Therapeutic Class Overview
Androgens

INTRODUCTION

- Male hypogonadism is characterized by a lack of function of the gonads (testes). It can be categorized by the level of the reproductive system in which the defect occurs (*Dandona and Rosenberg, 2010*).
  - Primary hypogonadism is hypogonadism resulting from a defect of the gonads.
  - Secondary hypogonadism, also known as hypogonadotropic hypogonadism, results from defects in the hypothalamus or pituitary.
- Male hypogonadism may manifest with testosterone deficiency and/or infertility. Clinical signs and symptoms depend primarily on the age at the onset of the condition (*Petak et al, 2002*).
- Postpubertal hypogonadism usually results in slowly evolving clinical manifestations that may include a progressive decrease in muscle mass, loss of libido, impotence, oligospermia or azoospermia, poor ability to concentrate, and an increased risk of osteoporosis and fractures (*Petak et al, 2002*).
- Intramuscular (IM) and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients. The oral alkylated androgens are generally not recommended because of poor androgen effects, adverse lipid changes, and hepatic side effects (*Bhasin et al, 2018; Mulhall et al, 2018; Petak et al, 2002; Wang et al, 2008*).
- Androgens included in this review are Androderm (testosterone) transdermal system; Androgel, Fortesta, Testim, and Vogelxo (testosterone) topical gels; Methitest (methyltestosterone) oral tablets, methyltestosterone oral capsules; Aveed (testosterone undecanoate) injection; testosterone topical solution; danazol oral capsules; Depo-Testosterone (testosterone cypionate) injection; Natesto (testosterone) nasal gel; Striant (testosterone) buccal system; Testopel (testosterone) pellets for subcutaneous implantation; and testosterone enanthate injections including Xyosted subcutaneous autoinjector.
- With the exception of danazol, all agents in this review are Food and Drug Administration (FDA)-approved for the management of male hypogonadism. Danazol is FDA-approved for the treatment of endometriosis and hereditary angioedema.
- Methyltestosterone capsules and tablets; Testopel (testosterone) pellets for subcutaneous implantation; and testosterone enanthate are also FDA-approved for the treatment of delayed puberty in males.
- Methyltestosterone capsules and tablets and testosterone enanthate are also FDA-approved for metastatic mammary cancer in females.
- All testosterone products are controlled substances (C-III). Danazol, an androgen, is not a controlled substance.
- Testosterone gels and solutions have risk evaluation and mitigation strategy (REMS) programs consisting of a medication guide with information on proper application, potential adverse effects, and preventing inadvertent exposure to others, specifically women and children. Aveed has a REMS program related to post-injection reactions (*Drugs@FDA, 2019*).
- This review primarily focuses on the use of androgens for the management of male hypogonadism.
- Non-labeled indications, such as anemia, hormone therapy for transgender patients, and acquired immunodeficiency syndrome (AIDS)-associated wasting syndrome are not addressed in this review.
  - Due to the number of branded products in different formulations, generic names and formulations will be used throughout the review.
  - The agents included in this review are listed in Table 1.
  - Other androgen products are not included in this review.
    - Oxandrolone is a synthetic testosterone derivative FDA-indicated for cachexia.
    - Oxymetholone is an anabolic steroid with androgenic properties FDA-indicated for anemias and myelofibrosis (*Micromedex, 2019*).
- Compounded products and combination products containing testosterone are not included in this review.
- Medispan therapeutic class: Androgens

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Androderm (testosterone transdermal system) patch	-
Androgel, Fortesta, Testim, Vogelxo (testosterone) topical gel	✔ *
Methitest (methyltestosterone) tablets, methyltestosterone capsules	-/ ✔ §
Aveed (testosterone undecanoate)	-
testosterone topical solution	✔ ¥
danazol	✔ †
Depo-Testosterone (testosterone cypionate)	✔
Natesto (testosterone) nasal gel	-
Striant (testosterone) buccal system	-
Testopel (testosterone) pellets for subcutaneous implantation	-
testosterone enanthate	✔ ‡
Xyosted (testosterone enanthate) autoinjector for subcutaneous injection	-

* A-B rated generics are available for Androgel 1% and 1.62% gel. An authorized generic is also available for Androgel 1.62%, Testim, Vogelxo, and Fortesta. In addition, the FDA has determined that Testim and Vogelxo are therapeutically equivalent.
¥ Branded product, Axiron, is no longer manufactured, but it is still available as a generic.
† Branded product, Danocrine, is no longer manufactured, but it is still available as a generic.
‡ Branded product, Delatestryl, is no longer manufactured, but it is still available as a generic.
§ Branded products, Android and Testred (methyltestosterone capsules), are no longer manufactured, but are still available as generics. Methitest is only available as a branded product.

