems, and it is illegal to obtain or use without a prescription.
- Pregnant women should never use testosterone as it may cause major health problems for the developing baby.

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Research Questions:

1. In adult males with hypogonadism, is there any new comparative evidence for testosterone therapy based on long-term clinically meaningful outcomes (e.g. quality of life, bone density, vitality, etc.)?
2. Is there new comparative evidence on the harms of testosterone products (e.g. prostate cancer, cardiovascular disease, mortality, etc.)?
3. Are there subpopulations of men in which certain testosterone products have demonstrated superior efficacy or increased risk of harms?

Conclusions:

- Since the last review, 6 systematic reviews, 3 guidelines, and 2 safety warnings were identified.
- There is low quality evidence from one systematic review by the American College of Physicians that evaluated testosterone replacement therapy (TRT) for men with hypogonadism found little to no difference in self-reported measures of physical function, quality of life, fatigue, mood, or adverse events (e.g. cardiovascular events, prostate cancer, or serious adverse events).[1]
- A Cochrane review evaluated the use of TRT in men with testosterone deficiency and sexual dysfunction and found little to no difference between testosterone therapy and placebo for risk of cardiovascular mortality (relative risk [RR] 0.83, 95% confidence interval [CI] 0.21 to 3.26; I^2 = 0%; moderate-quality evidence), prostate-related events (RR 1.65, 95% CI 1.08 to 2.51; I^2 = 0%; moderate-quality evidence), lower urinary tract symptoms (mean difference [MD] -0.62, 95% CI -1.51 to 0.27; I^2 = 63%; low-quality evidence), and in treatment withdrawal due to adverse events (RR 0.74, 95% CI 0.52 to 1.05; I^2 = 0%; low-quality evidence).[2]
- There was low quality evidence from one systematic review of TRT therapy compared to placebo that reported an improved quality of life as measured by the Aging Males' Symptoms (AMS) scale (MD –2.62; 95% CI –4.02 to –1.23). The AMS scale score ranges from 17 to 85 with higher scores indicative of more severe symptoms. The minimal clinically important difference for the AMS scale is unknown.[3]
- Three systematic reviews evaluated harms with TRT. Low quality evidence from one systematic review reported TRT did not influence the risk of arterial thrombosis, stroke, myocardial infarction, venous thromboembolism (VTE), pulmonary embolism (PE), or mortality compared to placebo.[4] Another systematic review found low quality evidence that TRT did not result in increased risk of VTE, deep vein thrombosis (DVT), or PE compared to placebo or active comparator.[5] A third systematic review reported that TRT compared to placebo had no increased risk of VTE based on moderate quality evidence.[6]
- Guideline updates from the American College of Physicians (ACP), the Endocrine Society, and European Association of Urology (EAU) support the current policy for testosterone therapy.[7-9]
- Four new formulations of testosterone were approved since the last review in 2014.
    - Xyosted™ 50 mg/0.5 ml, 75 mg/0.5 ml, and 100 mg/0.5 ml is a once-weekly solution for subcutaneous injection.[10]
    - Jatenzo™ 158 mg, 198 mg, and 237 mg oral capsules, Tlando™ 112.5 mg capsules, and Kyzatrex™ 100 mg, 150 mg, and 200 mg capsules are new oral therapies of testosterone undecanoate.[8-10]
    - All four products are approved for TRT in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[11-13]
    - None of the new products are interchangeable with one another.[10-13]
- There was insufficient evidence on subgroup populations, such as differences in ethnicities and race or subpopulations, or that one product has superior efficacy or increased risk of harms, that support any changes to the current preferred drug list (PDL).

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on evaluation of the clinical evidence.
- After cost evaluation in executive session, no changes to PDL were made.

Summary of Prior Reviews and Current Policy:

- No changes were made to the testosterone derivatives preferred drug list (PDL) as a result of the literature update in 2014.
- In 2018 there was a prior authorization (PA) update to align fee-for-service PA criteria with the Health Evidence Review Commission (HERC) guidance for use of testosterone replacement for testicular hypofunction.
- Current policy consists of PA criteria requiring an FDA approved diagnosis and Oregon Health Plan (OHP) funded diagnosis.

Background:

Male hypogonadism is a syndrome defined by diminished functional activity of hypothalamic-pituitary-testicular axis hormones that leads to diminished sperm production, low serum concentrations of testosterone, and a wide range of health consequences.[14] Hypogonadism may be a result of testicular disease (primary) or hypothalamus/pituitary dysfunction (secondary) or even a part of the aging process.[14] Both primary and secondary hypogonadism may be of congenital origin or acquired through disease, substance exposure, or other means.[15] Symptoms of hypogonadism are diverse and may manifest at different times to varying degrees.[16,17] Some of the more common features of hypogonadism are decreased libido, erectile dysfunction, and infertility, but other signs such as body hair loss and gynecomastia may be evident as well.[15,16] There is some research to suggest an association of hypogonadism with increased risk of fractures, metabolic syndrome, depression, and cardiovascular mortality, but the evidence is conflicting.[2,18] Common signs and symptoms of hypogonadism reported in the literature are summarized in **Table 1**.

Table 1. Common Signs and Symptoms in Males with Hypogonadism[14]

• Incomplete or delayed sexual development, eunuchoidism	• Decreased energy, motivation, initiative, and self-confidence
• Reduced libido and activity	• Feeling sad or blue, depressed mood, dysthymia
• Decreased spontaneous erections	• Poor concentration and memory
• Breast discomfort, gynecomastia	• Sleep disturbance, increased sleepiness
• Loss of body (axillary and pubic) hair, reduced shaving	• Mild anemia (normochromic, normocytic)
• Very small (especially < 5 ml) or shrinking testes	• Reduced muscle bulk and strength
• Low or zero sperm count	• Increased body fat, body mass index
• Height loss, low trauma fracture, low bone mineral density	• Diminished physical or work performance
• Hot flashes, sweats	

Some studies have estimated the prevalence of low serum testosterone is roughly 10% in men aged 50 to 59 years, 20% in men aged 60 to 69 years, 30% in men aged 70 to 80 years and 50% of men in their 80s.[19] At age 30 years and beyond, testosterone levels may decrease by up to 2% per year.[20] However, men with low-serum levels of testosterone may show few to no symptoms.[21] Many symptoms attributed to hypogonadism occur gradually and may not necessarily correlate with low testosterone levels.[21] Therefore, most guidelines agree that diagnosis of hypogonadism requires the presence of characteristic symptoms and signs in addition to a decreased serum concentration of testosterone.[7-9] Hypogonadism not only increases with age but is more prevalent in those with chronic health conditions such as metabolic syndrome, type 2 diabetes, and cardiovascular disease.[22] There is no reliable evidence to show that the prevalence of hypogonadism differs among people of various racial groups or ethnicities.[23]

Testosterone is regulated by a negative feedback mechanism within the hypothalamus-pituitary-gonadal (HPG) axis in men.[24] Secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the anterior pituitary to produce follicle stimulating hormone (FSH) and luteinizing hormone (LH).[24] FSH stimulates spermatogenesis while LH signals the Leydig cells to produce testosterone.[24] Typically, LH secretion occurs in bursts throughout the day.[24,25] Elevated testosterone levels inhibit GnRH release while low levels increase GnRH release and LH and FSH secretion.[24] Therefore, disruption in the regulation or production of testosterone can lead to hypogonadism.[24]

