Current Data and Considerations

Novel Testosterone Formulations
Objectives

- Identify desirable characteristics of ideal testosterone formulations
- Review efficacy and safety of testosterone therapy
- Review testosterone formulations
  - Dosage and administration
  - Pharmacokinetic parameters
The ideal testosterone formulation should provide treatment for hypogonadism that produces physiologic levels of testosterone for prolonged periods and has a favorable safety profile. The dosing schedule and administration method should be convenient for the patient. Ideally, all of these attributes would be found in a formulation that was reasonably priced.

Testosterone Update

Current and Novel Testosterone Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injectables</strong></td>
<td></td>
</tr>
<tr>
<td>Pellet implants&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4 (200 mg) subcutaneous pellets Q 5 to 7 months</td>
</tr>
<tr>
<td>Testosterone cypionate/enanthate&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>50 to 400 mg Q 2 to 4 weeks</td>
</tr>
<tr>
<td>Testosterone undecanoate&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1,000 mg Q 6 weeks during first 12 weeks then 1,000 mg Q 3 months</td>
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<tr>
<td><strong>Topical</strong></td>
<td></td>
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<tr>
<td>Topical gel&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>5 to 10 g daily</td>
</tr>
<tr>
<td>Transdermal patch system&lt;sup&gt;7&lt;/sup&gt;</td>
<td>5 mg daily</td>
</tr>
<tr>
<td><strong>Oral</strong></td>
<td></td>
</tr>
<tr>
<td>Buccal system&lt;sup&gt;8&lt;/sup&gt;</td>
<td>30 mg Q 12 hours</td>
</tr>
<tr>
<td>Fluoxymesterone&lt;sup&gt;9&lt;/sup&gt;</td>
<td>5 to 20 mg daily</td>
</tr>
<tr>
<td>Testosterone undecanoate&lt;sup&gt;10&lt;/sup&gt;</td>
<td>120 to 160 mg daily during first 2 to 3 weeks then 40 to 120 mg daily</td>
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</tbody>
</table>

<sup>1</sup>In development in United States.
<sup>2</sup>Not available in United States.

A variety of injectable, topical, and oral testosterone formulations are available or in development. Testosterone pellets are implanted in outpatient minor surgical procedures. Four 200-mg pellets are implanted under the skin of the lateral abdominal wall or the buttocks, according to patient preference. Depending on individual patient characteristics, the pellets are effective for 5 to 7 months.<sup>1</sup>

Testosterone cypionate and testosterone enanthate are available for intramuscular injection. The replacement dosage of either testosterone cypionate or testosterone enanthate for hypogonadal men is 50 mg to 400 mg administered every 2 to 4 weeks.<sup>2,3</sup>

Testosterone undecanoate for intramuscular injection is a novel, long-acting formulation in development in the United States. It has an improved pharmacokinetic profile compared with oral testosterone undecanoate. After 2 initial injections of 1,000 mg every 6 weeks, the dosage interval can be increased to 1,000 mg every 3 months.<sup>4</sup>

Topical testosterone gel is available in non-aerosol metered-dose pumps and unit-dose aluminum foil packets. The recommended starting dose is 5 g/day, which can be increased to 7.5 g and 10 g as needed to achieve testosterone concentrations in the normal range.<sup>5,6</sup>

The testosterone transdermal patch system provides continuous delivery of testosterone for 24 hours after application to intact, nonscrotal skin (eg, back, abdomen, thighs, upper arms). The usual starting dose is one 5-mg patch or two 2.5-mg patches applied nightly for 24 hours, providing a total dose of 5 mg/day. Serum testosterone concentrations outside the normal range may require increasing the daily dose to 7.5 mg (ie, one 5-mg and one 2.5-mg patch, or three 2.5-mg patches) or decreasing the daily dose to 2.5 mg (ie, one 2.5-mg patch), maintaining nightly application.<sup>7</sup>

The testosterone buccal system adheres to the gum or inner cheek and releases a controlled, sustained amount of testosterone through the buccal mucosa as the system gradually hydrates. One system, containing 30 mg of testosterone, is inserted twice daily.<sup>8</sup>

Tablets containing 10 mg of the androgenic hormone fluoxymesterone are available in the United States; however, the product label warns that prolonged use of high doses of androgens has been associated with the development of hepatic adenomas, hepatocellular carcinoma, and peliosis hepatis, which are potentially life-threatening conditions.<sup>9</sup>