(*Drugs@FDA, 2019; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	danazol	methyltestosterone	testosterone buccal	testosterone gel	testosterone nasal gel	testosterone implant	testosterone patch	testosterone topical solution	testosterone cypionate	testosterone enanthate	testosterone undecanoate*	testosterone enanthate autoinjector
Replacement therapy in males for deficiency or absence of endogenous testosterone due to primary hypogonadism (congenital or acquired)		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Replacement therapy in males for deficiency or absence of endogenous testosterone due to hypogonadotropic hypogonadism (congenital or acquired)		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Stimulation of puberty in carefully selected males with clearly delayed puberty that is not secondary to a pathological disorder		✔				✔				✔		
Treatment of metastatic mammary cancer in women with inoperable metastatic (skeletal) mammary cancer who are 1 to 5 years postmenopausal		✔								✔		
Treatment of endometriosis amenable to hormonal management	✔											
Prevention of attacks of angioedema of all types	✔											
Limitations of Use:												
Safety and efficacy in men with "age-related hypogonadism" have not been established		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Safety in males under the age of 18 years has not been established			✔	✔	✔		✔	✔			✔	✔
Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure				✔ †								

*Aveed should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism (POME) and anaphylaxis.
† Androgel, Testim, and Vogelxo only

(*Prescribing information: Androderm, 2018; Androgel 1%, 2016; Androgel 1.62%, 2016; Android, 2015; Aveed, 2018; danazol, 2018; Depo-Testosterone, 2018; Fortesta, 2017; Methitest, 2016; Natesto, 2016; Striant, 2016; Testim, 2018; Testopel, 2018; testosterone enanthate, 2017; testosterone topical solution, 2018; Testred, 2015; Vogelxo, 2017; Xyosted 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Male Hypogonadism
  - In clinical studies, testosterone transdermal system (Androderm), topical gel (Androgel, Fortesta, Testim), and topical solution have been shown to increase serum testosterone and lean body mass, decrease body fat, and improve sexual function in men with hypogonadism. Increases in hemoglobin, hematocrit, and prostate specific antigen (PSA) were observed (*Brock et al, 2016, Dobs et al, 2012; Grober et al, 2008; McNicholas et al, 2003; Roy et al, 2017; Steidle et al, 2003; Swerdloff et al, 2000; Wang et al, 2000; Wang et al, 2004; Wang et al, 2011*).
  - A network meta-analysis of 87 randomized and 51 non-randomized studies concluded that testosterone replacement therapies, as a class, improved quality of life, libido, depression, and sexual function as compared to placebo (*Elliott et al, 2017*). Additionally, individual product comparisons were also made. Most endpoints did not reveal significant differences between products, but the 1% testosterone gel was significantly better than the patch for improvement in libido.
  - A 36-month extension study demonstrated that long-term treatment with testosterone topical gel (Androgel) maintained increased levels of serum testosterone as well as improvements in sexual function, positive mood, and body composition. A gradual but significant improvement in hip and spine bone mineral density was also observed. Increases in hemoglobin and hematocrit plateaued at 12 months, and clinically insignificant increases in high-density lipoprotein cholesterol, serum creatinine, and total bilirubin were seen. Serum levels of PSA showed no further significant increases past 6 months of treatment. Treatment-emergent adverse events included application site reactions, acne, and gynecomastia (*Wang et al, 2004*).
  - Head-to-head studies comparing testosterone topical gel (Androgel, Testim) to testosterone patch (Androderm) have shown greater improvement in serum testosterone levels, lean body mass, and sexual function as well as fewer adverse events with testosterone gel compared to testosterone patches in men with hypogonadism (*McNicholas et al, 2003; Steidle et al, 2003; Swerdloff et al, 2000; Wang et al, 2000*).
  - In an open-label study, hypogonadal men on testosterone replacement therapy with suboptimal response underwent brand substitution and switched between Androgel and Testim. More patients who switched from Androgel to Testim experienced improvements in libido, erectile function, and energy levels compared to those who switched from Testim to Androgel. Changing from Testim to Androgel eliminated or minimized unwanted adverse effects (*Grober et al, 2008).*
  - Testosterone buccal system (Striant) was compared to testosterone transdermal system or testosterone topical gel in 2 randomized controlled studies with hypogonadal men. Testosterone buccal system was shown to lead to serum testosterone levels within normal ranges that were similar to testosterone topical gel and transdermal system (*Dobs et al, 2004; Korbonits et al, 2004*).
  - A double-blind, randomized controlled trial showed that testosterone cypionate improved grip strength and increased hemoglobin compared to placebo in hypogonadal men (*Sih et al, 1997*).
  - An open-label trial comparing 4 different dosing regimens of testosterone enanthate in men with primary hypogonadism showed that testosterone enanthate 200 mg every 2 weeks and 300 mg every 3 weeks were most effective in suppressing serum luteinizing hormone to normal, while 100 mg every week and 200 mg every 2 weeks were effective in suppressing follicle-stimulating hormone to normal (*Snyder et al, 1980*).
  - In a small, open-label study, methyltestosterone was associated with improvement in sexual function in men with profound testosterone deficiency but no noticeable changes in levels of energy, mood, or feeling of well-being (*Morales et al, 1994*).
  - Aveed was approved via the 505(b)(2) pathway. The primary clinical trial submitted for its approval was a Phase 3, multi-center, open-label, 84-week, pharmacokinetic and safety study of testosterone undecanoate in hypogonadal men. Adult males with primary or secondary hypogonadism and testosterone levels < 300 ng/dL were given 750 mg of testosterone undecanoate IM at baseline, 4 weeks, and every 10 weeks thereafter for a total of 9 injections (N = 130). At week 14 (after the third dose), the percentage of the 117 patients still enrolled with an average serum total testosterone concentration within the normal range (300 to 1000 ng/dL) was 94% (95% confidence interval [CI], 89.7 to 98.3%). The percentage of patients with a maximum total testosterone concentration < 1500 ng/dL was 92%. The authors concluded that testosterone undecanoate 750 mg achieved sustained, consistent serum testosterone in the normal range during a 10-week dosing interval (*Morgentaler et*