There are 3 types of hypogonadism: primary, secondary, and mixed.[26,27] Primary hypogonadism, or "testicular failure", is a result of testicular inability to synthesize sufficient testosterone levels.[26,27] Klinefelter syndrome, chemotherapy, undescended testicles, or even normal aging can cause primary hypogonadism. Elevated concentrations of FSH and LH are commonly observed in primary hypogonadism.[26,27] In contrast, secondary hypogonadism, or "pituitary failure" is a consequence of abnormal signaling of the hypothalamic or pituitary gland.[26,27] Morbid obesity or trauma may cause secondary hypogonadism as can congenital conditions such as sickle cell disease, Prader-Willi syndrome, or thalassemia.[26,27] An acquired pituitary tumor, hyperprolactinemia, or certain medications (e.g. opioids and anabolic steroids) can also lead to secondary hypogonadism.[26,27] In some circumstances, hypogonadism may be reversible after treatment of the underlying cause or discontinuation of the offending substance.[26,27] Low testosterone levels along with low LH and FSH levels are usually indicative of secondary hypogonadism.[26,27] Mixed hypogonadism involves defects in both the testes and the hypothalamic-pituitary axis.[26,27] Aging males who exhibit hypogonadism are likely to have developed it from an acquired mechanism, though it may be idiopathic in nature.[28]

A thorough workup is recommended for patients with suspected hypogonadism because signs and symptoms are variable.[7-9,29] More common symptoms include low libido, unexplained fatigue, and decreased testicular volume.[7-9,29] Less specific signs and symptoms linked to hypogonadism include muscle weakness, fatigue, mental fog, and increased adiposity.[7-9,29] Age at the onset of symptoms is important as many symptoms are nonspecific and are common in the normal aging process.[7-9,29] Although questionnaires have been developed to help assess the timing and symptoms of hypogonadism, it is not recommended to rely on them exclusively due to low sensitivity and specificity.[30,31] To confirm a hypogonadism diagnosis, laboratory measurements of serum total and free testosterone levels should be obtained in addition to symptom assessment.[7-9,29] Testosterone levels are affected by pulsatile and circadian variation and are typically highest in the morning hours.[32] Normal testosterone levels in adult males is considered 300 ng/dL and 1000 ng/dL but there is no consensus on the absolute threshold of a low testosterone level.[7-9,29] Clinical opinions differ as to what is considered an age-appropriate serum testosterone level, though a testosterone level below 300 ng/dL is commonly accepted for a hypogonadism diagnosis.[7,8] At least one repeat testosterone measurement should be obtained for confirmation.[7-9] In addition to testosterone levels, FSH and LH levels are often measured to help differentiate between primary and secondary hypogonadism.[7-9,29]

Males with asymptomatic hypogonadism generally do not require TRT.[33] The goal of therapy for testosterone replacement is to improve symptoms of deficiency while abating the potential for adverse effects.[7,8] However, evidence for the benefits and risks of testosterone treatment for age-related hypogonadism are inconsistent.[34-36] Some short-term studies suggest that testosterone replacement may have modest benefits for sexual function and quality of life, but there is insufficient evidence to evaluate cardiovascular risk and other long-term harms.[36] Quality of life (QoL) in TRT has been assessed with the Aging Males' Symptoms (AMS) scale (range 17 to 85) with higher scores indicative of more severe symptoms and believed to be consistent with low testosterone levels.[3] The AMS scale has 3 components: psychological, somatic, and sexual. The minimal clinically important difference (MCID) for the AMS scale has not been reported.[2] The 36-item Short-Form Health Survey (SF-36) or 12-item SF-12 have also been employed to measure QoL.[3] The SF-36 is an interview and self-administered questionnaire to assess health-related QoL in healthy and unhealthy adult populations.[39] The complete SF-36 has eight scaled scores; the scores are weighted sums of the questions in each section and range from 0-100 where lower scores indicate more disability. The MCID for the SF-36 has been reported to be roughly 7 points in studies of patients with chronic disease.[40,41]

There are a number of testosterone products that are FDA approved to treat primary or secondary hypogonadism. For a new formulation to gain approval, the product is only required to demonstrate that it can reliably increase low serum testosterone levels to the accepted normal range for healthy young men.[37] The formulation chosen by caregivers and patients may be determined by duration, frequency and route of administration, side-effect profile, and cost-effectiveness. Treatment of age-related hypogonadism is controversial as no agents are approved for that indication.[38] Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in adult males.[38] Testosterone replacement therapy should be avoided in pre-existing breast/prostate cancer, elevated hematocrit (>54%), untreated severe sleep apnea, severe lower urinary tract symptoms, severe heart failure, and in people desiring fertility or those who are pregnant.[8] Different formulations of FDA-approved testosterone products are listed in **Table 2.**

Table 2. Testosterone Formulations for Hypogonadism [8, 11-13]

Formulation/Route	Dosing Frequency	Comments
Testosterone oral capsule -Jatenzo™ -Kyzantrex™ -Tlando™	 Twice daily Once daily or twice daily Twice daily	Oral products not interchangeable
Testosterone nasal gel	3 times daily	Frequent dosing
Testosterone transdermal gel	Once daily for all strengths	Topical formulations not interchangeable; possible transfer during intimate contact; secondary exposure risk for children
Testosterone transdermal solution	Once daily	Topical formulations not interchangeable
Testosterone cypionate IM injection	Once weekly or every 2 weeks	Not for daily administration; SUBQ and IM formulation not interchangeable
Testosterone enanthate SUBQ injection	Once weekly or every 2 weeks	
Testosterone enanthate IM injection	Once weekly or every 2 weeks	
Testosterone undecanoate IM oil for injection	Every 10 weeks after initial dosing regimen	May cause POME reaction. Only available through REMS program.
Testosterone transdermal patch	Once daily	Skin reactions common
Testosterone pellet implant	Every 3 to 6 months	Fixed dosing; invasive procedure with risk of extrusion and infection
Methyltestosterone oral capsules, tablets	Once daily	Guidelines do not recommend due to liver toxicity
Key: IM = intramuscular; POME=pulmonary oil micro-embolism; REMS=Risk Evaluation and Mitigation Strategy; SUBQ = subcutaneous		

