ABSTRACT

The basic desire to restore that which makes a man feel vital again is essentially what drives hormone replacement therapy in hypogonadism. Therefore, the goals of therapy are focused on restoring sexual function, libido, and a sense of well-being. Therapeutic options are currently limited to testosterone products, which restore physiologic range serum testosterone levels, and allow for optimal virilization and normal sexual function. The benefits of testosterone therapy in hypogonadal men are supported by several trials and include improvements in sexual function, mood and energy, fat-free mass and muscle strength, hemoglobin levels, and bone mineral density. (Adv Stud Pharm. 2006;3(4):149-155)

TREATMENT

The basic desire to restore that which makes a man feel vital again is essentially what drives hormone replacement therapy in hypogonadism. Therefore, the goals of therapy are focused on restoring sexual function, libido, and a sense of well-being. Therapeutic objectives also include improving health outcomes, such as restoring fertility and virilization, raising hemoglobin levels, and increasing bone mineral density to prevent osteoporosis. Treatment of hypogonadism should be considered if the patient exhibits reduced testosterone levels and experiences symptoms, such as impaired sexual function, mood, and cognition, in addition to physiologic conditions such as reduced hemoglobin and bone mineral density. Therapeutic options are currently limited to testosterone products, which restore physiologic range serum testosterone levels (generally between 280 and 800 ng/dL), and allow for optimal virilization and normal sexual function. The benefits of testosterone therapy in hypogonadal men are supported by several trials and include improvements in sexual function, mood and energy, fat-free mass and muscle strength, hemoglobin levels, and bone mineral density. However, erectile dysfunction associated with hypogonadism may not improve after adequate androgen replacement if other secondary causes for erectile dysfunction are present.

Current formulations of testosterone include oral, buccal, sublingual, transdermal, intramuscular (IM), and implantable products. These various dosage forms are similar in efficacy, but differ in regard to dosing and side-effect profiles. Because of the extensive first-pass metabolism of orally administered testosterone products and toxicity profile of esterified oral testosterone, other available product formulations are preferred. Patient preference, individual side effects, and...
cost of these products influence the choice of drug therapy. Table 1 compares the currently available testosterone products. In general, testosterone products are tolerable. Prostate and breast cancer and a hematocrit above 55% are the only contraindications to the use of testosterone in men. Men should be screened for prostate cancer before treatment, and continual prostate-specific antigen (PSA) and digital rectal examination are recommended while on therapy, although evidence for the development of prostate cancer in testosterone-treated individuals is lacking.2 The use of testosterone in women has been studied, but is beyond the scope of this article. Testosterone has a pregnancy category X, and should not be used in women who are pregnant due to the risk of teratogenic effects.

Cardiovascular (CV) complications with testosterone replacement have been proposed but are unsubstantiated. Evidence is largely based on male-female event rate differences and reports of increased CV events in athletes using high doses of oral nonaromatizable androgens (anabolic steroids).3,4 Therapeutic use of testosterone in hypogonadal men has not been associated any increase in CV risk.5 In the majority of studies, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels remained unchanged with testosterone therapy. Few studies reported reductions in HDL cholesterol, and fewer noted changes in LDL cholesterol.6 Nevertheless, monitoring of serum lipids at baseline and follow-up are recommended in patients receiving testosterone therapy. Although testosterone replacement therapy is not correlated with increased CV risk, higher cholesterol levels are an independent risk factor, and it is therefore, appropriate to treat uncontrolled hyperlipidemia as per current accepted guidelines.7

Infertility is common due to the negative feedback loop of testosterone production on spermatogenesis. Sleep apnea also occurs more frequently in patients prescribed testosterone, and should be monitored throughout treatment. Testosterone replacement therapy also has been infrequently linked to fluid retention and hypertension, which generally occur within the first 1 to 3 months of therapy and appear to be more common with IM injections. Additional reported adverse effects include hepatotoxicity, erythrocytosis, and topical irritation (largely related to the product formulation; Table 1).