al, 2008). Additional trials of testosterone undecanoate have been completed, but published results are limited. In 1 trial, the dose was not specified, but testosterone undecanoate was demonstrated to be effective in a large number of patients (*Zitzmann et al, 2013*). One study demonstrated improvement in scores on the Aging Male Symptoms (AMS) scale, which is 1 measurement of health-related quality of life, when testosterone undecanoate 1000 mg was used (*Ho et al, 2012*).

- One study with a 6-year follow up measured mortality in patients with type 2 diabetes (N = 581) with low vs. normal testosterone levels (some of whom were treated with testosterone gel or testosterone undecanoate to maintain normal levels). The authors found that patients with low testosterone had higher mortality rates than those with normal levels (17.2 vs. 9%; p = 0.003) (*Muraleedharan et al, 2013*).
- The Testosterone Trials were a coordinated set of clinical trials designed to determine whether testosterone would benefit men with age-related low testosterone levels. Initial results from 3 of the 7 trials have been published (*Snyder et al, 2016*). Each participant was enrolled in 1 or more of the 3 trials (the Sexual Function Trial, the Physical Function Trial, and the Vitality Trial). In addition to the results for the individual trials, the primary efficacy outcome of each trial was assessed among participants across all 3 trials. Patients (N = 790) aged ≥ 65 years with serum testosterone levels < 275 ng/dL were assigned to receive either testosterone gel (Androgel 1%) or placebo for 1 year.
  - Sexual function: Participants taking testosterone experienced an increase in sexual activity as assessed by question 4 on the Psychosexual Daily Questionnaire (PDQ-Q4) in both the Sexual Function Trial (mean difference, 0.58; p < 0.001) and among all trial participants (mean difference, 0.62; p < 0.001). Testosterone treatment was also associated with increased sexual desire and improved erectile function.
  - Physical function: Among patients enrolled in the Physical Function Trial, testosterone was not associated with a significant difference vs. placebo in the percentage of patients achieving a ≥ 50 meter increase in the 6-minute walking distance (6MWD) (odds ratio [OR], 1.42; p = 0.2); there was also no difference in the mean change from baseline in 6MWD. There was no significant difference in the percentage of patients with an increase of ≥ 8 points in the physical function domain (PF-10) of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36); however, there was a significant difference in the mean change from baseline in PF-10 score (mean difference, 2.75 points; p = 0.03). When results from the 3 trials combined were considered, there was a significant difference in the percentage of patients with a ≥ 50 meter increase in 6MWD (OR, 1.76; p = 0.003) as well as each of the secondary physical function endpoints.
  - Vitality: Among patients in the Vitality Trial, testosterone was not associated with a significant difference vs. placebo in vitality as determined by an increase of ≥ 4 points on the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale (OR, 1.23; p = 0.3). However, improvements were observed on several secondary endpoints, including the SF-36 vitality score (mean difference, 2.41 points; p = 0.03), the positive and negative affect schedule (PANAS) positive affect score (mean difference, 0.47 points; p = 0.04), the PANAS negative affect score (mean difference, -0.49 points; p < 0.001), and the patient health questionnaire (PHQ-9) depression score (mean difference, -0.72 points; p = 0.004). There was no significant difference in the percentage of patients with an increase of ≥ 4 points on the FACIT-Fatigue score when results of the 3 trials combined were considered (OR, 1.23; p = 0.22); however, the effect of testosterone on the mean change from baseline in the FACIT-Fatigue score was significant (mean difference, 1.27; p = 0.006).
  - Safety: No significant differences between groups were demonstrated in cardiac adverse events. Seven men in each group had major adverse cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) during the treatment period, and 2 patients in the testosterone group and 9 in the placebo group had major adverse cardiovascular events in the subsequent year. More patients assigned to testosterone had an increase in PSA of ≥ 1 ng/dL (23 vs 8); 1 man (in the testosterone group) was diagnosed with prostate cancer during the treatment period, and 2 patients in the testosterone group and 1 in the placebo group were diagnosed in the subsequent year. A hemoglobin level ≥ 17.5 g/dL was observed in 7 men in the testosterone group and none in the placebo group. No difference was seen in the international prostate symptom score (IPSS).