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A 2020 review evaluated the literature to determine the benefits and harms of testosterone treatment in men without underlying conditions known to cause hypogonadism.[1] Studies published from January 1980 to May 2019 were identified. For efficacy outcomes, 38 RCTs met inclusion criteria and of those, 16 trials were from the United States, 14 were from Europe, and 8 were from Australia or Asia.[1] The mean age of trial participants was 66 years.[1] Eight studies were restricted to men of ages 65 or older, while 5 trials allowed patients as young as 18 years of age.[1] Nineteen trials included intramuscular injections and 19 used transdermal formulations.[1] Nine trials adjusted dosing to achieve a targeted testosterone level and 29 used a fixed treatment dose.[1] Dosing intervals varied from fixed daily doses to every 3 months based on the formulation and whether adjustments were required to achieve goal levels.[1] Mean baseline testosterone levels were 10.41 nmol/L (300 ng/dL) or less in 20 studies and less than 9.54 nmol/L (275 ng/dL) in 11 trials.[1] In 5 studies, patients had baseline testosterone levels greater than 13.88 nmol/L (400 ng/dL).[1] Thirteen of the included trials required 2 fasting morning testosterone levels and just 2 trials required the 2 morning testosterone levels to be 10.41 nmol/L (300 ng/dL) or less.[1] Some of the trials required the presence of specific symptoms attributed to hypogonadism (e.g. sexual symptoms, physical mobility limitations, etc) but many trials did not require any symptoms.[1] Race/ethnicity, comorbidities, and functional measures were rarely reported. The risk of bias was evaluated as high in 11 trials, medium in 19, and low in 8.[1] Trials categorized as high risk of bias had very high attrition rates (range, 30% to 56%) and two trials were open-label with no control group.[1] Safety outcomes included 20 additional observational studies.[1] Ten of the studies were excluded in the reporting due to high risk of bias or inadequate blinding methods.[1]

Although many trials reported outcomes of sexual function, this summary will focus on clinical outcomes of interest to Medicaid such as physical function, mental health, and quality of life. Moderate strength of evidence found little to no difference in serious adverse events after over one year of treatment.[1] There was low quality evidence that found little to no difference in self-reported measures of physical function, quality of life, fatigue, mood, or adverse events (e.g. cardiovascular, prostate cancer, or serious adverse events).[1] There was evidence that testosterone therapy may slightly reduce mortality, however, the evidence was very low to low quality and the trials were not adequately powered to detect differences for this outcome.[1] Findings are presented in **Table 3.**

Table 3. Evidence for Efficacy and Safety of Testosterone Treatment in Men with Low Testosterone Levels Not Associated with an Underlying Medical Condition known to cause Hypogonadism[1]

Outcome	Participants (n)	RCTs (n)	Absolute Effect (95% CI)		Mean Duration of Trials	Certainty of Evidence
			Testosterone	Placebo		
Physical Function; self-reported: (SF-36-PF or PASE)	1029	5	No Difference		78 weeks	Low
Physical Function: objective measures: (e.g. 6-MWT)	1063	7	No Difference		60 weeks	Low
Quality of Life (AMS)	1043	7	7.0 points	3.6 points	35 weeks	Low
			MD -3.3 (-5.2 to -1.3); I^2=32%			
ACE	2415	14	2.9%	2.2%	68 weeks	Low

			Peto OR 1.22 (0.66 to 2.23); I^2 = 18%			
Serious Adverse Events	2268	8	13.2% (3.6% to 27.4%)	12.8% (4.7% to 23.9%)	56 weeks	Moderate
			Peto OR 0.94 (0.73 to 1.21); I^2 = 0%			
Prostate Cancer (follow-up range, 6 mo-3 yr)	2143	10	0.3% (0.0% to 1.2%)	0.4% (0.0% to 1.9%)	NR	Very Low
			N/A			
Mortality (follow-up range, 6 mo-3 yr)	2727	12	0.4% (0.07% to 0.99%)	1.5% (0.48% to 2.89%)	NR	Low
			Peto OR, 0.47 (0.25 to 0.89); I^2 = 0			
Key: ACE=adverse cardiovascular events; AMS=aging male symptoms; CI=confidence interval; MD=mean difference; Mo=months; N/A=not applicable; NR=not reported; OR=odds ratio; PASE=Physical Activity Scale for the Elderly; RCT=randomized controlled trial; SF-36-PF=Short Form-36 Health Survey Physical Function Subscale; 6MWT=6-minute walk test; Yr=years						

A 2024 Cochrane review evaluated the use of testosterone in men with sexual dysfunction.[2] There were 43 randomized controlled trials included in the review (n=11,419) most of which lasted from 3 to 12 months.[2] Although many trials reported outcomes of sexual function, this summary will focus on clinical outcomes of interest to Medicaid such as cardiovascular mortality (10 trials; n=3525), prostate-related events (10 trials; n=3439), lower urinary tract symptoms (6 trials; n=1488), and treatment withdrawal due to adverse events (12 trials; n=2966).[2] Most trials with these outcomes were graded with a low or unclear risk of bias in most areas.[2] Testosterone therapy compared to placebo likely results in little to no difference in the following outcomes: cardiovascular mortality (RR 0.83, 95% CI 0.21 to 3.26; I^2 = 0%; moderate-quality evidence); prostate-related events (RR 1.65, 95% CI 1.08 to 2.51; I^2 = 0%; moderate-quality evidence); lower urinary tract symptoms (MD -0.62, 95% CI -1.51 to 0.27; I^2 = 63%; low-quality evidence), and treatment withdrawal due to adverse events (RR 0.74, 95% CI 0.52 to 1.05; I^2 = 0%; low-quality evidence).[2]

A 2023 systematic review investigated the symptomatic benefits of testosterone treatment in men of different ages and body mass index (BMI) measurements.[3] There were 17 studies from 9 countries that met inclusion criteria (n=3431).[3] The participants were age 40 or older (median age 67 years), most of whom were White (88%) and non-smokers (88%).[3] Over half the participants had a BMI greater than 30 kg/m^2.[3] Although most of the included trials focused on outcomes of sexual function as a primary endpoint, this summary will review the findings of clinical outcomes of interest to Medicaid such as quality of life and psychological symptoms at 12 months (or at the closest timepoint).[3] Quality of life (QoL) was assessed with the AMS scale, the SF-36, or SF-12.[3] The SF-12 is a similar tool but with a reduced number of items.[3] The SF-36 and SF-12 were transformed into t-scores to allow for direct comparison.[3] Psychological symptoms were assessed with the Beck Depression Inventory (BDI) for psychological symptoms (range 0 to 63; higher scores indicate more severe depression).[3] Of note, there were no statistical adjustments made for multiple secondary outcomes.[3] The overall risk of bias was assessed as low for most studies with individual participant data and unclear for most studies without individual participant data.[3] Seven studies (938 participants) showed that overall quality of life measured by AMS scale was improved with testosterone treatment versus placebo (MD –2.62; 95% CI –4.02 to –1.23).[3] Five studies (n=539) of individual participant data reported significant improvements in just three of the ten SF-36 (or SF-12) sub-scores during testosterone treatment versus placebo: social functioning (MD 1.74; 95% CI 0.14 to 3.34}, role limitations due to emotional problems (MD 1.66; 95% CI 0.57 to 2.76), and mental health composite score (MD 1.95; 95% CI 0.64 to 3.26).[3] Three

studies (246 participants) that assessed individual data with the BDI did not find a statistically significant effect of testosterone on psychological symptoms compared with placebo.[3]

