TREATMENT OPTIONS FOR MALE Hypogonadism

Bruce Biundo, RPh, FACA

Abstract Male hypogonadism is a common condition widely associated with the aging process. Understanding of this condition is continuing to grow as new information is available. Pharmacists are in a very unique position to work with patients and physicians in achieving better diagnosis and treatment plans for the hundreds of thousands of men in the U.S. who are hypogonadal. This article discusses various methods that can be employed to restore testosterone in men and the varying expectations associated with each treatment method.

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Hypogonadism in men is primarily a state involving lower than expected levels of testosterone, and traditionally this condition has been treated almost exclusively with testosterone supplementation. However, low testosterone can be fairly complex, involving a myriad of factors including:

• Inability of the testes to produce sufficient testosterone
• Improper brain signaling
• Excess estrogen

Primarily seen as female hormones, estrogens are also very important in men since declining testosterone can alter the androgen:estrogen relationship. While there is not an established target value for the androgen:estrogen ratio, changes in this relationship can result in complications such as declining prostate health.

In some men, clear reasons behind low testosterone can be difficult to determine. The end result, however, can be the same—insufficient testosterone that results in an unhealthy life and is often characterized by symptoms such as:

• Depressed mood
• Erectile dysfunction
• Lethargy
• Loss of libido

After proper diagnosis, including testing for testosterone, estrogen, and luteinizing hormone (LH), properly directed therapy can be dramatically effective in reversing these symptoms and providing a healthier, more robust lifestyle. In this document, we will discuss various methods that can be employed to restore testosterone in men and the varying expectations associated with each treatment method (see Figures 1 and 2).

In this review, we will consider the following ways to increase and/or maintain testosterone levels within at least the mid-physiologic levels, while also keeping the androgen:estrogen relationship in mind:

• Lifestyle changes
• Reduce estrogen levels
• Increase testicular output of testosterone
• Testosterone supplementation

**LIFESTYLE CHANGES**

Lifestyle modifications can boost testosterone production and keep the androgen:estrogen relationship healthy. Sedentary lifestyles, central adiposity, and unhealthy habits such as smoking and excessive alcohol use work against that goal. Whenever and to whatever extent possible, we should recommend an active exercise program that involves both aerobic and weight-resistant activities, along with a healthy eating plan that promotes loss of excess weight and fat. Many men who follow these tenets of healthy eating, appropriate dieting, and adequate exercise will find that their hormone levels correlate positively with their lifestyles. This, by far, is the simplest and soundest basis for hormonal health.

**REDUCE ESTROGEN LEVELS**

Adverse effects have been reported with changes in the androgen:estrogen relationship; these changes can occur because of declining testosterone levels and increasing (or even constant) levels of estrogens. As mentioned previously, changes in this relationship are patient-specific, and there is not a desired target value. Estradiol has been identified as a primary mediator in the hypothalamus/pituitary axis (HPA) (see Figure 3) for gonadotropin-releasing hormone (GnRH) and thus LH and follicle-stimulating hormone (FSH) in men. Thus, it becomes important to monitor estrogen levels (primarily estradiol, but also estrone) so that corrective action can be initiated when estrogen levels are high.
**FIGURE 1.** Treatment guidelines for hypogonadism.

*Total serum T levels were used in this diagram for more universal application and understanding, despite free T levels being more representative of the amount of active T available.
The following is a discussion of the most common drugs used in the treatment of hypogonadism and their dosage information (see Figure 2).

Some studies have shown that, instead of actual testosterone supplementation, testosterone levels can be increased by using aromatase inhibitors to decrease the synthesis of estrogen. High estradiol levels, through the negative feedback mechanism, can shut down or slow down GnRH secretion, thus decreasing the levels of LH and FSH. LH is the primary messenger hormone to signal the Leydig cells in the testes to produce more testosterone. Therefore, decreasing the action of estradiol with an aromatase inhibitor increases the production of testosterone. Another reason to be aware of estrogen levels is the role that estrogen plays in the level of Sex Hormone Binding Globulin (SHBG). Estrogen elevation contributes to the elevation of SHBG, a protein that binds testosterone and decreases the level of free testosterone. This free form is the active form of testosterone; therefore, agents that lower estrogen are proposed to increase the amount of active testosterone available.