INTRAMUSCULAR LONG-ACTING TESTOSTERONE ESTERS

Testosterone has been used intramuscularly since the early part of the 1900s. Testosterone cypionate and testosterone enanthate are both available in esterified oil soluble formulations and have very similar pharmacokinetic profiles.8 Doses range from 100 mg IM weekly to 300 mg every 2 to 3 weeks. Peak concentrations occur approximately 10 hours after administration and the terminal half-life is 4 to 5 days. The typical dosing interval is every 2 to 3 weeks. One potential disadvantage of this regimen is that blood testosterone levels often rise sharply to supraphysiologic values during the first few days following injection and then fall over time until the next dose. As a result, patients lose the normal circadian fluctuations of testosterone with this dosing formulation and are likely to experience periods of symptomatic improvement followed by inefficacy prior to the next dose. Injection site discomfort and the need for frequent office visits further limit IM testosterone acceptability. Acne, gynecomastia, polycythemia, and erythrocytosis are common side effects due to the high peak concentrations following injection. Despite the aforementioned problems with IM injections, longtime use and lower medication cost assures continued use of this product formulation.9

TRANSDERMAL TESTOSTERONE PATCHES AND GEL

These products were designed to improve the tolerability of IM administered testosterone and maintain more steady concentrations of testosterone in the body.10 Transdermal preparations are generally more convenient to use than other preparations. When dosed properly, they produce more physiologic testosterone blood levels and cause fewer side effects than injectable testosterone esters. Although these products are significantly more costly than injections, the elimination of office visits for injections may make this form of treatment cost effective.11 Transdermal testosterone is available in scrotal and nonscrotal transdermal systems and gel. Because of the large amount of testosterone needed for absorption, the scrotal site provides the advantage of increased permeability versus other skin surfaces (20–30 times better penetration).8 The scrotal patch is available as a thin film covered with 10 to 15 mg of testosterone.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Names</th>
<th>Dosage</th>
<th>Time to Peak Concentrations</th>
<th>Product-specific Side Effects</th>
<th>Pearls of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular testosterone</td>
<td></td>
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<tr>
<td>Testosterone cypionate</td>
<td>Depo-Testosterone</td>
<td>50 mg–400 mg every 2–4 weeks</td>
<td>24 hours</td>
<td>Injection site bleeding/pain; mood swings; polycythemia; erythrocytosis</td>
<td>- Dosing weekly or every other week</td>
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<tr>
<td>Testosterone enanthate</td>
<td>Delatestryl</td>
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<tr>
<td>Topical testosterone</td>
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<tr>
<td>Scrotal patches</td>
<td>Testoderm; Testoderm with adhesive</td>
<td>6 mg/day applied to scrotal skin and worn for 22–24 hours</td>
<td>Product specific; 2–24 hours</td>
<td>Scrotal: application difficulty; discomfort and irritation; increased DHT levels</td>
<td>- Scrotal: apply in AM to clean, dry, shaven scrotal skin</td>
</tr>
<tr>
<td>Nongenital patches</td>
<td>Androderm</td>
<td>5 mg–7.5 mg/day applied nightly for 24 hours</td>
<td></td>
<td>Nongenital patch: topical irritation</td>
<td>- Nongenital: apply at bedtime</td>
</tr>
<tr>
<td>Gel</td>
<td>Androgel</td>
<td>5–10 g applied daily in the morning</td>
<td>4–8 hours, depending on product and dose</td>
<td>Gel: topical irritation</td>
<td>- Gel: apply to skin of shoulders and/or upper arms; potential of transfer to a female partner or child by vigorous skin-to-skin contact. Avoid applying to abdomen or genitals</td>
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<tr>
<td></td>
<td>Testim</td>
<td>5–10 g applied daily in the morning</td>
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<tr>
<td>Oral alkylated testosterones</td>
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<tr>
<td>Methyl testosterone</td>
<td>Androtest, Testrid, Vinilon, and Methitest</td>
<td>10 to 50 mg daily</td>
<td>6 hours</td>
<td>Not used due to hepatotoxicity</td>
<td>- Alkylation at 17α-position improves bioavailability</td>
</tr>
<tr>
<td>Fluoxymesterone</td>
<td>Halotestin</td>
<td>5 to 20 mg daily</td>
<td></td>
<td></td>
<td>- Dose-independent hepatotoxicity</td>
</tr>
<tr>
<td>Buccal testosterone</td>
<td>Striant</td>
<td>One buccal system (30 mg) BID, 12 hours apart</td>
<td>0.4–12 hours</td>
<td>Gum irritation; erythrocytosis</td>
<td>- Patient acceptability is favorable</td>
</tr>
<tr>
<td>Subcutaneous testosterone</td>
<td>Testopel</td>
<td>75 mg</td>
<td>63 days</td>
<td>Localized infection, bleeding, and fibrosis; extrusion</td>
<td>- Should be placed in a comfortable position just above the incisor tooth on either side of the mouth; rotate to alternate sides of the mouth with each application</td>
</tr>
<tr>
<td>Testosterone pellets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Hold the buccal system in place against the gum with a finger over the lip for 30 seconds</td>
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<td></td>
<td></td>
<td></td>
<td>- Should not be chewed or swallowed</td>
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</table>