Oral capsules containing testosterone undecanoate are not available in the United States. The initial dosage required is usually 120 mg to 160 mg daily for 2 to 3 weeks, which can then be reduced to 40 mg/day to 120 mg/day depending on the clinical effect obtained during the first weeks of therapy.<sup>10</sup>

A randomized, multicenter, parallel study compared 2 doses of testosterone gel (T gel) with a testosterone patch (T patch) in 227 hypogonadal men. The study was double-blind with regard to T gel dosage and open label for the T patch. For the first 90 days of the study, subjects received 50 mg/day (N=73) or 100 mg/day (N=78) for the T gel or 2 nonscrotal patches delivering 5 mg/day (N=76). Dosage adjustments were made in the T gel group if the serum concentration of testosterone on day 90 was outside the normal range (10.4–34.7 nmol/L). Only data for the first 90 days are shown here.

Sexual function and mood were assessed by patients who completed questionnaires daily for 7 consecutive days before clinic visits at baseline and every 30 days thereafter. Patients rated their sexual desire on a 7-point Likert-type scale and assessed the percentage of full erection from 0 to 100%.

Maximum improvement in sexual desire was achieved by day 30 of treatment in the T gel 100 mg/day group and by day 60 in the other treatment groups. No further improvements were seen after dosage adjustment on day 90 (data not shown). Overall, transdermal treatment significantly increased sexual desire ($P=0.0001$), without differences between groups.

Overall, men receiving testosterone replacement with either T gel or T patch transdermal formulations reported a significant increase in the percentage of full erections ($P = .0001$), with no significant differences between treatment groups. In all 3 treatment groups, the maximum therapeutic effect was achieved at 60 days.

A cross-sectional population-based study of 856 community-dwelling men aged 50 to 89 years (mean age, 70.2 years) examined the association between endogenous sex hormones and depressed mood, assessed with the Beck Depression Inventory (BDI). Higher scores on the BDI indicate a depressed mood.

Bioavailable testosterone decreased significantly with age. As shown here, after adjusting for age, as bioavailable testosterone levels decreased, the level of depression increased significantly ($P_{trend} < .01$).

This study comparing 2 doses of T gel and the T patch in 227 hypogonadal men found that transdermal testosterone replacement improves mood.

Men receiving T gel 50 or 100 mg/day or T patch 5 mg/day rated their mood on a scale from 0 to 7. Both positive mood responses (alert, friendly, energetic, well/good feelings) and negative mood responses (angry, irritable, sad, tired, nervous) were rated, and weekly average scores were calculated.

Overall, the men receiving transdermal testosterone replacement showed significant improvements in positive mood scores and decreases in negative mood scores during the first 90 days of treatment, with no between-group differences.

Changes seen as men age include a decrease in serum testosterone levels, an increase in body fat mass, and a decrease in lean body mass. These changes are similar to those seen in hypogonadal men. Therefore, changes in body composition were measured in 108 men older than 65 years who were randomized in double-blind fashion to treatment with either a testosterone patch or a placebo patch for 36 months. Men with a serum testosterone concentration 1 SD or more below the mean normal for young men (<475 ng/dL) were included in the study; men with diseases or taking medications known to cause hypogonadism were excluded. Changes in body composition were measured by dual energy x-ray absorptiometry (DEXA).

Ninety-six men completed the 36-month protocol. In men treated with testosterone, mean serum testosterone concentrations increased significantly (*P*<.001) from 367 ng/dL before treatment to 625 ng/dL by the sixth month of treatment and remained stable for the remainder of the study. No increase in mean serum testosterone levels occurred in placebo-treated men.

Testosterone-treated men, but not placebo-treated men, experienced a significant decrease in fat mass (-3.0 kg, *P*=.001) during the 36 months of treatment. The changes seen in the testosterone-treated group were a function of the pretreatment serum testosterone level but not the increase in testosterone during treatment. Decreases in fat mass in the testosterone group were significant in the arms (-0.7 kg, *P*<.001) and legs (-1.1 kg, *P*<.001) but not in the trunks of the men studied.

Changes in lean mass in the 96 men who completed 36 months of treatment with either a testosterone patch or a placebo patch are shown here. At 36 months, lean mass increased significantly from baseline (1.9 kg, \( P < .001 \)) in those treated with testosterone but not in those treated with placebo. The changes seen in the testosterone-treated group were a function of the pretreatment serum testosterone level but not the increase in testosterone during treatment. In contrast to the decrease in fat mass, the increase in lean mass was significant in the trunk (1.7 kg, \( P < .001 \)) but not in the arms and legs of the men studied.