A 2024 systematic review and meta-analysis evaluated the relationship between TRT and the risk of arterial and/or venous thrombosis in patients with low testosterone.[4] The literature search was conducted in 4 separate databases from inception through November 2022.[4] Twenty-four studies were included in the meta-analysis that consisted of 14 RCTs, 4 observational studies, 5 retrospective cohort studies, and 1 prospective controlled registry study.[4] Study duration ranged from 12 weeks to 624 weeks, with a median of 36 weeks for RCTs and 165 weeks for observational studies.[4] The quality of included RCTs was evaluated with the Cochrane risk of bias methodology and graded with a high risk of bias.[4] The observational studies were assessed with the Cambridge Quality Checklist.[4] Based on RCT-derived data, TRT did not influence the risk of arterial thrombosis (odds ratio [OR] 1.27, 95% CI, 0.47 to 3.43, P = 0.64), stroke (OR 1.34, 95% CI, 0.09 to 18.97, P = 0.83), myocardial infarction [MI] (OR 0.51, 95% CI, 0.11 to 2.31, P = 0.39), VTE (OR 1.42, 95% CI, 0.22 to 9.03, P = 0.71), PE (OR 1.38, 95% CI, 0.27 to 7.04, P= 0.70), or mortality (OR 0.70, 95% CI, 0.20 to 2.38, P = 0.56).[4]

A 2021 systematic review and meta-analysis of RCTs investigated the association of TRT and the risk of VTE.[5] The literature search was conducted through December 2019.[5] Thirteen RCTs were included (n=5050) and duration of TRT ranged from 3 to 36 months.[5] Five studies had a high risk of bias, 6 studies had a moderate risk of bias, and 2 studies had a low risk of bias.[5] The overall quality of evidence according to the GRADE criteria was low for the primary outcome of VTE and secondary outcomes of deep-vein thrombosis (DVT) and pulmonary embolism (PE).[5] The pooled results of the studies did not show that testosterone therapy had an increased risk of VTE compared to placebo or active comparator (RR 1.03; 95% CI 0.49 to 2.14; I^2 = 0%; low-quality evidence).[5] Likewise, TRT was not associated with the risk of DVT (RR 1.14; 95% CI 0.46 to 2.82; I^2 = 0%; low-quality evidence) or PE (RR 0.81; 95% CI 0.29, 2.26; I^2: 0%; low-quality evidence).[5]

Another systematic review of RCTs and observational studies investigated the association of testosterone therapy in men with hypogonadism and the risk of VTE.[6] The literature search was conducted through October 2018.[6] Five observational studies (n=1,249,640) and 6 RCTs (n=2,236) met inclusion criteria.[6] One study was conducted in the United Kingdom while the remainder were performed in the United States.[6] Four of the observational studies excluded patients with a history of VTE and had an overall low risk of bias according to comparability and outcomes assessed.[6] However, half the observational studies had unclear or high risk of selection bias.[6] The RCTs ranged from 3 to 12 months duration and the mean age of participants was over 50 years of age.[6] Five of the 6 RCTs were double-blinded that compared testosterone (any route) to placebo and one open-label study compared testosterone to routine care.[6] Overall, the body of evidence had a moderate risk of bias.[6] The pooled results of the studies found no statistically significant association between testosterone use and VTE either when results were pooled (Odds Ratio [OR] 1.41; 95% CI 0.96 to 2.07, I^2=84.4%) or when they were stratified by study design (RCTs; OR 2.05 [95% CI 0.78 to 5.39]; observational studies: OR 1.06 [95%CI 0.85 to 1.33] and case-control studies OR 1.34 [95% CI 0.78 to 2.28].[6]

After review, 31 systematic reviews were excluded due to poor quality (e.g, indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials, comparator, or outcome studied.

New Guidelines:
High Quality Guidelines:

American College of Physicians (ACP) - Testosterone Treatment in Adult Men With Age-Related Low Testosterone[7]
Guidelines from the ACP for the treatment of adult men with age-related low testosterone were published in 2020.[7] The evidence review was conducted by the ACP Clinical Guidelines Committee.[7] The evidence review included 38 randomized controlled trials of older men (mean age 66 years) with a duration of 6 to 36

months.[7] Evidence was evaluated using the GRADE methodology.[7] Main outcomes assessed of clinical interest to the Medicaid population included quality of life, cognitive function, and harms, which included serious adverse events, MACE, DVT or PE, prostate cancer, and mortality.[7] Data were reported in standardized mean differences (SMDs) and were interpreted as small (SMD, 0.2), medium (SMD, 0.5), and large (SMD, 0.8) effects.[7] The committee recommended that clinicians not initiate testosterone treatment in men with age-related low testosterone to improve energy, vitality, physical function, or cognition based on low-certainty evidence.[7] In addition, evidence on long-term harms was unavailable and the studies were not powered to detect mortality differences.[7] Relevant outcome measures reported in the guideline are highlighted in **Table 4.**[7]

Table 4. Summary of Evidence for Testosterone Treatment in Adult Men with Age-Related Low Testosterone[7]

Outcome	Included Trials	Standardized Mean Difference (SMD) Testosterone Therapy versus Placebo	Quality of Evidence
Quality of Life (AMS scale*)	7	-0.33 [95% CI -0.50 to -0.16] (lower = improvement)	Low
Physical Function (Walk Test; SF-36)	7 7	Walk Tests: 0.14 [CI 0.02 to 0.27] (higher = improvement) SF-36: 0.15 [CI 0.19 lower to 0.50] (higher = improvement)	Low Low
Adverse Cardiovascular Events	14	Small to no increase in risk: Peto OR, 1.22 [CI 0.66 to 2.23]	Low
Serious Adverse Events	8	No evidence of increased risk: Peto OR 0.94 [CI 0.73 to 1.21] No evidence of increased risk of withdrawals due to adverse events: Peto OR 0.92 [CI 0.65 to 1.28]	Moderate Moderate
Mortality	12	Fewer deaths**: Peto odds ratio 0.47 [CI 0.25 to 0.89]	Low
Key: *= sexual function was one of the subscales included in the AMS and may have driven the positive outcome **= Studies not powered to detect mortality differences; evidence insufficient due to very serious imprecision, low event rates, and potential fragility of the results. AMS = Aging Male's Symptoms; CI = confidence interval; OR = odds ratio; SF-36 = Short Form-36 Health Survey			

Endocrine Society - Testosterone Therapy in Men with Hypogonadism [8]

Guidelines published in 2018 by the Endocrine Society made recommendations for testosterone therapy in men with hypogonadism.[8] The findings were based on 2 systematic reviews of the literature and only included trials that used testosterone or its esters.[8] The first review focused on whether testosterone replacement therapy improved sexual function, physical function, fatigue, mood, cognition, anemia, and bone mineral density in men with hypogonadism.[8] The review included 11 reports of 4 placebo-controlled RCTs (n=1779) that ranged from 12 to 52 weeks in duration.[8] The mean baseline total testosterone concentrations ranged from 201 to 239 ng/dL.[8] All studies were assessed as a low risk of bias. The second review assessed whether testosterone therapy was associated with an increased risk of lower urinary tract symptoms and erythrocytosis in men with hypogonadism.[8] The review included 3 placebo-controlled RCTs (n=1581) that ranged from 12 to 52 weeks in duration.[8] The mean baseline total testosterone concentrations ranged from 201 to 236 ng/dL.[8] All studies were assessed with a low to moderate risk of bias.[8] Recommendations that were strong used the statement "we recommend" followed by the number 1.[8] Conditional recommendations used the statement "we suggest" followed by the number 2.[8] Quality of evidence graded on a 4-point "plus" scale that indicated high- (4+), moderate- (3+), low- (2+) or very low-quality (1+).[8] The strength of evidence for the majority of recommendations was low to very low.[8] The recommendations and evidence grades are summarized in **Table 5.**[8]