BID = twice daily; DHT = dihydrotestosterone.
Scrotal skin must be shaved prior to application. Patients wear the patch for 22 to 24 hours, then replace it. Serum testosterone levels peak in 2 to 4 hours and remain therapeutic while the patch is adhered. Discomfort, irritation, and inadequate scrotal surface adhesion limit use. Because genital skin contains high concentrations of 5α-reductase, increased dihydrotestosterone (DHT) levels have been noted in patients using the scrotal patch. Although DHT is known to be involved in prostate development, no correlation between patch use and prostate cancer has been found. Nevertheless, careful monitoring of prostate growth is recommended.

Nonscrotal testosterone patches are also available, and although less absorption occurs at the nonscrotal dermal areas of the body, a reservoir of testosterone allows for daily administration on nonhairy areas of the body, such as the back, abdomen, upper arms, and thighs. Nighttime application is recommended because it reproduces diurnal testosterone levels similar to those seen in younger men, in whom morning values are somewhat higher than evening ones. Rotation of sites is recommended daily due to the high incidence of localized skin irritation in approximately 50% of patients. This side effect may be reduced by assuring that the patient does not apply the patch to bony areas or pressure points. A steroid cream or spray may also be used to reduce allergic-type reactions, but some patients may still require discontinuation of use.8,10

Another transdermal option is testosterone gel, a hydroalcoholic preparation that is usually dosed at 5 to 10 g of gel a day (50–100 mg of testosterone).10 The gel should be applied once daily to clean, dry intact skin of the shoulders and/or upper arms (avoiding the abdomen and genitals), and patients should be instructed to rub the gel vigorously into the skin until the application area is dry. Absorption is not improved by increased body surface area exposure, so patients should be advised to limit application to one area at a time.11 Once applied, the steroid is absorbed into the stratum corneum where it acts as a reservoir for systemic testosterone absorption. Despite the application of the gel without any occlusive barrier, transmission of testosterone is not likely after the gel has dried. Even washing the skin 10 minutes after application will not result in observable changes in drug absorption.12 Nevertheless, pregnant and nursing women should avoid skin contact with gel application sites in men. Depending on the product and dose used, peak testosterone levels are achieved in 4 to 8 hours (depending on dose) and levels remain constant over 24 hours. In a multicenter study evaluating 1 testosterone gel product, adequate testosterone levels were maintained over 12 months of treatment in most patients, with increases in sexual function seen at 30 days of therapy, decreases in fat mass and increases in lean body mass seen at 90 days of therapy, and increases in bone mineral density noted at 12 months of therapy. Compared to transdermal patch formulations, testosterone gel is associated with less skin irritation.

Initial starting doses of the 2 currently marketed testosterone gel formulations are 5 mg/day (50 mg of gel), followed by 2.5 mg dose titrations every 2 to 4 weeks to achieve therapeutic testosterone levels or a maximum dose of 10 mg/day. Absorption characteristics of the 2 gels are slightly different, with Testim 1% (Auxilium Pharmaceuticals, Inc., Malvern, PA) topical gel allowing for approximately a one-third greater bioavailability over Androgel 1% (Solvay Pharmaceuticals, Marietta, GA).13 Patients taking Testim 1% gel at the same dose as Androgel 1% gel should be expected to achieve greater changes from baseline in testosterone levels. Well-designed comparative efficacy studies between the products have not been published to date, but it is reasonable to conclude that titration of doses would be required more frequently with Androgel 1% versus Testim 1% in order to achieve therapeutic testosterone concentrations and improved efficacy.