Testosterone therapy is known to increase bone mineral density (BMD) in healthy, hypogonadal men, but its effects on fracture risk in older hypogonadal men, who are at increased risk of fractures, remain unclear. Therefore, a 36-month, randomized, double-blind, placebo-controlled trial was conducted in 70 men aged 65 years and older with a serum testosterone level less than 350 ng/dL on 2 occasions to determine the effects of intramuscular testosterone enanthate (200 mg every 2 weeks) with or without oral finasteride (5 mg/day) on BMD. Serial measurements of BMD at the lumbar spine (L1-L4; anteroposterior view only) and in the nondominant hip were obtained at baseline and every 6 months thereafter using dual x-ray absorptiometry (DEXA).

A total of 50 men completed the 36-month study; but all men were included in an intent-to-treat analysis for as long as they contributed data. At baseline, BMD for the hip and lumbar spine in study participants was similar to that for a standard male population of the same age. As shown here, treatment with testosterone with and without finasteride significantly increased lumbar spine BMD from baseline ($P<.01$). Increases in lumbar BMD correlated positively with the magnitude of increase in serum total testosterone ($r=0.44$, $P=.001$).

In the 36-month study of men with late-onset hypogonadism, treatment with testosterone with and without finasteride significantly increased total hip BMD from baseline at the end of treatment ($P<.01$). Total hip BMD was unchanged in the placebo group.

## Potential Class Adverse Effects of Testosterone Treatment

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>Prostate cancer&lt;sup&gt;1-8&lt;/sup&gt;</td>
<td>Controversial; no causal relationship established</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia&lt;sup&gt;1-6&lt;/sup&gt;</td>
<td>Infrequently worsened in men with mild or moderate LUTS; avoid in men with severe LUTS (weak data)</td>
</tr>
<tr>
<td>Testicular atrophy or infertility&lt;sup&gt;1-6&lt;/sup&gt;</td>
<td>Common, especially in young men; usually reversible when treatment stops</td>
</tr>
<tr>
<td>Sleep apnea&lt;sup&gt;3,5,7&lt;/sup&gt;</td>
<td>Infrequent; controversial</td>
</tr>
<tr>
<td>Acne and oily skin&lt;sup&gt;1-6&lt;/sup&gt;</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Gynecomastia&lt;sup&gt;1-6&lt;/sup&gt;</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Fluid retention&lt;sup&gt;1-6&lt;/sup&gt;</td>
<td>Rarely of clinical significance; of concern only in men with class III or IV heart failure, chronic renal insufficiency, or severe liver disease</td>
</tr>
</tbody>
</table>

In the United States, product labels for testosterone replacement formulations contain standard warnings regarding prostatic hypertrophy and prostatic hyperplasia, suppression of spermatogenesis, acne and oily skin, gynecomastia, and fluid retention<sup>1-6</sup>. In addition, the product labeling for the testosterone buccal system includes a warning that treatment of hypogonadal men with testosterone esters may potentiate sleep apnea, especially in patients with risk factors such as obesity or chronic lung disease. However, the Endocrine Society Clinical Practice Guideline for testosterone therapy notes that this condition arises infrequently in young hypogonadal men.<sup>3,7</sup>

With regard to prostate cancer, the American Association of Clinical Endocrinologists guidelines for the treatment of hypogonadism in adult males state that, despite anecdotal reports, no causal relationship has been established between testosterone treatment and prostate cancer.<sup>8</sup>

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Formulation-specific adverse effects can occur with testosterone replacement therapy. Testosterone pellets are implanted in an office-type minor surgical procedure, which carries the risk of infection or expulsion. Intramuscular injections of testosterone cypionate, enanthate, or undecanoate (in development in the United States) may cause pain at the injection site. Testosterone cypionate or enanthate may cause fluctuations in mood or libido and excessive erythrocytosis, particularly in older patients. The testosterone topical gel can potentially be transferred to the patient’s partner. Patients should cover the application site with clothing and wash skin and hands with soap before having skin-to-skin contact. Transdermal testosterone patches may cause skin irritation at the application site. The testosterone buccal system may cause alterations in taste and gum irritation.

