

2370 TESTOSTERONE REPLACEMENT

Androgen therapy is indicated to restore testosterone levels to normal to correct features of androgen deficiency. Testosterone replacement improves libido and overall sexual activity; increases energy, lean muscle mass, and bone density; and decreases fat mass. The benefits of testosterone replacement therapy have only been proven in men who have documented androgen deficiency, as demonstrated by testosterone levels that are well below the lower limit of normal.

Testosterone is available in a variety of formulations with distinct pharmacokinetics (Table 411-3). Testosterone serves as a prohormone and is converted to 17β-estradiol by aromatase and to 5α-dihydrotestosterone by steroid 5α-reductase. Therefore, when evaluating testosterone formulations, it is important to consider whether the formulation being used can achieve physiologic estradiol and DHT concentrations, in addition to normal testosterone concentrations. Although testosterone concentrations at the lower end of the normal male range can restore sexual function, it is not

TABLE 411-3 CLINICAL PHARMACOLOGY OF SOME TESTOSTERONE FORMULATIONS

Formulation	Regimen	Pharmacokinetic Profile	DHT and E ₂	Advantages	Disadvantages
Testosterone enanthate or cypionate	150–200 mg IM q2wk or 75–100 mg/wk	After a single IM injection, serum T levels rise into the supra-physiologic range, then decline gradually into the hypogonadal range by the end of the dosing interval	DHT and E ₂ levels rise in proportion to the increase in T levels; T:DHT and T:E ₂ ratios do not change	Corrects symptoms of androgen deficiency; relatively inexpensive, if self-administered; flexibility of dosing	Requires IM injection; peaks and valleys in serum T levels
Topical testosterone gels and axillary testosterone solution	Available in sachets, tubes, and pumps	When used in appropriate doses, these topical formulations restore serum T and E ₂ levels to the physiologic male range	Serum DHT levels are higher and T:DHT ratios are lower in hypogonadal men treated with the transdermal gels than in healthy eugonadal men	Corrects symptoms of androgen deficiency, provides flexibility of dosing, ease of application, good skin tolerability	Potential of transfer to a female partner or child by direct skin-to-skin contact; skin irritation in a small proportion of treated men; moderately high DHT levels; considerable interindividual and intraindividual variation in on-treatment T levels
Transdermal testosterone patch	1 or 2 patches, designed to nominally deliver 5–10 mg T over 24 h applied every day on nonpressure areas	Restores serum T, DHT, and E ₂ levels to the physiologic male range	T:DHT and T:E ₂ levels are in the physiologic male range	Ease of application, corrects symptoms of androgen deficiency	Serum T levels in some androgen-deficient men may be in the low-normal range; these men may need application of 2 patches daily; skin irritation at the application site occurs frequently in many patients
Buccal, bioadhesive, testosterone tablets	30-mg controlled-release, bioadhesive tablets bid	Absorbed from the buccal mucosa	Normalizes serum T and DHT levels in hypogonadal men	Corrects symptoms of androgen deficiency in healthy, hypogonadal men	Gum-related adverse events in 16% of treated men
Testosterone pellets	2–6 pellets implanted SC; dose and regimen vary with formulation	Serum T peaks at 1 month and then is sustained in normal range for 3–6 months, depending on formulation	T:DHT and T:E ₂ ratios do not change	Corrects symptoms of androgen deficiency	Requires surgical incision for insertions; pellets may extrude spontaneously
17-α-Methyl testosterone	This 17-α-alkylated compound should not be used because of potential for liver toxicity	Orally active			Clinical responses are variable; potential for liver toxicity; should not be used for treatment of androgen deficiency
Oral testosterone undecanoate ^a	40–80 mg PO bid or tid with meals	When administered in oleic acid, T undecanoate is absorbed through the lymphatics, bypassing the portal system; considerable variability in the same individual on different days and among individuals	High DHT:T ratio	Convenience of oral administration	Not approved in the United States; variable clinical responses, variable serum T levels, high DHT:T ratio
Injectable long-acting testosterone undecanoate in oil ^a	European regimen 1000 mg IM, followed by 1000 mg at 6 weeks, and 1000 mg every 10–14 weeks	When administered at a dose of 750–1000 mg IM, serum T levels are maintained in the normal range in a majority of treated men	DHT and E ₂ levels rise in proportion to the increase in T levels; T:DHT and T:E ₂ ratios do not change	Corrects symptoms of androgen deficiency; requires infrequent administration	Requires IM injection of a large volume (4 mL); cough reported immediately after injection in a very small number of men
Testosterone-in-adhesive matrix patch ^a	2 × 60 cm ² patches delivering approximately 4.8 mg of T/d	Restores serum T, DHT, and E ₂ to the physiologic range	T:DHT and T:E ₂ are in the physiologic range	Lasts 2 d	Some skin irritation

^aThese formulations are not approved for clinical use in the United States, but are available outside the United States in many countries. Physicians in those countries where these formulations are available should follow the approved drug regimens.

Abbreviations: DHT, dihydrotestosterone; E₂, estradiol; T, testosterone.