have encouraged the development of SARMs that are preferentially anabolic and spare the prostate.

Testosterone administration induces hypertrophy of both type 1 and 2 fibers and increases satellite cell (muscle progenitor cells) and myonuclear number. Androgens promote the differentiation of mesenchymal, multipotent progenitor cells into the myogenic lineage and inhibit their differentiation into the adipogenic lineage. Testosterone may have additional effects on satellite cell replication and muscle protein synthesis, which may contribute to an increase in skeletal muscle mass.

Other indications for androgen therapy are in selected patients with anemia due to bone marrow failure (an indication largely supplanted by erythropoietin) or for hereditary angioedema.

Male Hormonal Contraception Based on Combined Administration of Testosterone and Gonadotropin Inhibitors Supraphysiologic doses of testosterone (200 mg testosterone enanthate weekly) suppress LH and FSH secretion and induce azoospermia in 50% of Caucasian men and >95% of Chinese men. The WHO-supported multicenter efficacy trials have demonstrated that suppression of spermatogenesis to azoospermia or severe oligozoospermia (<3 million/mL) by administration of testosterone enanthate to men results in highly effective contraception. Because of concern about long-term adverse effects of supraphysiologic testosterone doses, regimens that combine other gonadotropin inhibitors, such as GnRH antagonists and progestins with replacement doses of testosterone, are being investigated. Oral etonogestrel daily in combination with intramuscular testosterone decanoate every 4–6 weeks induced azoospermia or severe oligozoospermia (sperm density <1 million/mL) in 99% of treated men over a 1-year period. This regimen was associated with weight gain, deceased testicular volume, and decreased plasma high-density lipoprotein (HDL) cholesterol, and its long-term safety has not been demonstrated. SARMs that are more potent inhibitors of gonadotropins than testosterone and spare the prostate hold promise for their contraceptive potential.

Recommended Regimens for Androgen Replacement Testosterone esters are administered typically at doses of 75–100 mg intramuscularly every week, or 150–200 mg every 2 weeks. One or two 5-mg nongenital testosterone patches can be applied daily over the skin of the back, thigh, or upper arm away from pressure areas. Testosterone gels are typically applied over a covered area of skin at initial doses that vary with the formulation; patients should wash their hands after gel application. Bioadhesive buccal testosterone tablets at a dose of 30 mg are typically applied twice daily on the buccal mucosa.

Establishing Efficacy of Testosterone Replacement Therapy Because a clinically useful marker of androgen action is not available, restoration of testosterone levels to the mid-normal range remains the goal of therapy. Measurements of LH and FSH are not useful in assessing the adequacy of testosterone replacement. Testosterone should be measured 3 months after initiating therapy to assess adequacy of therapy. There is substantial interindividual variability in serum testosterone levels, especially with transdermal gels, presumably due to genetic differences in testosterone clearance and transdermal absorption. In patients who are treated with testosterone enanthate or cypionate, testosterone levels should be 350–600 ng/dL 1 week after the injection. If testosterone levels are outside this range, adjustments should be made either in the dose or in the interval between injections. In men on transdermal patch, gel, or buccal testosterone therapy, testosterone levels should be in the mid-normal range (500–700 ng/dL) 4–12 h after application. If testosterone levels are outside this range, the dose should be adjusted. Multiple dose adjustments are often necessary to achieve testosterone levels in the desired therapeutic range.

Restoration of sexual function, secondary sex characteristics, energy, and well-being and maintenance of muscle and bone health are important objectives of testosterone replacement therapy. The patient should be asked about sexual desire and activity, the presence of early morning erections, and the ability to achieve and maintain erections adequate for sexual intercourse. Some hypogonadal men continue to complain about sexual dysfunction even after testosterone replacement has been instituted; these patients may benefit from counseling. The hair growth in response to androgen replacement is variable and depends on ethnicity. Hypogonadal men with prepubertal onset of androgen deficiency who begin testosterone therapy in their late twenties or thirties may find it difficult to adjust to their newly found sexuality and may benefit from counseling. If the patient has a sexual partner, the partner should be included in counseling because of the dramatic physical and sexual changes that occur with androgen treatment.

Contraindications for Androgen Administration Testosterone administration is contraindicated in men with a history of prostate or breast cancer (Table 411-4). Testosterone therapy should not be administered without further urologic evaluation to men with a palpable prostate nodule or induration; to men with prostate-specific antigen levels >4 ng/mL or >3 ng/mL in men at high risk for prostate cancer such as African Americans or men with first-degree relatives with prostate cancer; or to men with severe lower urinary tract symptoms (American Urological Association lower urinary tract symptom score >19). Testosterone replacement should not be administered to men with baseline hematocrit ≥50%, severe untreated obstructive sleep apnea, uncontrolled or poorly controlled congestive heart failure, or myocardial infarction, stroke, or acute coronary syndrome in the preceding 6 months.

Monitoring Potential Adverse Experiences The clinical effectiveness and safety of testosterone replacement therapy should be assessed 3 to 6 months after initiating testosterone therapy and annually thereafter (Table 411-5). Potential adverse effects include acne, oiliness of skin, erythrocytosis, breast tenderness and enlargement, leg edema, induction and exacerbation of obstructive sleep apnea, and increased risk of detection of prostate events. In addition, there may be formulation-specific adverse effects such as skin irritation with transdermal patch, risk of gel transfer to a sexual partner with testosterone gels, buccal ulceration and gum problems with buccal testosterone, and pain and mood fluctuation with injectable testosterone esters. Older men with preexisting heart disease may be at increased risk of cardiovascular events after initiation of testosterone therapy.

HEMOGLOBIN LEVELS Administration of testosterone to androgen-deficient men is typically associated with a ~3% increase in hemoglobin

TABLE 411-4 CONDITIONS IN WHICH TESTOSTERONE ADMINISTRATION IS ASSOCIATED WITH A RISK OF ADVERSE OUTCOME

Conditions in which testosterone administration is associated with very high risk of serious adverse outcomes:
Metastatic prostate cancer
Breast cancer
Conditions in which testosterone administration is associated with moderate to high risk of adverse outcomes:
Undiagnosed prostate nodule or induration
PSA >4 ng/mL (>3 ng/mL in individuals at high risk for prostate cancer, such as African Americans or men with first-degree relatives who have prostate cancer)
Erythrocytosis (hematocrit >50%)
Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by American Urological Association/International Prostate Symptom Score >19
Uncontrolled or poorly controlled congestive heart failure
Myocardial infarction, stroke, or acute coronary syndrome in the preceding 6 months

Abbreviation: PSA, prostate-specific antigen.

Source: Reproduced from the Endocrine Society Guideline for Testosterone Therapy of Androgen Deficiency Syndromes in Men (S Bhasin et al: J Clin Endocrinol Metab 95:2536, 2010).