An open-label, nonrandomized clinical trial in Germany investigated the efficacy and safety of an injectable testosterone undecanoate (TU) formulation in 7 men aged 20 to 57 years with hypogonadism who had participated in a previous trial of 6-week injections of TU and agreed to continue treatment.\(^1\),\(^2\)

The men received 4 injections of TU at 6-week intervals. Between the 5th and 10th weeks, the intervals were increased, and from the 10th week onward, TU was injected every 12 weeks. As shown here, weekly measurements of testosterone concentrations demonstrated steady-state kinetics after the 13th injection. With extended injection intervals, testosterone levels measured before the next injection decreased and were at the lower limit of normal, measuring 12.6±3.7 nmol/L before the final injection.\(^1\),\(^2\)


Testosterone Update

Results From Long-Term Safety Study* of Testosterone Undecanoate IM

- Serum trough testosterone levels within normal range
- Individual dosing intervals ranged from 10 to 14 weeks
- Patients treated for up to 8.5 years
- Patients reported restoration of sexual function and positive mood changes
- No report of mood fluctuations
- Hemoglobin and hematocrit within normal range
- Prostate size <30 mL
- PSA concentrations <2.0 µg/L
- Bone density improved

*N=22 patients aged 30 to 65 years (mean 43.8 ± 8 years), study duration 8.5 years.

Twenty-two hypogonadal patients aged 30 to 65 years (mean age 43.8 years) were treated with the long-acting ester testosterone undecanoate injected in a dosage of 1,000 mg at intervals of 10 to 14 weeks. Patients reported restored sexual function, improved vigor, and decreased depression. Fluctuations in mood often seen with short-acting testosterone preparations were not reported. Although treatment was associated with elevations in hemoglobin and hematocrit, values remained within normal limits. Prostate size remained less than 30 mL, and prostate-specific antigen (PSA) values were ≤2.0 µg/L. Quantitative computed tomography of the lumbar spine showed improvements in bone density. Testosterone undecanoate was well tolerated. The only adverse effect was moderate local irritation at the injection site that did not last more than 3 days.

Pharmacokinetics: Testosterone Enanthate

Mean serum concentrations of testosterone in 10 hypogonadal men receiving intramuscular injection of 200 mg of testosterone enanthate every 2 weeks for 12 weeks were measured weekly. The average serum concentration during the 2 weeks after the last 200-mg dose was 943 ng/dL.

An open-label, randomized 30-week trial compared the pharmacokinetics of testosterone undecanoate (TU) and testosterone enanthate (TE) in 40 hypogonadal men (20 men per treatment). TE was administered intramuscularly in a dosage of 250 mg every 3 weeks. TU was administered in a dosage of 1000 mg given as 3 doses every 6 weeks (loading dose) followed by one 1,000-mg dose after an additional 9 weeks.

Serum testosterone concentrations in the 2 treatment groups were comparable at baseline and well below the normal adult range of 10-30 nmol/L, with values of 2.67±2.31 nmol/L in the TE group and 3.94±3.35 nmol/L in the TU group. As shown here, men receiving TU had significantly higher trough levels of serum testosterone after 12 and 30 weeks of therapy than men receiving TE. Values in the TU and TE groups were 14.14±4.48 and 8.02±3.66 nmol/L (P<.001), respectively. After 30 weeks, values were 16.31±5.66 in the TU group and 8.29±3.99 nmol/L in the TE group. Slow accumulation of serum T was detected in men receiving TU at the end of the 6-week dosing intervals, but was prevented by increasing the dosing interval to 9 weeks.

These findings indicate that TU maintained physiologic levels of testosterone throughout the dosing interval when administered every 6 to 9 weeks, whereas TE levels declined to the lower limits of the normal range.

A randomized, multicenter, parallel study compared 2 doses of testosterone gel (T gel) with a testosterone patch (T patch) in 227 hypogonadal men. The average age of the patients was 51 years (range 19-68 years), and all had serum testosterone levels of 10.4 nmol/L (300 ng/dL) or less at screening. For the first 90 days of the study, the dosage was stable at 50 mg/day (N=73) and 100 mg/day (N=78) for the T gel or 2 nonscrotal patches delivering 5 mg/day (N=76). Dosage adjustments were made in the T gel group if the serum concentration of testosterone on day 90 was below or above the normal range (10.4-34.7 nmol/L). Only data for the first 90 days are shown here.