Table 5. Endocrine Society Recommendations for Testosterone Therapy for Men with Hypogonadism[8]

Category	Recommendation	Strength of Recommendation/ Strength of Evidence
Diagnosis of men with suspected hypogonadism	We recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated).	1 - Moderate
Screening and case detection for hypogonadism	We recommend against routine screening of men in the general population for hypogonadism.	1- Low
Distinguishing between primary or secondary hypogonadism	In men who have hypogonadism, we recommend distinguishing between primary (testicular) and secondary (pituitary–hypothalamic) hypogonadism by measuring serum luteinizing hormone and follicle-stimulating hormone concentrations.	1- Low
Evaluation for determining the etiology of hypogonadism	In men with hypogonadism, we suggest further evaluation to identify the etiology of hypothalamic, pituitary, and/or testicular dysfunction.	2 -Low
Treatment of hypogonadism with testosterone	We recommend testosterone therapy in men with hypogonadism to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency.	1-Moderate
	We recommend against testosterone therapy in men planning fertility in the near term or in men with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen level > 4 ng/mL, a prostate-specific antigen level > 3 ng/mL combined with a high risk of prostate cancer (without further urological evaluation), elevated hematocrit, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia.	1- Low
	In men with hypogonadism 55 to 69 years old, who are being considered for testosterone therapy and have a life expectancy > 10 years, we suggest discussing the potential benefits and risks of evaluating prostate cancer risk and prostate monitoring and engaging the patient in shared decision making regarding prostate cancer monitoring. For patients who choose monitoring, clinicians should assess prostate cancer risk before starting testosterone treatment and 3 to 12 months after starting testosterone	2- Very Low
	In men with hypogonadism being considered for testosterone therapy who are 40 to 69 years old and at increased risk of prostate cancer (e.g., African Americans and men with a first-degree relative with diagnosed prostate cancer), we suggest discussing prostate cancer risk with the patient and offering monitoring options.	2-Very Low
Older men with age-related decline in	We suggest against routinely prescribing testosterone therapy to all men 65 years or older with low testosterone concentrations.	1- Low

testosterone concentration	In men >65 years who have symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone concentrations, we suggest that clinicians offer testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits.	2 - Low
Men living with HIV with weight loss	We suggest that clinicians consider short-term testosterone therapy in men living with HIV with low testosterone concentrations and weight loss (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain.	2- Low
Men with type 2 diabetes mellitus	In men with type 2 diabetes mellitus who have low testosterone concentrations, we recommend against testosterone therapy as a means of improving glycemic control.	1- Low
Monitoring of testosterone replacement therapy	In men with hypogonadism who have started testosterone therapy, we recommend evaluating the patient after treatment initiation to assess whether the patient has responded to treatment, is suffering any adverse effects, and is complying with the treatment regimen.	Ungraded Good Practice Statement
	We recommend a urological consultation for men with hypogonadism receiving testosterone treatment if during the first 12 months of testosterone treatment there is a confirmed increase in prostate-specific antigen concentration > 1.4 ng/mL above baseline, a confirmed prostate-specific antigen > 4.0 ng/mL, or a prostatic abnormality detected on digital rectal examination. After 1 year, prostate monitoring should conform to standard guidelines for prostate cancer screening based on the race and age of the patient.	2- Low

European Association of Urology (EAU) - Guidelines on Male Hypogonadism[9]

The EAU updated guidelines on male hypogonadism in 2018.[9] Findings were based on a systematic review of the literature through July 2017.[9] The focus of the review was diagnosis and treatment of male hypogonadism, recommendations on how to manage primary and secondary forms of hypogonadism, age-related decline in testosterone in men, as well as the treatment of testosterone deficiencies.[9] The panel used a modified GRADE methodology to assess the quality of evidence with respect to the magnitude of benefit, certainty of results, benefits and harms, and patient values and preferences.[9] The strength of each recommendation is represented by the words “strong” or “weak” based on the level and type of evidence:

1a = Evidence obtained from meta-analysis of randomized trials
1b = Evidence obtained from at least one randomized trial
2a = Evidence obtained from one well-designed controlled study without randomization
2b = Evidence obtained from at least one other type of well-designed quasi-experimental study
3 = Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4 = Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

The findings of the EAU for the management of adult male hypogonadism that were given a strong recommendation based on high-quality evidence (1a or 1b) are summarized in **Table 6**. [9]

Table 6. EAU Recommendations for the Management of Adult Male Hypogonadism[9]

Diagnostic Evaluation and Screening	
Summary of Evidence	Level of Evidence
Sexual symptoms are the most specific symptoms associated with late-onset hypogonadism (LOH).	1a
Diagnosis of LOH should be based on specific signs and symptoms of androgen deficiency, together with consistently low serum testosterone levels.	
Total testosterone 12 nmol/L (3.5 ng/mL) represents a reliable threshold to diagnose LOH.	
Recommendation	Strength Rating
Check for concomitant diseases, drugs and substances that can interfere with testosterone production/action.	Strong
Measure total testosterone in the morning (between 07.00 and 11.00 hours) and in the fasting state, with a reliable laboratory assay.	
Repeat total testosterone on at least two separate occasions when < 12 nmol/L (350 ng/L) and before starting testosterone therapy.	
Use 12 nmol/L total testosterone (350 ng/L) as a reliable threshold to diagnose late onset hypogonadism (LOH).	
Measure sex hormone-binding globulin and free-testosterone calculation when indicated	
Analyze luteinizing hormone and follicle-stimulating hormone serum levels to differentiate between the different types of hypogonadism.	
Measure prolactin (PRL) levels if evidence of low sexual desire (or other suggestive signs/symptoms) and secondary hypogonadism is present.	
Perform pituitary magnetic resonance imaging (MRI) in secondary hypogonadism, with elevated PRL or symptoms specific of a pituitary mass and/or presence of other anterior pituitary hormone deficiency.	
Check for concomitant diseases, drugs and substances that can interfere with testosterone production/action.	
Measure total testosterone in the morning (between 07.00 and 11.00 hours) and in the fasting state, with a reliable laboratory assay.	
Repeat total testosterone on at least two separate occasions when < 12 nmol/L and before starting testosterone therapy.	
Screen for late onset hypogonadism (LOH) only in symptomatic men.	
Do not use structured interviews and self-reported questionnaires for systematic screening for LOH as they have a low specificity.	
Testosterone Therapy Outcome	
Summary of Evidence	Level of Evidence
Testosterone therapy can improve:	
Milder forms of ED and libido in hypogonadal men;	1a
Body composition and insulin resistance.	
Mild depressive symptoms in hypogonadal men.	
Bone mineral density, but information related to fracture risk is lacking.	