For many men, the simplest and least invasive steps to reduce estrogen levels are to lose weight, practice good nutrition, and engage in regular exercise. Because aromatase, the enzyme system that is responsible for converting testosterone to estradiol (as well as converting androstenedione to estrone), is more abundant in fatty rather than lean tissue, fat reduction through exercise can improve the relationship of androgen and estrogen levels.

A potent aromatase inhibitor that has been studied for use in men with high estrogen levels is anastrozole, available commercially as a 1-mg tablet or as bulk powder. Some pharmacists and physicians have found that it can be very effective in oral doses ranging from 0.25 mg three times per week to 2.5 mg daily. As a means of gauging the effectiveness of letrozole, as well as anastrozole, one should obtain baseline levels of estradiol, and then compare them with levels 30 to 60 days after initiation of therapy.

Nutritional supplements that may be useful as aromatase inhibitors are zinc (50 mg to 100 mg elemental zinc per day), vitamin C (1 g per day), and chrysin (at oral doses of 250 mg to 500 mg three times per day). However, there is little supporting literature for these agents.

A very important consideration is that we do not lower estradiol so greatly that we induce hot flashes or contribute to osteoporosis. Another important reason to avoid drastic lowering of estradiol levels is that estradiol may possess libido-enhancing effects.

For many men, the simplest and least invasive steps to reduce estrogen levels are to lose weight, practice good nutrition, and engage in regular exercise.
FIGURE 2. Andropause diagnosis and laboratory values.

Andropause – Diagnosis and Laboratory Values

Andropause is a condition of hormonal imbalance, and may be related to declining levels of testosterone, elevated levels of estrogens, or a mixture of both. Proper diagnosis and screening will facilitate effective therapy.

Diagnosis:
1. Patient History and Physical
   a. Include a questionnaire on symptoms (PCCA Male Hormone Screening Form (PCCA Fax Document #94123) or ADAM questionnaire) with particular emphasis on libido and sexual function.
   b. Physical symptoms to note: presence of decreased body hair (esp. legs and chest), obesity, gynecomastia, decreased muscle mass and osteoporosis.

2. Laboratory Value
   a. Essential labs to order include total and free testosterone and estradiol. These values should be measured in the morning.

<table>
<thead>
<tr>
<th>Testosterone Serum Levels:</th>
<th>Units</th>
<th>Alt. Units</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Testosterone</td>
<td>300-1000 ng/dL</td>
<td>10.4-41.6 nmol/L</td>
<td>Optimal Range: 600-750 ng/dL</td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>47-244 pg/mL</td>
<td>190-560 pmol/L</td>
<td>Also expressed as a percent: 1.5-3.2% of total testosterone</td>
</tr>
<tr>
<td>Test. Bioavailable</td>
<td>130.5-681.7 ng/dL</td>
<td>3-12 nmol/L</td>
<td>Also expressed as 84-402 ng/dL</td>
</tr>
<tr>
<td>Note: pg/mL = ng/L</td>
<td>Thus, pg/mL = ng/dL x 10</td>
<td></td>
<td>Example: 47-244 pg/mL = 4.7-24.4 ng/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Testosterone and Estrogen Saliva Levels:</th>
<th>Units</th>
<th>Alt. Units</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free Testosterone</td>
<td>40-200 pg/mL</td>
<td></td>
<td>With topical use, range is likely higher (500-2500 pg/mL)</td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.76-2.18 pg/mL</td>
<td>2.8-8.0 pmol/L</td>
<td>Optimal Range: 0.76-1.63 pg/mL, 2.8-6.0 pmol/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estradiol (E2) and Estrone Serum Levels:</th>
<th>Units</th>
<th>Alt. Units</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>0-50 pg/mL</td>
<td>0-5 ng/dL</td>
<td>Optimal Range: 20-30 pg/mL (2-3 ng/dL)</td>
</tr>
<tr>
<td>Estrone</td>
<td>&lt;65 pg/mL</td>
<td></td>
<td>Range: 10-65 pg/mL</td>
</tr>
</tbody>
</table>
Increasing testicular output of testosterone may be the desired option in the case of secondary hypogonadism, a condition in which the testes may be fully intact but are not receiving proper or sufficient signals to produce testosterone. The signal hormones LH and FSH may be mimicked by Human Chorionic Gonadotropin (hCG); an injection of hCG can often reactivate the testicular secretion of testosterone by binding at LH receptors. Dosage requirements vary from patient to patient, with some responding to injections of 500 units three times weekly and others requiring up to 1500 units three times weekly. For some men, this may be a very effective way of restoring testosterone to physiologic levels while not suppressing the male’s ability to produce sperm. Testosterone supplementation can decrease sperm production by suppressing FSH through the negative feedback system. It should be noted that treatment to stimulate testicular output of testosterone would not be useful in a man diagnosed with primary testicular failure, in which the testes are unable to produce testosterone (a condition referred to as primary hypogonadism).