Preapplication levels of serum testosterone in the T patch group remained at the lower limit of normal throughout the 90-day treatment period. After 1 to 2 days of T gel application, mean serum testosterone levels remained at 17 nmol/L to 20 nmol/L in the 50-mg group and 22 nmol/L to 30 nmol/L in the 100-mg group.

The pharmacokinetic profiles of 2 testosterone gels, Testim™ (T-gel T) and AndroGel® (T-gel A), were compared in a 2-period, randomized, crossover study in 29 hypogonadal men. Each subject received a single dose of 50 mg of each formulation applied 7 days apart.

As shown here, serum concentrations of testosterone increased rapidly after application of either T-gel T or T-gel A. Concentrations peaked at approximately 3 to 4 hours, again at 8 to 10 hours, and finally at 18 to 24 hours after application. Concentrations began to decline after 24 hours.

Application of the transdermal testosterone patch to nonscrotal skin provides continuous absorption of testosterone during a 24-hour period. Daily application of the testosterone patch at 10 pm produces a serum testosterone concentration profile that mimics the normal circadian variation observed in healthy young men. Mean steady-state serum testosterone concentrations during nightly application of 2.5-mg testosterone patches in 29 hypogonadal male patients are shown here. Twenty-seven men used 2 patches nightly, and 2 patients used 3 systems nightly.
A multicenter, single-arm, open-label, phase III study determined the pharmacokinetics of the mucoadhesive testosterone buccal system containing 30 mg of testosterone when applied twice daily in 82 hypogonadal men for 3 months. Testosterone pharmacokinetics determined from 24-hour sampling at week 12 of treatment are shown here.

During the 2 consecutive 12-hour sampling periods after application of each buccal system, serum testosterone levels were within the normal range for adult males. During the 24-hour period, mean testosterone levels ranged from 14.9 to 22.6 nmol/L (4.3-6.5 ng/mL). Total serum T concentrations were above the lower limit of the adult male range 80.1% of the time during the 24-hour period.

A single-dose, open-label study determined testosterone pharmacokinetics after implantation of testosterone pellets in 14 hypogonadal men. Six pellets, each containing 200 mg of fused crystalline testosterone, were implanted in the subdermal fat tissue of the lower abdominal wall of each subject. Blood samples were obtained at 0, 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hours and on day 21 after implantation and then every 3 weeks until day 189. Blood samples were also obtained on days 246 and 300 during follow-up.1

Within 48 hours after implantation, a short-lived burst release of testosterone was seen in all patients and accounted for less than 1.49% of the total testosterone released. From day 2 to day 63, a stable plateau was maintained; testosterone concentrations were 35.2±2.3 nmol/L on day 2 and 34.8±2.6 nmol/L on day 63. After day 63, serum testosterone levels gradually declined, approaching baseline levels on day 300. The apparent terminal elimination half-life was 70.8±10.7 days, and the mean residence time (MRT) was 87.0±4.45 days. The mean serum concentration of testosterone was less than 10 nmol/L after 180 days. However, testosterone levels stayed above the lower normal limit of 10 nmol/L until day 246 in 2 patients, day 189 in 6 patients, day 168 in 5 patients, and day 147 in 1 patient. Although not statistically significant, men with larger body mass tended to have a shorter apparent half-life and MRT.1

Pooled data from 3 randomized, controlled trials have shown that a lower dosage of four 200-mg pellets is clinically effective for 5 to 7 months.2

Testosterone Update

Summary

- Testosterone therapy is safe and efficacious, when used appropriately, resulting in improvement or reversal of hypogonadal symptoms
- Desirable testosterone therapy provides a steady state of testosterone serum levels in mid-normal range over time
- Testosterone formulations (available and in development) offer patients therapeutic options

When used appropriately, testosterone therapy is safe and efficacious and improves or reverses symptoms of hypogonadism. Studies have shown that testosterone therapy in hypogonadal men has a favorable impact on sexual function, mood, body composition, and bone mineral density.

The ideal testosterone formulation provides physiologic levels of testosterone for prolonged periods. However, it is important to ensure that testosterone replacement does not cause erythrocytosis, an abnormal rise in PSA, or sleep apnea. Older men are more prone to develop these changes, so it may be wise to start with a shorter-acting testosterone delivery system and switch to a longer-acting delivery system when it is known that a patient will not require rapid discontinuation of testosterone treatment.

A variety of testosterone formulations currently available and in development offer patients a choice of therapeutic options so that, with their physician, they can select one that has a dosing schedule and method of administration best suited to their individual needs.