- Conclusions: Testosterone supplementation had small-to-moderate effects on all measures of sexual function and some measures of physical function, mood, and depressive symptoms. Although cardiovascular events were not increased with testosterone supplementation, the trial was not large enough to exclude smaller increases in risk. In addition, safety with respect to prostate cancer and urinary symptoms cannot be generalized because men with a high risk of prostate cancer and men with moderately severe urinary symptoms were excluded from the trial.

- Separate publications reported additional results from the Testosterone Trials. The Cognitive Function Trial included a subgroup of men (n = 493) with age-associated memory impairment (*Resnick et al, 2017*). Testosterone replacement did not improve delayed paragraph recall in these patients at 6 and 12 months (adjusted estimated difference, -0.07; p = 0.88). In the Cardiovascular Trial (n = 170) coronary computed tomographic angiography (CCTA) was used to determine whether testosterone slowed the progression of noncalcified coronary artery plaque. It was found that testosterone treatment was associated with a significantly greater increase in noncalcified plaque volume after 12 months of treatment compared with placebo: estimated difference, 41 mm^3; p = 0.003 (*Budoff et al, 2017*). The Bone Trial (n = 211) found testosterone treatment to significantly improve mean spine and hip volumetric bone mass density compared with placebo (*Snyder et al, 2017*).
- A randomized, double-blind, placebo-controlled trial found that once daily application of testosterone 2% solution for 12 weeks restored normal testosterone levels, and led to significant improvements in sex drive in men with hypogonadism; improvements in energy levels were variable (*Brock et al, 2016*).
- Meta-analyses have evaluated the potential adverse effects associated with testosterone use. One found that patients treated with testosterone had higher rates of cardiovascular-related events than patients treated with placebo (*Xu et al, 2013*). However, another meta-analysis that included both randomized controlled and epidemiological studies found no difference in the risk of major cardiovascular events between testosterone and placebo (*Corona et al, 2018*). Calof and colleagues found that patients treated with testosterone had a greater rate of prostate events and elevated hematocrit compared to patients treated with placebo (*Calof et al, 2005*).
- The efficacy and safety of Xyosted were evaluated in an open-label, single-arm, dose-blinded, 52-week study in 150 men with hypogonadism (*Kaminetsky et al, 2018*). Patients were started on 75 mg Xyosted self-administered on a weekly basis with dose adjustments made at week 7 based on total testosterone trough concentrations. Results revealed that 92.7% of subjects achieved an average total testosterone concentration of 300 to 1100 ng/dL at week 12 with a maximum serum concentration of < 1500 ng/dL achieved by 91.3% of patients and 0 patients with levels > 1800 ng/dL. At week 52, the mean testosterone trough concentration was 487.2 ± 153.33 ng/dL. The most frequently reported treatment-related adverse events were increases in hematocrit, hypertension, and PSA; no serious treatment-related adverse events were reported.

- Delayed puberty and delayed growth
  - Testosterone products, including testosterone enanthate and methyltestosterone have been studied in the treatment of delayed growth and puberty in adolescent males. These products have demonstrated increased growth (weight and height) in the time periods studied, but it is difficult to determine the long-term effects on bone health as the trials had relatively limited durations and study populations (*Kaplan et al, 1973; Rosenfeld et al, 1982; Soliman et al, 1995*).
- Endometriosis
  - Danazol is used for the palliative treatment of endometriosis in patients in whom alternative hormonal therapy (eg, estrogen and progestin or testosterone) is ineffective, intolerable or contraindicated (*Micromedex, 2019*). A meta-analysis of 5 placebo-controlled trials concluded that danazol was effective in relieving pain and improving laparoscopic scores in women with endometriosis; however, its use was limited by the occurrence of androgenic adverse effects (*Selak et al, 2007*).
- Hereditary angioedema
  - Studies have reported that danazol was beneficial in reducing the frequency and severity of acute attacks and increasing the serum levels of C1 esterase inhibitor and the fourth component of complement (*Bork et al, 2008; Gelfand et al, 1976*).
- Treatment of metastatic mammary cancer
  - Studies on the use of methyltestosterone have not been included in the detailed review. Endocrine therapy (including androgens) may be used for metastatic breast cancer in post-menopausal women.

Androgens are rarely used (often considered last-line therapy) in the treatment of metastatic breast cancer. While response rates may be reasonable, adverse effects, including virilization, edema, and jaundice, limit their clinical applicability compared to other treatment options (*Ma, 2018*).