**ORAL 17-α ALKYLATED ANDROGENS**

Because first-pass metabolism of orally administered testosterone is extensive, alkylated formulations were developed. However, these formulations are not recommended for general use because of their association with poor androgen effects, adverse lipid changes, and hepatic side effects, such as hemorrhagic liver cysts, cholestasis, and hepatocellular adenoma.1 Research continues with promising prospects for other oral dosage forms in the future.

**SUBLINGUAL OR BUCCAL PREPARATIONS**

Continuous replacement of testosterone can also be achieved through buccal or sublingual absorption of testosterone. A buccal tablet is currently available, which, through proper administration, results in controlled and
sustained release of testosterone, with peak concentrations occurring in 10 to 12 hours. Testosterone levels reach steady state after two 12-hour doses of the product, and return to baseline within 2 to 4 hours after discontinuation. To apply, the tablet is inserted above the incisor tooth on one side of the mouth. Patients should be encouraged to rotate the side of the mouth when the tablet is replaced at the next dosing interval. The rounded side of the tablet should face the gum, and held in place with a finger over the lip for 30 seconds to assure good adhesion. The product is designed to stay in place throughout the 12-hour dosing interval, but if the tablet is dislodged within the first 8 hours of placement, the tablet should be removed and replaced. If the tablet dislodges within 4 hours of the next dose, the next tablet may be used and left in until the next scheduled dosing time. Patients should be encouraged to eat and drink as they normally do, but not to intentionally dislodge the medication. Patients have reported gum irritation and some intolerability with the buccal tablet, but, overall, the product is acceptable to most patients.14

**Implantable (Subcutaneous) Testosterone**

Minor surgical implantation of subcutaneous testosterone is also available. Slow release of the testosterone occurs over a 6-month time frame, after which, a new implantation can be inserted. The benefits of this formulation include compliance, steady testosterone levels, and patient acceptability. This formulation does not produce the normal diurnal variation of the daily patches or buccal products, and is not as readily accessible to patients. Patients are also at risk of localized infections and extrusions as a result of implantation.8

**Application in Clinical Practice**

Pharmacists should play a proactive role in identifying, treating, educating, and monitoring patients with hypogonadism (Table 2). Simple screening procedures can be implemented in pharmacies to help identify patients who might otherwise not approach their healthcare professional. Because drops in testosterone levels occur progressively, beginning at about the fifth decade of life in a gradual fashion,15 many patients and practitioners may not interpret the signs and symptoms of hypogonadism as requiring replacement therapy. However, the major complications of hypogonadism, including anemia, depression, and cognitive decline, occur in addition to decreased sexual function. Therefore, it seems only logical to treat the underlying cause of these multisystem dysfunctions, rather than the sign or symptom itself. Pharmacists are in a unique and influential position to help recognize hypogonadal patients and initiate patient and healthcare provider treatment and education.

The use of testosterone replacement therapy should be described to the patient in detail. Patients should be aware of the typical side effects of the product formulation they are taking, and have reasonable expectations in regard to the benefits of replacement therapy. Each product formulation has a different application procedure, which should be described to the patient and suggestions to improve tolerability should also be made.

**Monitoring**

Patient’s testosterone levels reach steady-state concentrations within hours to days following drug initiation, and symptom relief is expected early in therapy. Improvement in libido, mood, and cognitive function should be monitored closely, along with hematocrit, bone density, and lean body mass (Table 2). The patient is usually evaluated 3 months after treatment starts and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects. Prostate evaluations, including PSA levels, are usually performed

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**Table 2. Role of the Pharmacist**

- Screen patients (use a modified ADAM questionnaire)
- Assist in drug selection
  - Look for contraindications
  - Identify cost-effective, patient-preferred therapy
- Educate on drug use
- Assure appropriate follow-up
  - Efficacy: improvement in symptoms, serum testosterone
  - Safety: baseline–HCT, PSA, lipid profile
  1. Follow-up: drug-specific SE, HCT, and lipid profile in 3 months, PSA in 6 months, urinary function, DRE, sleep apnea, and blood pressure