Clomiphene also works to increase testosterone production. It has been known for many years that clomiphene could be used to test the integrity of the HPA, but several papers have been published in recent years that chronicle the use of this agent as a potentially important means of maintaining sufficient testosterone levels on effects in men and these effects may decrease with declining estradiol levels.

**INCREASE TESTICULAR OUTPUT OF TESTOSTERONE**

In men, the effects of testosterone decline as levels decrease, reducing muscle mass, bone density, sexual function, and energy levels. Reversing these effects can be achieved by increasing the production of testosterone. This can be accomplished through the use of exogenous testosterone, which includes injections, gels, and patches. The choice of treatment depends on the individual's medical history and the specific needs of the patient.

**TESTOSTERONE INJECTIONS**

Testosterone injections are a popular method for increasing testosterone levels. The recommended dosage varies from person to person, and it is important to consult with a healthcare provider to determine the appropriate dose. In general, injections are given every 2 to 4 months. One of the main benefits of testosterone injections is that they have a slow onset, allowing for a gradual increase in testosterone levels.

**TESTOSTERONE GELS AND PATCHES**

Testosterone gels and patches are alternatives to injections. These delivery methods provide a more convenient and user-friendly option for some patients. They also offer a slow-release effect, allowing for a steady increase in testosterone levels.

**BIOFEEDBACK**

Some patients may be candidates for biofeedback therapy. Biofeedback involves the use of specialized technology to monitor and train the body to control physical processes, such as muscle tension and heart rate, that are not usually under voluntary control. This type of therapy can help improve sleep quality, reduce stress, and increase energy levels.

**PERSPECTIVES ON MONITORING AND TREATMENT**

Monitoring testosterone levels and adjusting treatment as needed is crucial for maintaining optimal health. Regular blood tests are performed to measure testosterone levels, and adjustments are made to the treatment plan if needed. This ensures that testosterone levels remain within a healthy range, and any potential side effects are minimized.

**CONCLUSION**

Testosterone therapy is a safe and effective way to treat low testosterone levels. The choice of treatment depends on the individual's specific needs and preferences. It is important to consult with a healthcare provider to determine the best course of action. By working closely with your healthcare provider, you can achieve optimal health and quality of life.
**FIGURE 3. Hypothalamus/pituitary axis.**

<table>
<thead>
<tr>
<th>Hypothalamus</th>
<th>GnRH</th>
<th>Pituitary</th>
<th>LH/FSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (T)</td>
<td>FSH</td>
<td>LH</td>
<td>Sertoli Cells</td>
</tr>
<tr>
<td>Spermatids</td>
<td>Mature Sperm</td>
<td>Epididymis</td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 4. Drugs used in the treatment of hypogonadism and their dosage information.**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE FORM</th>
<th>DOSE RANGE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole</td>
<td>Capsules</td>
<td>0.1 mg daily to 0.5 mg every other day</td>
<td></td>
</tr>
<tr>
<td>Letrozole</td>
<td>Sublingual</td>
<td>0.1 mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tablets</td>
<td>2.5 mg 3 times per week to 2.5 mg daily</td>
<td></td>
</tr>
<tr>
<td>Human Chorionic</td>
<td>IM injection or SQ injection</td>
<td>500 units to 1500 units 3 times per week</td>
<td></td>
</tr>
<tr>
<td>Gonadotropin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomiphene</td>
<td>Tablets or Capsules</td>
<td>• 25 mg every other day • 50 mg daily • 50 mg twice daily</td>
<td>Used to avoid highs and lows associated with every 3-week dosing</td>
</tr>
<tr>
<td>Testosterone</td>
<td>IM injection</td>
<td>75 mg to 100 mg weekly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SQ injection</td>
<td>Limited clinical data; dosing is similar to the IM formulation</td>
<td>Anecdotal evidence shows a benefit</td>
</tr>
<tr>
<td></td>
<td>Topical gel</td>
<td>• 40 mg to 120 mg • Initially: 50 mg/mL</td>
<td>• ~10% absorption • For comparison, 50 mg gel = VersaBase gel OR 5-mg patch 5% carbomer alcohol gel • Gel should be applied to a 2” × 2” patch of skin once daily (may be divided into 2 daily doses)</td>
</tr>
<tr>
<td></td>
<td>Topical cream Sublingual or Buccal</td>
<td>5% in Lipoderm base 10 mg to 25 mg per dose 3 to times daily</td>
<td>Not used frequently Level peaks in approximately 30 minutes and returns to normal in 4 to 6 hours</td>
</tr>
<tr>
<td></td>
<td>Implantable pellets</td>
<td>One dose (multiple pellets) lasts 3 to 4 times daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>400 mg to 500 mg daily</td>
<td>Inefficient due to extensive first-pass effect</td>
</tr>
</tbody>
</table>