CLINICAL GUIDELINES

- Male hypogonadism
  - The American Urological Association recommends the use of testosterone replacement therapy in men with testosterone deficiency but provides no specific guidance other than to avoid methyltestosterone (*Mulhall et al, 2018*). The European Association of Urology (EAU) recommends that choice of therapy should be based on risk vs benefit decisions between the provider and patient and states that short-acting therapies may be preferred when initiating therapy (*Dohle et al, 2018*). The Endocrine Society recommends all testosterone products in appropriate doses, with the exceptions of danazol and methyltestosterone (*Bhasin et al, 2018*). A joint statement by the International Society of Andrology (ISA), International Society for the Study of the Aging Male (ISSAM), EAU, European Academy of Andrology (EAA), and American Society of Andrology (ASA) agrees that decisions should be made based on patient and prescriber preference and tolerability, but states that methyltestosterone should be avoided due to potential liver toxicity (*Wang et al, 2008*). The American Association of Clinical Endocrinologists (AACE) also agrees with the recommendation to avoid methyltestosterone (*Petak et al, 2002*).
- Endometriosis
  - Both the American Society for Reproductive Medicine (ASRM) and American Congress of Obstetricians and Gynecologists (ACOG) have guidelines for the treatment of endometriosis, but only the ASRM specifically addresses danazol (*ACOG, 2010 [reaffirmed in 2018]; ASRM, 2014*). This guideline states that danazol has been used for the treatment of endometriosis, but hyperandrogenic side effects (hirsutism, acne, weight gain, and deepening of the voice) are common (*ASRM, 2014*).
- Hereditary angioedema
  - The international World Allergy Organization/European Academy of Allergy and Clinical Immunology 2017 guideline for the management of hereditary angioedema does not advise using danazol for on-demand treatment of attacks as the drug shows no or only minimal effects when used in this manner (*Maurer et al*, 2018). For long-term prevention of attacks, danazol is a recommended second-line therapy after C1-inhibitor administration.

SAFETY SUMMARY

- Boxed Warnings:
  - Danazol: use in pregnancy is contraindicated; thromboembolism, thrombotic and thrombophlebitic events, and life-threatening or fatal strokes have been reported; experience with long-term therapy is limited; and therapy has been associated with several cases of benign intracranial hypertension.
  - Testosterone, topical gel and solution: virilization has been reported in children who were secondarily exposed to testosterone gel.
  - Testosterone undecanoate has a boxed warning for post-injection pulmonary oil microembolism (POME) and anaphylactic reactions.
  - Xyosted has a boxed warning regarding increases in blood pressure that may elevate the risk of major adverse cardiovascular events. Blood pressure should be monitored before initiation, and periodically during, therapy.
- REMS programs
  - Testosterone topical gel and solution have REMS programs consisting of a medication guide to promote proper use, limit unwanted exposure, and provide safety information.
  - Testosterone undecanoate products have a single shared REMS program that restricts its use to specific healthcare facilities and providers who have been adequately trained to assess and treat post-injection reactions, including POME and anaphylaxis.
- Major contraindications include active thrombosis or thromboembolic disease (danazol only); androgen-dependent tumors or breast or prostate cancer; known hypersensitivity; serious cardiac, hepatic, or renal disease; use in pregnant or breastfeeding women or women who may become pregnant; porphyria (danazol only); and undiagnosed abnormal genital bleeding (danazol only).