Other sexual symptoms, including intercourse frequency, orgasm and overall satisfaction.	1b
Recommendations	Strength rating
Do not use testosterone therapy in eugonadal men.	Strong
Use testosterone therapy as first-line treatment in hypogonadal patients with mild erectile dysfunction (ED).	
Use conventional medical therapies for severe depressive symptoms and osteoporosis.	
Do not use testosterone therapy to improve cognition vitality and physical strength in aging men.	

Choice of Treatment for LOH	
Summary of evidence	Level of Evidence
Weight loss obtained through a low-calorie diet and regular physical activity results in a small improvement in testosterone levels.	1a
Testosterone gels and long-acting injectable testosterone undecanoate preparations provide optimal safety profiles.	
Gonadotropin treatment can be used to restore fertility in men with secondary hypogonadism.	
Recommendations	Strength rating
Treat, when indicated, organic causes of hypogonadism (e.g., pituitary masses, hyperprolactinemia, etc).	Strong
Improve lifestyle and reduce weight (e.g., obesity); withdraw, when possible, concomitant drugs that can impair testosterone production; treat other co-morbidities, when possible, before starting testosterone therapy.	
Fully inform patients about the expected benefits and adverse effects of any treatment option. Select the testosterone preparation in a joint decision process, and fully inform patients of the risks and benefits.	

Additional Guidelines for Clinical Context:
Guidance for the evaluation and management of testosterone deficiency was published by the American Urological Association (AUA) in 2018.[29] Findings were based on a systematic review of the literature between January 1980 through February 2017.[29] Outcomes of interest included QoL, sexual function, cardiovascular events, anemia, bone health, insulin resistance, cardiovascular risk factors, mood, cognitive function, body composition, and numerous adverse events.[29] Due to the inability to review the search strategy and the criteria used for study inclusion/exclusion, the link between clinical recommendation and supportive evidence could not validated, therefore, the guideline was excluded from the review.

After review, 4 guidelines were excluded due to poor quality.

New Formulations or Indications:

- Xyosted™ is a new formulation of testosterone enanthate that was FDA approved in 2018 for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[10] Xyosted™ was evaluated in a 52-week, open-label study (NCT02159469) of efficacy and safety when administered subcutaneously once weekly to 150 adult males with hypogonadism.[10] The primary endpoint was the percentage of patients with a time-averaged serum total testosterone concentration over the 7-day dosing interval within the normal range (300 to 1100 ng/dL) at Week 12.[10] One hundred and thirty-five (90%) of the 150 men with hypogonadism who received Xyosted™ had a serum total testosterone concentration within the normal range at Week 12.[10] Xyosted is supplied in 50 mg/0.5 ml, 75 mg/0.5 ml, and 100 mg/0.5 ml strengths pre-

assembled in an autoinjector.[10] The most commonly reported adverse events were increased hematocrit (8%) and injection site hemorrhage (6%).[10] The labeling for this product contains a boxed warning for the potential to cause an increase in blood pressure that can heighten the risk of MACE, including non-fatal MI, non-fatal stroke and cardiovascular death.[10]

- Jatenzo™ is a new oral formulation of testosterone undecanoate that was FDA approved in 2019 for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[11] The efficacy and safety of Jatenzo™ were evaluated in 166 adult men with hypogonadism in an open label study of approximately 4 months duration (NCT02722278).[11] The primary endpoint was the percentage of patients with mean plasma total testosterone concentration over 24-hours within the normal eugonadal range on the final visit of the study.[11] One hundred and forty-five (87%) of the 166 men with hypogonadism who received JATENZO had a mean total testosterone concentration within the normal eugonadal range at the end of treatment.[11] Jatenzo™ capsules are available in three strengths of 158 mg, 198 mg, and 237 mg and taken twice daily.[11] The most commonly reported adverse events were headache (5%) and increased hematocrit (5%).[11] The labeling for this product contains a boxed warning for the potential to cause an increase in blood pressure that can heighten the risk of MACE.[11] Jatenzo™ is not substitutable with other oral testosterone undecanoate products.[11]

- Tlando™ is a new formulation of testosterone undecanoate that was FDA approved in 2022 for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[12] The efficacy and safety of Tlando™ was evaluated in 233 men with hypogonadism during two clinical studies: Study LPCN 1021-18-001 (18-001) and Study LPCN 1021-16-002 (16-002).[12] Study 18-001 was an uncontrolled ambulatory blood pressure monitoring (ABPM) study (n=138) while Study 16-002 was a multicenter, open-label, single-arm study in 95 patients (NCT03242590).[12] The primary endpoint of Study 16-002 was the percentage of patients who achieved a 24-hour average serum testosterone concentration within the normal range of 300-1080 ng/dL on the final visit of the study.[12] Eighty percent of the patients treated with Tlando™ had a serum total testosterone concentration within the normal range at day 24.[12] In The most commonly reported adverse events in Study 16-002 was an increased blood prolactin level (6%).[12] Tlando™ capsules for oral administration are available containing 112.5 mg of testosterone undecanoate and is taken twice daily.[12] The labeling for this product contains a boxed warning for the potential to cause an increase in blood pressure that can heighten the risk of MACE.[12] Tlando™ is not substitutable with other oral testosterone undecanoate products.[12]

- Kyzatrex™ is a new oral formulation of testosterone undecanoate that was FDA approved in 2022 for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[13] The efficacy and safety of Kyzatrex™ were evaluated in Study MRS-TU-2019EXT (NCT04467697) a multi-center, open-label study of approximately 6 months of duration in 155 hypogonadal males.[13] Patients received KYZATREX at a starting dose of 200 mg twice daily with meals.[13] The primary efficacy endpoint was the percentage of Kyzatrex™-treated patients with mean plasma total testosterone concentration over 24-hours within the normal range of 222-800 ng/dL on the final PK visit of the study at Day 90.[13] At day 90, 88% of Kyzatrex-treated patients achieved testosterone levels in what was defined as the normal range.[13] The most commonly reported adverse event in treated patients was hypertension (3%).[13] Kyzatrex™ capsules are available in three strengths of 100 mg, 150 mg, and 200 mg.[13] As with other testosterone agents, the labeling contains a boxed warning for the potential to cause an increase in blood pressure that can heighten the risk of MACE.[13] Kyzatrex™ is not substitutable with other oral testosterone undecanoate products.[13]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Testosterone	All testosterone products	October 2016	Warnings and Precautions	Approved class-wide labeling changes for all prescription testosterone products, added: *Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions.*
	Androgel™	May 2019	Contraindication	Pregnant women – virilization of female fetus
	Aveed™ Fortesta™	March 2020		
	Vogelxo™	April 2020		

Randomized Controlled Trials:

