

TREATMENT OPTIONS FOR ANDROPAUSE

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Updated October 2011

Andropause is a condition of hormonal imbalance, primarily involving declining testosterone levels, but possibly also involving changes in estrogen levels. The hormonal imbalances can cause erectile dysfunction, low libido, depressed mood, declining muscle tone, osteoporosis, and associations with many other conditions such as Type II diabetes and cardiovascular disease. After proper diagnosis, including screening of testosterone and estrogen levels, therapy has been shown to be dramatically effective in relieving symptoms of andropause and restoring drive, health, potency and a sense of renewed vitality.



We will consider restoring hormone balance as our overall goal, and consider the following ways this may be accomplished: 1 – Lifestyle Changes; 2 - Reduce estrogen levels; 3 – Increase testicular output of testosterone; and 4 - Androgen supplements: pro hormone supplements and testosterone supplements.

Lifestyle Changes

Lifestyle modifications could boost testosterone production and keep the androgen/estradiol relationship healthy. Sedentary lifestyles, central adiposity, unhealthy habits (e.g., smoking, excessive alcohol use) work against healthy testosterone levels. Whenever and to whatever

extent possible, we should recommend an active exercise program, particularly involving weight-resistant activities, and healthy eating that promote loss of excess weight and fat. Many men who follow these tenets of healthy eating, dieting, and exercise will find that their hormone levels correlate with their healthy lifestyles.

Reduce Estrogen Levels

Adverse effects have been reported with changes in the androgen/estrogen ratios; these changes can occur because of declining testosterone levels and increasing or constant levels of estrogens. In addition, estradiol has been identified as a primary mediator of the hpa axis for Gonadotrophin-Releasing Hormone (GNRH) and leutenizing hormone (LH)/follicle-stimulating hormone (FSH) secretion in men. Thus, it becomes important to monitor estrogen levels (estradiol primarily, but also estrone) so that corrective action can be initiated when those levels are high. In doing so, some studies have shown that testosterone levels can be increased without actual testosterone supplementation. This is because high estradiol, in the negative feedback mechanism, can shut down the GNRH secretion, which is responsible for signaling the pituitary to produce more LH and FSH. LH is the primary messenger hormone to signal the leydig cells in the testes to produce more testosterone. Another reason to be aware of estrogen levels is the role that estrogen plays in Sex Hormone Binding Globulin (SHBG). Because estrogen elevation contributes to the elevation of SHBG levels, which then binds more testosterone, agents that lower estrogen are believed to make more free testosterone, the active form, 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, weight reduction and exercise can reduce fat and increase lean muscle mass. In doing so, a better environment for a healthier androgen/estrogen ratio is provided. A potent aromatase inhibitor that has been studied for its use in men with high estrogen levels is anastrozole, available commercially in a 1 mg tablet form, or in bulk powder. Some pharmacists and physicians have found that it can be very effective in oral doses ranging from 0.25 mg three to five times per week to 0.5 mg every other day. It also has been prepared in a sublingual form, with a dose of 0.1 mg per day. Yet another commercially available aromatase inhibitor is letrozole, which is available in a 2.5mg tablet. It has been shown to be effective at a dose of 2.5mg per day. Regardless of the dose, obtain baseline levels of estradiol and then compare with levels after the anastrozole or letrozole has been administered for 30 to 60 days. Nutritional supplements that may be useful as aromatase inhibitors are zinc (50 mg to 100 mg elemental per day) and Vitamin C (1 Gm per day), although there is little supporting literature.

Increase Testicular Output

Increasing testicular output of testosterone may be the desired option in the case of secondary hypogonadism, in which the testes may be fully intact, but are not receiving proper signals to secrete testosterone. The signal hormones FSH (follicle-stimulating hormone), and especially LH

(Leutenizing Hormone) may be mimicked by HCG (Chorionic Gonadotrophin); an injection of HCG can often reactivate the testicular secretion of testosterone. Dosage requirements vary from patient to patient, with some responding to a singular injection of 500 units per week, while others may require up to 1,500 U three times a week. For some men, this may be a very effective way of restoring testosterone to physiologic levels, with less likelihood of suppression of the body's own production. However, it should be noted this kind of treatment would not be useful in a man diagnosed with primary testicular failure, in which the testes are unable to produce testosterone.

Androgen Supplementation

Androgen supplementation has a primary goal of increasing testosterone levels. This can be accomplished indirectly through the use of pro hormones, or directly through testosterone administration.

Pro Hormone Supplementation

Pro Hormones are precursor hormones; they do not necessarily have much direct androgenic activity, but rely on the body for conversion to more active hormones. Probably the best known of these pro hormones is androstenedione; others commonly used are dehydroepiandrosterone (DHEA), pregnenolone and androstenediol. These agents are considered food supplements, and often can be purchased without a prescription.

Like other hormones, these pro hormones have relatively low oral bioavailability, and may be more active when given in a topical application. The comparison between androstenedione and androstenediol is interesting; while both serve as immediate precursors to testosterone, androstenedione also is a direct precursor to estrone. Thus, androstenediol may be a more attractive and efficient pro hormone, as it does not show a direct estrone pathway.

Progesterone is a hormone that possibly has a role in men's health: it may be active in both the aromatase and 5-alpha reductase systems in reducing the conversion of testosterone to estradiol and to dihydrotestosterone, respectively. In low (2.5mg) daily topical doses, progesterone may be an important adjunct in andropause therapy.