IM = intramuscular, SQ = subcutaneous

An ongoing basis. Many are familiar with the use of clomiphene in female fertility: it can also be useful in male fertility. At doses ranging from 25 mg every other day to as high as 100 mg daily, clomiphene acts as a selective estrogen receptor modulator (SERM), effectively blocking estradiol from binding to its receptor. With less estrogen binding, GnRH levels increase and lead to increases in LH and FSH secretion. Clomiphene has been compared in at least one head-to-head study with testosterone supplementation and has been shown to be very effective in both restoring hormone levels and reducing signs and symptoms of hypogonadism. Clomiphene overcomes the previously mentioned problem of decreased sperm production seen with testosterone supplementation. For these reasons, clomiphene is one of the best options for men interested in maintaining their fertility.

**TESTOSTERONE SUPPLEMENTATION**

Testosterone supplementation is the form of treatment most familiar to all. For many men, this will be the treatment of choice—it is easily understood and, when properly administered, can be very effective in boosting testosterone levels. Prior to beginning testosterone supplementation, patients should have some labs drawn in addition to those labs mentioned previously in this review (see Figure 4). Hemoglobin and hematocrit, two very commonly measured labs, along with prostate-specific antigen (PSA), are important levels to acquire at baseline before beginning testosterone therapy. The importance of hemoglobin and hematocrit measurements is the fact that testosterone can raise these levels. Elevated numbers can result in polycythe-
mia, a potentially risky condition for the patient. A discussion of the various dosage forms and doses recommended with each form follows.

**PARENTERAL DOSING**

Giving testosterone by *intramuscular* (IM) injection is probably the most common form of dosing over the past twenty to thirty years, and it seems to work well for many men. However, a serious and confusing drawback is the erratic release of testosterone; there is no way to provide a steady-state release over the three to four week intervals at which the injections were usually recommended. Many times the physician would measure levels after a three-week interval and find them surprisingly low. Not understanding that effective dosing is a matter of finding the proper interval, physicians would increase the dose (e.g., 200 mg up to 300 mg or even 400 mg). This would not lengthen the duration of action but would rather sharpen the peaks and valleys associated with testosterone ester injections. The patient would experience supraphysiologic levels in the first week, then have declining levels after that; results of the supraphysiologic levels include increased conversion to estradiol and the previously mentioned polycythemia. Gynecomastia has also been associated with this kind of therapy. It has been proposed multiple times in recent years that a better method of dosing intramuscularly is to give a lower dose at weekly intervals; a suggestion of 75 mg to 100 mg is quite common. In this way, there is a more continuous release of the hormone without the peaks and valleys of the traditional dosing pattern.

Subcutaneous (SQ) dosing is being looked at as a potentially more favorable route of dosing, allowing the patient more freedom to dose himself than was possible with the IM injections. In a pilot study, *testosterone enanthate* in oil was given by SQ injection on a weekly basis. All of the patients were within the normal range for testosterone following injection. Patients also reported that the SQ route was easy to use and well tolerated. In general, SQ injections are preferred over IM injections because they are less painful, more convenient, allow for smoother release of the drug, are patient controlled, and are associated with better compliance. If testosterone can be incorporated into a pen delivery system, as mentioned in the study on SQ injection of testosterone, patients will benefit even more with the improved convenience.
In general, SQ injections are preferred over IM injections because they are less painful, more convenient, allow for smoother release of the drug, are patient controlled, and are associated with better compliance.