A total of 10 clinical trial citations were manually reviewed from the initial literature search. After further review, 7 citations were excluded because of wrong study design, comparator, or outcome studied. The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome of Interest	Results	Notes/Limitations
Lincoff AM et al.[47]	T vs PBO (n=5204)	Males 45 to 80 years; preexisting CVD or elevated CVD risk; $\geq$ 1 symptom of hypogonadism; two fasting serum T levels of less than 300 ng/dL	First occurrence of any major adverse cardiac event; composite of death from CVD causes; nonfatal MI; nonfatal stroke	Primary cardiovascular event: T: 7.0% PBO: 7.3% HR 0.96 (95% CI 0.78 to 1.17); P<0.001 for noninferiority	Levels of adherence and retention were low; possible bias due to informative censoring.
Pencina K et al.[48]	T 1.62% transdermal gel vs PBO (n=815)	Males 45 to 80 years; 2 T levels below 300 ng/dL; hypogonadal symptoms, and CVD or increased CVD risk	Proportion of participants with anemia (hemoglobin below 12.7 g/dL) whose anemia remitted (hemoglobin 12.7 g/dL or above) over the study duration	Anemia corrected in a greater proportion of testosterone group compared to placebo, respectively. 6 months: 41.0% vs 17.5% 12 months 45.0% vs 33.9%	-Findings should not be applied to men who are not hypogonadal, women, transgender and gender diverse people, or to men using supraphysiologic doses of T

				24 months 42.8% vs 30.9% 36 months 43.5% vs 33.2% 48 months 44.6% vs 39.2% (P = 0.002)	-Cause of anemia unknown -Study medication discontinuation rates were high
Snyder PJ et al.[49]	T vs PBO (n=690)	Males aged 65 years and older	Physical Function: Percentage of men who increased the distance walked in the 6-minute walk test by at least 50 meters. Vitality: Percentage of men whose score on the FACIT–Fatigue scale increased by at least 4 points	No statistically significant difference in physical function: OR 1.42; P=0.20 No statistically significant difference in vitality: OR 1.23; P=0.30	Results only applicable to men 65 years of age or older whose T levels averaged < 275 ng/dL

Abbreviations: CVD=cardiovascular disease; dL=deciliter; FACIT=Functional Assessment of Chronic Illness Therapy; THR=hazard ratio; MI= myocardial infarction; ng=nanograms; OR=odds ratio; PBO=placebo; T=testosterone

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
testosterone	TESTIM	GEL (GRAM)	Transdermal	Y
testosterone	TESTOSTERONE	GEL (GRAM)	Transdermal	Y
testosterone	VOGELXO	GEL (GRAM)	Transdermal	Y
testosterone	ANDROGEL	GEL MD PMP	Transdermal	Y
testosterone	TESTOSTERONE	GEL MD PMP	Transdermal	Y
testosterone	VOGELXO	GEL MD PMP	Transdermal	Y
testosterone	ANDROGEL	GEL PACKET	Transdermal	Y
testosterone	TESTOSTERONE	GEL PACKET	Transdermal	Y
testosterone	VOGELXO	GEL PACKET	Transdermal	Y
testosterone cypionate	DEPO-TESTOSTERONE	VIAL	Intramuscular	Y
testosterone cypionate	TESTOSTERONE CYPIONATE	VIAL	Intramuscular	Y
testosterone enanthate	TESTOSTERONE ENANTHATE	VIAL	Intramuscular	Y
testosterone	NATESTO	GEL MD PMP	Nasal	N
testosterone	FORTESTA	GEL MD PMP	Transdermal	N
testosterone	TESTOSTERONE	GEL MD PMP	Transdermal	N
testosterone	ANDRODERM	PATCH TD24	Transdermal	N
testosterone	TESTOSTERONE	SOL MD PMP	Transdermal	N
testosterone enanthate	XYOSTED	AUTO INJCT	Subcutaneous	N
testosterone undecanoate	AVEED	VIAL	Intramuscular	N
testosterone	TESTOPEL	PELLET(EA)	Implant	

Appendix 2: Abstracts of Comparative Clinical Trials

Cardiovascular Safety of Testosterone-Replacement Therapy.

Lincoff AM, Bhasin S, Flevaris P, et al.

Abstract

BACKGROUND

The cardiovascular safety of testosterone-replacement therapy in middle-aged and older men with hypogonadism has not been determined.

METHODS

In a multicenter, randomized, double-blind, placebo-controlled, noninferiority trial, we enrolled 5246 men 45 to 80 years of age who had preexisting or a high risk of cardiovascular disease and who reported symptoms of hypogonadism and had two fasting testosterone levels of less than 300 ng per deciliter. Patients were randomly assigned to receive daily transdermal 1.62% testosterone gel (dose adjusted to maintain testosterone levels between 350 and 750 ng per deciliter) or placebo gel. The primary cardiovascular safety end point was the first occurrence of any component of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, assessed in a time-to-event analysis. A secondary cardiovascular end point was the first occurrence of any component of the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, assessed in a time-to-event analysis. Noninferiority required an upper limit of less than 1.5 for the 95% confidence interval of the hazard ratio among patients receiving at least one dose of testosterone or placebo.

RESULTS

The mean (±SD) duration of treatment was 21.7±14.1 months, and the mean follow-up was 33.0±12.1 months. A primary cardiovascular end-point event occurred in 182 patients (7.0%) in the testosterone group and in 190 patients (7.3%) in the placebo group (hazard ratio, 0.96; 95% confidence interval, 0.78 to 1.17; P<0.001 for noninferiority). Similar findings were observed in sensitivity analyses in which data on events were censored at various times after discontinuation of testosterone or placebo. The incidence of secondary end-point events or of each of the events of the composite primary cardiovascular end point appeared to be similar in the two groups. A higher incidence of atrial fibrillation, of acute kidney injury, and of pulmonary embolism was observed in the testosterone group.

CONCLUSIONS

In men with hypogonadism and preexisting or a high risk of cardiovascular disease, testosterone-replacement therapy was noninferior to placebo with respect to the incidence of major adverse cardiac events. (Funded by AbbVie and others; TRAVERSE ClinicalTrials.gov number, NCT03518034.)

Efficacy of Testosterone Replacement Therapy in Correcting Anemia in Men With Hypogonadism: A Randomized Clinical Trial.

Pencina KM, Travison TG, Artz AS, et al.

Abstract

Importance: Testosterone deficiency causes mild anemia. Whether testosterone replacement therapy (TRT) can correct anemia or prevent the development of anemia in men with hypogonadism remains incompletely understood.

Objective: To assess the efficacy of TRT in correcting anemia in men with hypogonadism and anemia, and reducing the risk of developing anemia in those without anemia.