Testosterone Supplementation

Now, we will discuss the therapy more familiar to patients and physicians – direct testosterone supplementation. For many men, this will be the treatment of choice – it is easily understood and, when properly administered, can be very effective in restoring testosterone levels. Prior to beginning testosterone therapy, the physician should administer an office examination that includes gathering usual laboratory values, such as those for cholesterol, CBC, hematocrit, PSA, testosterone (total and free are recommended), and estradiol. The baseline testosterone and estradiol numbers should be established so that, after therapy is undertaken, it will be very clear whether or not the patient's levels are moving in the desired direction.

DOSAGE FORMS

INTRAMUSCULAR INJECTION

Giving testosterone by intramuscular injection is probably the most common form of dosing, and for some men, it seems to work well. However, a serious drawback is its erratic ratio of release. Although it is suggested to be dosed at a two- or three- week intervals, there is no controlled-release mechanism. Many men will experience the IM injection as a bolus dose, primarily achieving high testosterone levels in the first week, with noticeable declining effects beyond that. Worse, there is a heightened possibility of increasing estradiol conversion as the body cannot properly store the excess testosterone. Instead of reaching a more positive testosterone-estrogen ratio, the opposite effect sometimes occurs with gynecomastia as an occasional outcome. Because of the problems encountered with the suggested dosage schedule, it has been proposed that a better way of dosing intramuscular injections is to use a lower dose, such as 75-100 mg, on a weekly basis. In this way, there is a more continuous release of the hormone without the peak and valley effect of the traditional dosing pattern. Subcutaneous is possibly an effective route, allowing the patient more freedom to dose himself; however, there have not been clinical studies to evaluate this. There are three other methods of dosing which clinicians find acceptable, effective, and less likely to cause side effects: topical, sublingual or buccal, and implant pellets. Each of these offers a gradual and constant means of raising testosterone levels.

TOPICAL

At this time, topical administration appears to be the most effective means of dosing testosterone – creams, lotions, and gels have been used with good results. We will focus on gels because more clinical information is available with this type of vehicle (as of June 2004, studies have followed testosterone gels for 42 months with good results), and because compliance can be achieved and maintained with an easy-to-follow regimen. Testosterone shows better absorption when it is formulated in a gel. The gels have more than 10 years of data to support them. Creams are less effective and require much higher doses. Testosterone is completely dissolved in the gel and it goes on readily and is easily absorbed without leaving behind residue. The dosing range found to be safe and effective for gels is 40 mg -120 mg. A suggested starting dose is 50 mgs per day, using 1 mL of VersaBase™ Gel or a 5% carbomer-alcohol gel. If an increase in dose is necessary, prepare a 5% gel and administer 2 mL to deliver 100mg of testosterone (NOTE: topical gel application will result in approximately 10% absorption, likely higher than from other vehicles.) For comparison with a patch, 50 mg of a gel equates to a 5 mg patch. While that may look confusing, it means that the dosing systems are quite different from one another, and one cannot go from patch to gel and use the exact same dosing. It is important to note that some pharmacists have seen a need for an alternative topical delivery system, and compounded 5% testosterone in Lipoderm® may be an effective application. The dosing range is expected to be the same as that for the gel. Research has shown that application of topical testosterone to a surface area of approximately 2 inches by 2 inches produces greater absorption than when dosed to a smaller area. The larger surface area that 2 mL require, compared with a more concentrated, smaller volume, is an important factor in restoring testosterone levels and maintaining them in a consistent manner. In addition to the gel vehicles, topical applications may be successful using creams, lotions and transdermal vehicles. Studies have shown that a once-a-day application can be sufficient to elevate and maintain levels consistently in a gel that covers a larger than

customary surface area, such as 2 mL would offer. Because of individual differences in the way patients absorb testosterone, some men may require their daily dose divided into two applications. Along with the topical administration comes the risk of transference. Several companies are coming out with new studies on the absorption of testosterone under the armpit and on the front or back of the thigh. This is thought to reduce the risk of transfer to loved ones in close contact.

SUBLINGUAL OR BUCCAL

Sublingually or buccally, testosterone is given three to four times a day for andropause therapy. While absorption is efficient and rapid (peak levels obtained after approximately 30 minutes), metabolism is also fairly quick, with peak levels returning to normal after 4 to 6 hours. Effective sublingual or buccal doses can range from 10 to 25mg per dose, suggested to be dosed 3 times a day. While this is a relatively inexpensive and non-invasive method of dosing, the patient must understand his daily compliance of multiple dosing is necessary for him to obtain maximum benefit of the hormone. Sublingual dosing may be very useful for a male who is already supplementing testosterone but needs an extra boost to enhance sexual function.

IMPLANTABLE PELLETS

A method many physicians and patients find acceptable and effective is the use of implantable pellets. This is an office procedure that is relatively simple and offers a major compliance advantage: effectiveness can last from three to five months from a procedure, eliminating the compliance issue. Due to high start-up cost and issues involving testing, the decision to compound pellets should be thoroughly thought-out in advance.

ORAL

This is an inefficient way of dosing because of the high first-pass effect, in which the liver converts most of the testosterone into inactive metabolites. Most researchers and experienced clinicians do not recommend oral dosing of testosterone, as doses as high as 400mg per day may be required to achieve physiologic levels by this route. Note: methyltestosterone has greater bio-availability by oral administration, but is not recommended because of its adverse side-effect profile, primarily involving liver toxicity. (Literature citing use of oral testosterone is usually referring to either methyltestosterone or the undecanoate ester, which is available in other countries, but not in the U.S.)

In summary, andropause is a common progression in the aging process. While men are affected to varying degrees and at different ages, virtually all experience effects of hormonal imbalance. By taking positive steps to restore normal balance, many men can regain vitality and zest for life and enjoy their mature years fully and healthily.

For more detailed information, contact the Pharmacy Consulting Department at PCCA. PCCA has over 600 full-text articles on the subject of men's health. For those of you interested in finding the science in this area of men's health, be assured that it is available.