- Although Depo-Testosterone, methyltestosterone, Testopel, and testosterone enanthate do not specifically list breastfeeding as a contraindication within their prescribing information, breastfeeding should be halted if these agents are required (*Briggs et al, 2017*).
- Key warnings include bone growth changes, adverse effects on spermatogenesis, cardiovascular risk (eg, myocardial infarction, stroke, etc.), serum lipid changes, blood glucose changes, edema with or without heart failure, gynecomastia, hepatic adverse effects, polycythemia, prostate cancer, priapism, virilizing effects in women and/or children, worsening of benign prostatic hyperplasia (BPH), and the potential for abuse of testosterone products. Additionally, use of testosterone has been subject to abuse leading to serious cardiovascular and psychiatric adverse reactions. If suspected, serum testosterone concentrations should be monitored.
- Transdermal testosterone patches contain aluminum that may burn the skin if worn during a magnetic resonance imaging scan. Testosterone gel and topical solution formulations are flammable until dry.
- Common side effects include application-related reactions for topical and buccal products, injection site reactions for injected products, edema, hepatic adverse effects, prostate effects, increased hematocrit, weight gain, and virilizing effects.
- In January 2014, the FDA announced that it was investigating the risk of cardiovascular events (ie, stroke, heart attack, and death) in men taking FDA-approved testosterone products, based on the results of 2 trials that suggested an increased cardiovascular risk. At that time, the FDA had not made any conclusions and recommended that patients not discontinue prescribed testosterone products without first discussing any questions or concerns with their health care provider (*FDA drug safety communication, 2014*). On March 3, 2015, the FDA issued an updated safety announcement clarifying the approved uses of prescription testosterone products for men who have low testosterone caused by certain medical conditions and not for treating low testosterone due to aging. Additionally, the manufacturers of all approved testosterone products were required to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. Manufacturers are also required to conduct a well-designed clinical trial to more clearly address the question of whether an increased risk of heart attack or stroke exists among users of these products. In April 2015, the FDA approved labeling revisions to several sections of the prescribing information for all of the testosterone products to clarify the approved uses, confirm the medical condition causing low testosterone using lab testing, and add a new warning related to potential increased cardiovascular risk (*FDA drug safety communication, 2015*). In October 2016, the FDA finalized labelling regarding abuse and dependence of testosterone along with the adverse health outcomes associated with abuse (*FDA drug safety communication, 2016*). The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) issued a joint position statement in September 2015 on the association of testosterone and cardiovascular risk. Although they agreed with the FDA that the risk/benefit of testosterone replacement therapy is not well established in aging-associated hypogonadism and large-scale, prospective, randomized controlled trials are needed, the joint committee determined that the FDA directive lacked clarity. They recommended that decisions on testosterone replacement should be guided by the signs, symptoms, and testosterone concentrations rather than the underlying cause (*Goodman et al, 2015*). Newer data suggest that increases in cardiovascular events may be due to widespread use of testosterone therapies without appropriate monitoring, and patients with cardiovascular disease may safely receive androgen therapy for the treatment of hypogonadism (*Tanna et al, 2016*).
- A trial (N = 308) was designed to determine the effect of testosterone administration on subclinical atherosclerosis progression in men ≥ 60 years of age with low or low-normal baseline testosterone levels. Treatment continued for a 3-year period. In this study, testosterone replacement did not result in a significant difference in the rate of change in common carotid artery intima-media thickness or coronary artery calcium. However, the trial was not designed to determine the effects of testosterone replacement on cardiovascular events (*Basaria et al, 2015*).
- A European observational study of hypogonadal, elderly men (mean age 59 years) (N = 115) evaluated the effects of testosterone undecanoate on various parameters for up to 10 years of use. Injections of testosterone were given every 12 weeks. Body weight and body mass index were significantly reduced from the previous year for 8 years and waist circumference was significantly lower from the previous year for 7 years. The hemoglobin A1C and ratio of triglycerides to high-density lipoprotein were significantly reduced from the second year onward. Fasting blood glucose showed improvement after

the first year of testosterone replacement. No major cardiovascular events were observed (*Yassin et al, 2016*).

- A European observational study of hypogonadal men with a history of cardiovascular disease (N = 77, mean age 61 years) evaluated the effects of testosterone therapy for up to 8 years. A marked and significant weight loss was observed after 8 years of continuous use. Beneficial effects were also observed on body mass index, lipid parameters, blood pressure, and glycemic control. No patient suffered a major adverse cardiovascular event during the full observation time (*Haider et al, 2016*).
- In a European multinational longitudinal disease registry of 99 men with hypogonadism, 750 (75%) initiated testosterone replacement therapy. CV event rates for men receiving testosterone were not statistically different from untreated men (p = 0.70). Regardless of treatment assignment, CV event rates were higher in older men and in those with increased CV risk factors or a prior history of CV events (*Maggi et al, 2016*).
- In a European prospective registry of men with hypogonadism, 360 men who received testosterone undecanoate were compared to 296 men who did not receive testosterone treatment (*Traish et al, 2017*). Deaths and CV parameters were tracked for 8 years. In contrast to previous studies, patients receiving testosterone had a lower mortality rate than the control group (estimated incidence difference, 0.0804; 95% CI, 0.0189 to 0.3431). In this cohort, there were no CV-related deaths in the testosterone group and 19 CV-related deaths in the control group.
- Although testosterone therapy was previously thought to be contraindicated in men with a history of prostate cancer, recent data suggest that use does not increase risk of de novo prostate cancer, progression of the disease, or biochemical recurrence in men with hypogonadism and a history of non-high-risk prostate cancer; safety data for testosterone use in high-risk cancer patients are limited and use in this patient population remains controversial (*Davidson et al, 2016; Nguyen et al, 2016*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Androderm (testosterone transdermal system) (C-III)	Transdermal system	top	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Apply once nightly	Apply patches to back, abdomen, upper arms or thighs. Rotate the site of application with an interval of 7 days between applications to the same site. Avoid swimming, showering or washing the application site for a minimum of 3 hours after application. When discarding a used patch, it should be folded in half so the sticky sides stick together and thrown away in household trash.
Androgel, Fortesta, Testim, Vogelxo (testosterone) (C-III)	Topical gel	top	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism	Apply the topical gel in the following area: Androgel 1%: shoulders, upper arms and/or abdomen Androgel 1.62%: upper arms and shoulders