Design, setting, and participants: This randomized, placebo-controlled trial included men with hypogonadism at 316 US sites enrolled between May 2018 and February 2022. This study was nested within the Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) Study, which evaluated the effect of TRT on major adverse cardiovascular events in middle-aged and older men with

hypogonadism. Eligible participants were aged 45 to 80 years, with 2 testosterone concentration results below 300 ng/dL, hypogonadal symptoms, and cardiovascular disease (CVD) or increased CVD risk. The last study visit took place in January 2023. Data were analyzed between March and August 2023.
Intervention: Participants were randomized with stratification for preexisting CVD to 1.62% testosterone gel or placebo gel daily for the study duration.
Main outcomes and measures: Proportion of participants with anemia (hemoglobin below 12.7 g/dL) whose anemia remitted (hemoglobin 12.7 g/dL or above) over the study duration. Secondary end points included incidence of anemia among men who were not anemic. Binary end points were analyzed using repeated-measures log-binomial regression.
Results: A total of 5204 men were included, 815 with anemia (mean [SD] age, 64.8 [7.7] years; 247 Black [30.3%], 544 White [66.7%], 24 other [2.9%]) and 4379 without anemia (mean [SD] age, 63.0 [7.9] years; 629 Black [14.4%], 3603 White [82.3%], 147 other [3.4%]). Anemia corrected in a significantly greater proportion of testosterone-treated than placebo-treated men at 6 months (143 of 349 [41.0%] vs 103 of 375 [27.5%]), 12 months (152 of 338 [45.0%] vs 122 of 360 [33.9%]), 24 months (124 of 290 [42.8%] vs 95 of 307 [30.9%]), 36 months (94 of 216 [43.5%] vs 76 of 229 [33.2%]), and 48 months (41 of 92 [44.6%] vs 38 of 97 [39.2%]) (P = .002). Among participants without anemia, a significantly smaller proportion of testosterone-treated men developed anemia than placebo-treated men. Changes in hemoglobin were associated with changes in energy level.
Conclusions and relevance: In middle-aged and older men with hypogonadism and anemia, TRT was more efficacious than placebo in correcting anemia. Among men who were not anemic, a smaller proportion of testosterone-treated men developed anemia than placebo-treated men.
Trial registration: ClinicalTrials.gov Identifier: NCT03518034.

Effects of Testosterone Treatment in Older Men.
Snyder PJ, Bhasin S, Cunningham GR, et al.
Abstract
BACKGROUND
Serum testosterone concentrations decrease as men age, but benefits of raising testosterone levels in older men have not been established.
METHODS
We assigned 790 men 65 years of age or older with a serum testosterone concentration of less than 275 ng per deciliter and symptoms suggesting hypoandrogenism to receive either testosterone gel or placebo gel for 1 year. Each man participated in one or more of three trials — the Sexual Function Trial, the Physical Function Trial, and the Vitality Trial. The primary outcome of each of the individual trials was also evaluated in all participants.
RESULTS
Testosterone treatment increased serum testosterone levels to the mid-normal range for men 19 to 40 years of age. The increase in testosterone levels was associated with significantly increased sexual activity, as assessed by the Psychosexual Daily Questionnaire (P<0.001), as well as significantly increased sexual desire and erectile function. The percentage of men who had an increase of at least 50 m in the 6-minute walking distance did not differ significantly between the two study groups in the Physical Function Trial but did differ significantly when men in all three trials were included (20.5% of men who received testosterone vs. 12.6% of men who received placebo, P=0.003). Testosterone had no significant benefit with respect to vitality, as assessed by the Functional Assessment of Chronic Illness Therapy–Fatigue scale, but men who received testosterone reported slightly better mood and lower severity of depressive symptoms than those who received placebo. The rates of adverse events were similar in the two groups.
CONCLUSIONS
In symptomatic men 65 years of age or older, raising testosterone concentrations for 1 year from moderately low to the mid-normal range for men 19 to 40 years of age had a moderate benefit with respect to sexual function and some benefit with respect to mood and depressive symptoms but no benefit with respect to vitality or walking distance. The number of participants was too few to draw conclusions about the risks of testosterone treatment. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT00799617.)

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to July 25, 2024

1)	Testosterone/ or testosterone.mp.	114375
2)	hypogonadism.mp. or Hypogonadism/	17164
3)	1 and 2	7207
4)	limit 3 to (english language and male and humans and yr="2015 -Current" and ("all adult (19 plus years)" or "adolescent (13 to 18 years)") and (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review"))	49

Appendix 4: Key Inclusion Criteria

Population	Adult males for conditions associated with a deficiency or absence of endogenous testosterone
Intervention	Testosterone formulations
Comparator	Placebo or other active treatments for male hypogonadism
Outcomes	Improvements in quality of life, decreased fracture rates, vitality, physical function, or cognition
Timing	Onset of mild to moderate hypogonadal symptoms or relevant diagnosis
Setting	Outpatient

Testosterone

Goal(s):

- Restrict use to medically appropriate conditions funded under the Oregon Health Plan (use for sexual dysfunction or body-building is not covered)
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- Up to 12 months

Requires PA:

- All testosterone products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the medication requested for AIDS-related cachexia?	**Yes:** Go to #7	**No:** Go to #3

Approval Criteria		
3. Is the medication requested for one of the following diagnoses? • Primary Hypogonadism (congenital or acquired): defined as testicular failure due to such conditions as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, trauma, or toxic damage from alcohol or heavy metals OR • Hypogonadotropic Hypogonadism (congenital or acquired): as defined by idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma or radiation	**Yes:** Go to #4	**No:** Go to #6
4.Is there documentation of 2 morning (between 8 a.m. to 10 a.m.) tests (at least 1 week apart) demonstrating low testosterone levels at baseline as defined by the following criteria: • Total serum testosterone level less than 300 ng/dL (10.4 nmol/L); OR • Total serum testosterone level less than 350 ng/dL (12.1 nmol/L) AND free serum testosterone level less than 50pg/mL (or 0.174 nmol/L)	**Yes:** Go to #5	**No:** Deny; medical appropriateness

Approval Criteria		
5.Is there documentation based on submitted chart notes of any of the following diagnoses: • A recent major cardiovascular event (i.e., myocardial infarction, stroke or acute coronary syndrome) within the past 6 months • Heart failure with uncontrolled symptoms (i.e., NYHA Class III-IV, presence of edema, or evidence of fluid retention) • Benign prostate hyperplasia with uncontrolled symptoms or presence of severe lower urinary tract symptoms (i.e., frequent symptoms of incomplete emptying, increased frequency, intermittency, urgency, weak stream, straining, or nocturia) • Breast cancer • Prostate cancer (known or suspected) or elevated prostate specific antigen (PSA) with prior use of testosterone • Untreated obstructive sleep apnea with symptoms • Elevated hematocrit (>50%)	**Yes:** Deny; medical appropriateness	**No:** Go to #8
6. Is the medication requested for gender-affirming care?	**Yes:** Go to #7	**No:** Go to #8
7. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a co-pay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve the preferred product for up to 12 months.	**No:** Approve the requested agent for up to 12 months.

Approval Criteria		
8. RPh only: all other indications need to be evaluated for medical appropriateness under the OHP. Note: Testosterone should not be prescribed to patients who have any contraindicated diagnoses listed in question #5. Testosterone is FDA-approved only for primary hypogonadism and hypogonadotropic hypogonadism as defined in question #3. Safety and efficacy of testosterone therapy have not been established in people with late-onset (age-related) hypogonadism.	If medically appropriate therapy and prescriber provides supporting literature: Approve for up to 12 months. If current age < 21 years: prescriber provides documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc) AND supporting literature: Approve for up to 12 months.	If current age ≥ 21 years and there is not adequate documentation to support therapy: Deny; medical appropriateness. If current age < 21 years and there is not adequate documentation to support therapy: Deny; medical appropriateness.

P&T Review: *10/24 (DE); 8/23 (SS); 11/18; 11/15; 2/12; 9/10; 2/06; 2/01; 9/00*
Implementation: *9/1/23; 1/1/19; 5/1/16; 1/1/16; 7/31/14; 5/14/12, 1/24/12, 1/1/11, 9/1/06*