Topical Administration

At this time, topical administration appears to be the most effective way of dosing testosterone. While creams, solutions, and lotions have been used, over the past dozen years the greatest benefit seems to come from topical gels. We will focus on this type of vehicle (topical gels), as it has more clinical information available compared with other vehicles, and compliance has been shown to be relatively easy to achieve. At concentrations of 1% to 5%, testosterone gels leave no residue. However, higher concentrations, such as 10% and above, may leave a residue, as the hormone is incompletely dissolved at such concentrations. It has been suggested that gels, unlike creams, do not depot in the skin dermis but rather proceed more directly to blood vessels. Various studies over the past 10 to 12 years have shown that with an efficient vehicle, a topical dosing range of 40 mg to 120 mg daily can be used. An approximate absorption of 10% of testosterone from gel vehicles has been established, suggesting that an application of 50 mg in a topical gel will result in 5-mg net absorption. For comparison with a patch, 50 mg of a gel equates to about 5 mg from a patch. Some practitioners prefer a topical solution to a gel, using a propylene glycol/alcohol mixture as the base and a suggested concentration of 6% testosterone. At this time, there is no known benefit to using a smaller volume of a higher concentration, as high concentrations have the downside of leaving a residue. A risk associated with topical dosing is the transfer to a child or female, and every precaution should be taken to mitigate that risk.

Sublingual or Buccal Administration

When administering testosterone sublingually or buccally, it is best given three to four times a day to maintain something approaching steady-state release.

While absorption is efficient (higher than topical) and rapid (peak levels can be obtained after approximately 30 minutes), metabolism is also rapid due to the short half-life of testosterone, and levels return to baseline after four to six hours. Effective sublingual or buccal doses can range from 10 mg to 25 mg per dose, suggested to be dosed at six- to eight-hour intervals. While this is a relatively inexpensive and noninvasive method of dosing, the patient must understand that daily compliance of multiple dosing is necessary to obtain maximum benefit of the hormone. The use of a high dose once daily (e.g., 100 mg to 200 mg) will simply drive the levels very high into the supraphysiologic levels for several hours, making it an unfavorable route of administration. Sublingual dosing may be useful for a male who is already supplementing testosterone but needs an extra testosterone boost to enhance sexual function.

Implantable Pellets

This is a method some physicians prefer, particularly due to the fact that it gives them the ability to directly control patient dosing with an in-office surgical procedure. The advantage to the patient is that compliance is not an issue; the patient has the procedure done at three- to five-month intervals and does not have to be concerned with daily or weekly dosing. A disadvantage is that there is no way to adjust the dose during the life of the pellet in the body. For compounding pharmacists, pellets offer the challenge of providing the patient with a preparation that both releases the hormone consistently and is sterile, requiring compounding procedures that are very unique in methodology.

Oral Dosing

Oral dosing of testosterone is inefficient unless one is speaking of ester forms, which are not available in the U.S., or the synthetic forms of testosterone, such as methyltestosterone. The latter was widely used until 30 to 40 years ago when an association with liver toxicity halted its use. Recent studies have attempted to produce more bioavailable forms of oral testosterone dosing, but doses up to and exceeding 500 mg per day are required to overcome the extensive first-pass effect.

Conclusion

In summary, male hypogonadism is a common condition widely associated with the aging process. Understanding of this condition is continuing to grow as new information is available. Pharmacists are in a very unique position to work with patients and physicians in achieving better diagnosis and treatment plans for the hundreds of thousands of men in the U.S. who are hypogonadal. Improved management of this condition results in better health for each patient.

Resources

ANASTROZOLE


• Gomaa A, Eissa M, El-Gebaley A. The effect of topically applied vasoactive agents and testosterone versus testosterone in the treatment of erectile dysfunction in aged men with low sexual

CLOMIPHENE


HCG


TESTOSTERONE

• Guay AT, Smith TM, Offutt LA. Absorption of testosterone gel 1% (Testim) from three different application sites. *J Sex Med* 2009; 6(9): 2601–2610.
• Da Ros CT, Averbeck MA. Twenty-five milligrams of clomiphene citrate presents positive effect on treatment of male testosterone deficiency—a prospective study. *IBJU* 2012; 38(4): 512–518.

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