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			(congenital or acquired in males): Apply once daily (preferably in the morning)	Fortesta: front and inner thighs Testim, Vogelxo: shoulders and/or upper arms Allow application sites to dry before dressing. Cover the application sites with clothing to prevent transfer to another person. Wash hands with soap and water after application. Avoid swimming, showering or washing the application site for a minimum of: ○ 2 hrs after Androgel 1.62%, Fortesta, Vogelxo, and Testim ○ 5 hrs after Androgel 1%
Methitest, (methyltestosterone) tablets, methyltestosterone capsules (CIII)	Capsules Tablets	oral	Delayed puberty (males): 10-50 mg/d for a limited duration (eg, 4-6 mos) Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): 10-50 mg/d Metastatic mammary cancer (females): 50-200 mg/d	Dosage will depend on age, sex, diagnosis, patient's response to treatment, and appearance of adverse effects.
Aveed (testosterone undecanoate) (C-III)	Injectable solution	IM	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males):	Observe patients in the healthcare setting for 30 minutes following injection for symptoms of serious POME reactions or anaphylaxis. Inject deeply into the gluteal muscle at a 90°

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Inject at initiation, 4 wks, and every 10 wks thereafter	angle over 60 to 90 seconds. Between consecutive injections, alternate the injection site between the left and right buttock.
Testosterone (C-III)	Topical solution	top	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Apply once daily in the morning	Apply to the axilla with an applicator. Use at least 2 minutes after antiperspirant or deodorant use. Allow application sites to dry before dressing. Cover the application sites with clothing to prevent transfer to another person. Rinse the metered dose pump applicator with water after application. Avoid swimming, showering or washing the application site for a minimum of 2 hours after application.
Danazol	Capsules	oral	Treatment of endometriosis (females): Twice daily; continue uninterrupted for 3-6 mos (up to 9 mos) Treatment of hereditary angioedema: Twice to 3 times daily; after a favorable response, decrease dose by 50% or less at intervals of 1 to 3 months or longer depending on the frequency of attacks; individualize dose based on patient response	Treatment of endometriosis should begin during menstruation; otherwise, ensure that patient is not pregnant while on treatment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Depo-Testosterone (testosterone cypionate) (C-III)	Injectable solution	IM	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Inject every 2-4 wks	Dosage will depend on age, sex, diagnosis, patient's response to treatment, and appearance of adverse effects. Inject the preparation slowly and deeply into the gluteal muscle.
Natesto (testosterone nasal gel) (C-III)	Nasal gel	intranasal	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Apply intranasally 3 times daily	Administer once in the morning, afternoon, and evening (6 to 8 hrs apart). Clear nasal passage prior to intranasal administration. Do not blow the nose or sniff for 1 hour after administration.
Striant (testosterone buccal system) (C-III)	Buccal system	oral	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Apply to gum region twice daily	The buccal system should be placed against the gum and held firmly in place with a finger over the lip and against the product for 30 seconds to ensure adhesion. Place Striant in a comfortable position just above the incisor tooth (on either side of the mouth). Rotate sides of mouth with each application. Remove by gently sliding it downwards from the gum. The system should be removed before brushing or flossing the teeth. Do not chew or swallow.
Testopel (testosterone) pellets for subcutaneous implantation (C-III)	Pellets	SC	Delayed puberty (males): Doses vary based on needs and are typically less than for hypogonadotropic hypogonadism; inject SC for a limited duration (eg, 4 to 6 months of treatment) Hypogonadotropic hypogonadism (congenital or	In the face of complications, the pellets should be removed. In addition, pellets may slough out. Pellet implantation is less flexible for dosage adjustment. Great care should be used when estimating the amount of testosterone needed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			acquired in males) and primary hypogonadism (congenital or acquired in males): Inject SC every 3-6 mos	Lower doses may be used on initiation and then increased gradually. Approximately one-third of the material is absorbed in the first month, one-fourth in the second month, and one-sixth in the third month. Frequency may vary based on patient needs.
testosterone enanthate (C-III)	Injectable solution	IM	Delayed puberty: Inject IM every 2-4 wks for a limited duration (eg, 4-6 mos) Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Inject IM every 2-4 wks Metastatic mammary cancer (females): Inject IM every 2-4 wks	Inject the preparation slowly and deeply into the gluteal muscle. Dosage and duration of therapy will depend on age, sex, diagnosis, patient's response to treatment and appearance of adverse effects.
Xyosted (testosterone enanthate) autoinjector for subcutaneous administration	Autoinjector	SC	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Inject SC once weekly	Inject in the abdominal region only.

See the current prescribing information for full details

CONCLUSION

- Androgens included in this review are Androderm (testosterone) transdermal system; Androgel, Fortesta, Testim, and Vogelxo (testosterone) topical gels; methyltestosterone oral capsules; Aveed (testosterone undecanoate) injection; testosterone topical solution; danazol oral capsules; Depo-Testosterone (testosterone cypionate) injection; Methitest (methyltestosterone) oral tablets; Natesto (testosterone) nasal gel; Striant (testosterone) buccal system; Testopel (testosterone) pellets for subcutaneous implantation; and testosterone enanthate injection including Xyosted subcutaneous autoinjector.