ADAM = Androgen Deficiency in Aging Males; DRE = digital rectal examination; HCT = hematocrit; PSA = prostate-specific antigen; SE = side effects.
before initiating treatment, at 3 months, and then in accordance with guidelines for prostate cancer screening. In addition, patients should have blood pressure readings and hematocrit measurements at 3 and 6 months after initiating treatment and annually thereafter. Monitoring for product-specific side effects, assessments for likelihood of side effects being drug-related, and alternative product suggestions are all essential functions that pharmacists should undertake. Patients treated with buccal testosterone tablets should be asked about alterations in taste and irritation of the gums. Those receiving injectable testosterone esters should be questioned about fluctuations in mood or libido. And, patients given testosterone patches should be evaluated for skin reactions at the application site.

**ONGOING AND COMPLETED TRIALS**

Necessity is certainly the mother of invention, especially when it comes to filling in for the lack of orally active androgen preparations with good efficacy. Thus, when looking toward future agents, orally active selective androgen receptor modulators (SARMs) appear to be promising. Analogous to selective estrogen receptor modulators, these investigational compounds are being designed to provide tissue selectivity by targeting certain androgen receptors, while leaving others intact. For the treatment of primary or secondary male hypogonadism, researchers are envisioning the ideal SARM to be a once-daily oral agent that is capable of stimulating the seminal vesicles and other sex accessory tissues at doses equipotent to those needed to increase muscle mass, support bone growth, and maintain/restore libido and virilization. By virtue of their selectivity, these agents should exert minimal undesirable testosterone-related effects, such as potential liver toxicity, hypertension, fluid retention, prostate growth, gynecomastia, and overstimulation of erythropoiesis. Thus far, animal studies with the SARM S-40503 have shown increases in osteoblastic activity with minimal prostate growth.

Another compound under development is 7α-methyl-19-nortestosterone (MENT), an agent that is approximately 10 times more potent than testosterone in anabolic activities and gonadotropin suppression, yet has minimal stimulatory effects on prostate growth. MENT has been shown in trials of hypogonadal men to enhance sexual function, energy, and mood, in addition to ameliorating depression and lethargy. Exogenous DHT has also sparked the interest of researchers because DHT is not a substrate for aromatase, thus it is not a source of estradiol. This feature appears favorable in hypogonadal men with gynecomastia or microphallus.

Also under investigation are various delivery forms of testosterone, such as testosterone buccilate, a long-acting IM testosterone injection that maintains activity for up to 12 weeks. Unlike other IM injections, this product is reported to produce more stable serum androgen levels, without the supraphysiologic peak that can occur within several days of administering long-acting injections. Injectable microcapsules consisting of 267 mg of testosterone encapsulated in a biodegradable matrix is another investigational delivery form that appeared promising but has not come to fruition. The product releases testosterone over 12 weeks, restoring androgen to eugonadal levels. And, although well tolerated, testosterone micro is fraught with chemical stability problems.

**CONCLUSIONS**

As with other drugs that cannot be used orally, testosterone has been reinvented in a variety of formulations that bring promise of a convenience similar to that of the irreplaceable pill. And, although these formulations are designed to be patient-friendly, each comes with specific instructions, which if not followed correctly, can result in inadequate absorption, needless discomfort, or other problems leading to patient noncompliance or physician-instructed discontinuation of therapy. By thoroughly counseling patients on the proper use of these products, pharmacists can ensure that patients receive optimal benefits from testosterone replacement therapy. And, with increasing focus on quality of life and increasing prevalence of age-related conditions, such as late-onset hypogonadism, pharmacists will find themselves dispensing more hormone replacement products, in addition to information about the actual condition and the expected effects of treatment. Many pharmacists have become experts in counseling patients on major disease states, such as asthma and hypertension. A 5-minute conversation with a pharmacist can prevent an asthma-related emergency room visit or a hypertensive crisis. Now it’s time that pharmacists offer those same kinds of second-nature services to patients who are willing to come forward with underdetected and undertreated conditions.
such as hypogonadism.

REFERENCES