- With the exception of danazol, all agents in this review are FDA-approved for the management of male hypogonadism. Danazol is FDA-approved for the treatment of endometriosis and hereditary angioedema.
- All androgen products, with the exception of danazol, are controlled substances (C-III). Testosterone gels and solutions have REMS programs consisting of a medication guide with information on proper application, potential adverse effects, and preventing inadvertent exposure to others, specifically women and children. Aveed has a REMS program related to post-injection reactions (*Drugs@FDA, 2019*).
- In clinical studies, testosterone buccal and topical products have been shown to increase serum testosterone levels and/or improve lean body mass, decrease body fat, and improve sexual function in men with hypogonadism (*Dobs et al, 2004; Dobs et al, 2012; Grober et al, 2008; Korbonits et al, 2004; McNicholas et al, 2003; Steidle et al, 2003; Swerdloff et al, 2000; Wang et al, 2000; Wang et al, 2004; Wang et al, 2011*).
- Initial results from a coordinated set of clinical trials in men with age-related low testosterone levels demonstrated small-to-moderate improvements in sexual function and some measures of physical function, mood, and depressive symptoms (*Snyder et al, 2016*).
- Head-to-head studies comparing testosterone topical gel to testosterone transdermal system have shown greater improvement in serum testosterone levels, lean body mass, and sexual function as well as fewer adverse events with testosterone gel compared to testosterone patches in men with hypogonadism (*McNicholas et al, 2003; Steidle et al, 2003; Swerdloff et al, 2000; Wang et al, 2000*).
- Increases in hemoglobin, hematocrit, and PSA have been observed in clinical studies (*Wang et al, 2000*). Severe hepatotoxicity has been associated more commonly with oral androgen than topical androgen therapy, and liver function tests should be monitored periodically.
- Meta-analyses have demonstrated an increased risk of cardiovascular events and prostate events, whereas a long-term observational study found reduced mortality in patients with type 2 diabetes who had low testosterone vs normal testosterone levels. A European 10-year observational study of elderly men demonstrated improvement in weight, body mass index, and glycemic parameters with no reports of major adverse cardiovascular events. Similarly, a European 8-year observational study of hypogonadal men with a history of cardiovascular disease demonstrated improvement in weight, body mass index, lipid parameters, blood pressure, and glycemic control with no major adverse cardiovascular events during the full observation time. Another European 8-year observational study observed lower rates of mortality, including CV-related deaths, in hypogonadal men receiving testosterone compared to those not receiving treatment (*Calof et al, 2005; Muraleedharan et al, 2013; Xu et al, 2013, Yassin et al, 2016, Haider et al, 2016; Traish et al, 2017*).
- Although testosterone therapy was previously thought to be contraindicated in men with a history of prostate cancer, recent data suggest that use does not increase risk of de novo prostate cancer, progression of the disease, or biochemical recurrence in men with hypogonadism and a history of non-high-risk prostate cancer; safety data for testosterone use in high-risk cancer patients are limited and use in this patient population remains controversial (*Davidson et al, 2016; Nguyen et al, 2016*).
- In March 2015, the FDA issued a safety announcement clarifying the approved uses of prescription testosterone products for men who have low testosterone caused by certain medical conditions, discouraging the treatment of low testosterone due to aging, and requiring manufacturers of all approved testosterone products to add information to the labeling regarding a possible increased risk of heart attacks and strokes in patients taking testosterone and to conduct a well-designed clinical trial to more clearly address the question of whether an increased risk of heart attack or stroke exists among users of these products. In April 2015, the FDA approved labeling revisions to several sections of the prescribing information for all of the testosterone products to clarify the approved uses, confirm the medical condition causing low testosterone using lab testing, and add a new warning related to a potential increased cardiovascular risk (*FDA drug safety communication, 2015*). The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) issued a joint position statement in September 2015 recommending testosterone replacement be guided by the signs, symptoms, and testosterone concentrations rather than the underlying cause (*Goodman et al, 2015*). Newer data suggest that increases in cardiovascular events may be due to widespread use of testosterone therapies without appropriate monitoring, and patients with cardiovascular disease may safely receive androgen therapy for the treatment of hypogonadism (*Tanna et al, 2016*).

- According to current consensus guidelines, IM and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients while the oral (capsule or tablet) androgen therapies are generally not recommended for this condition due to poor androgen effects, adverse lipid changes, and hepatic side effects. The selection of a specific testosterone replacement therapy should be a joint decision between an informed patient and physician after considering patient preferences, the pharmacokinetic profiles of the respective agents, treatment burden, and cost. Furthermore, currently available guidelines do not give preference to one topical preparation vs. another (*Bhasin et al, 2018; Dohle et al, 2018; Mulhall et al, 2018; Petak et al, 2002; Wang et al, 2008*).

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