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CASE HISTORY

Integrative Management of Erectile Dysfunction

By Dr. Sergey A. Dzugan

Erectile dysfunction (ED) is defined as a consistent or recurrent inability to achieve or maintain penile erection sufficient for satisfactory sexual function. A common disorder for men of all ages and ethnic and cultural groups, ED affects an estimated 152 million men worldwide¹ and 50% of men aged 40-70 in the United States.²

In aging men, tissue sensitivity to hormonal impulses usually decreases, secretory function from hormonal glands declines, and the endocrine system's central controlling mechanism changes. With the world's population growing rapidly and average male life expectancy increasing, we can expect to see erectile dysfunction become an important public health problem. Not only does ED adversely affect quality of life for millions of aging men, but this condition can also be the first warning sign of more serious underlying problems such as heart disease or diabetes. Your physician should consider erectile dysfunction as an important part of your larger health picture.



Dr. Sergey A. Dzugan



PHYSIOLOGY OF NORMAL ERECTION

Penile erection occurs through the synchronized action of psychological, neuronal, hormonal, vascular, and cavernous smooth muscle systems. Normally, neurovascular response is modulated by psychological factors and hormonal status.³ Normal erection requires a dynamic balance of excitatory and inhibitory forces.⁴ There are inputs to penis function from the central and autonomic (both the sympathetic and parasympathetic) nervous systems. The sympathetic nervous system works in one direction, the parasympathetic works in the other.

Stimulation of parasympathetic activity can lead to a release of nitric oxide from the terminal end of axons, which are nerve fibers that conduct impulses away from the body of the nerve cell. Nitric oxide then diffuses into the smooth muscle of the penile arteries. These arteries relax or dilate, and blood flow into the organ increases. The spongy erectile tissue of the penis fills with blood, leading to compression of the veins that normally remove blood from the penis. In other words, erection is produced by the trapping of blood in the corpus cavernosum (corporal body) of the penis. During rapid eye movement (REM) sleep, the dominance of the parasympathetic system normally triggers nocturnal erection.²

Stimulation of the sympathetic system works in the opposite direction, maintaining the penis in a flaccid condition. The sympathetic nervous system can be stimulated by stress, exercise, and low temperature.

CAUSES OF ERECTILE DYSFUNCTION

Erectile dysfunction can have both psychological and organic (physical) causes. The latter may involve various bodily pathologies or the effects of medications or alcohol. In addition, ED can be a symptom of numerous conditions, including cardiovascular disease.^{1,5,6}

In cases of psychological ED, most often the condition is related to depression, anxiety, psychiatric diseases, marital or relationship problems, or financial difficulties.⁷ Erectile dysfunction attributable to psychological factors most frequently occurs at a younger age.

Organic ED can have numerous causes. Age appears to be a strong risk factor, as organic erectile dysfunction becomes more prevalent as men grow older. Organic ED may be due to vascular causes when blood flow to and from the penis is disrupted. Medical conditions such as cardiovascular diseases (atherosclerosis, or hardening of the arteries, as well as hypertension and high cholesterol) and diabetes may lead to vascular dysfunction.^{5,8} Men with these conditions represent the largest group of ED patients. Penile injury and surgery in the pelvic and abdominal area can also cause reduced penile blood flow and erectile dysfunction. Smoking is an additional factor that can indirectly reduce genital blood flow by accentuating the effects of other risk

factors such as cardiovascular disease and hypertension.^{9,10}

Organic erectile dysfunction can also have neural causes. Disorders such as stroke, multiple sclerosis, Parkinson's disease, spinal cord damage, and, again, diabetes can lead to nerve damage and affect normal response to sexual stimulation.¹¹⁻¹⁵ ED is also common in men who have had surgical treatment for prostate enlargement or prostate cancer.



Hormonal deficiencies or imbalances are another major component of organic erectile dysfunction. In aging men, an impaired feedback mechanism of the pituitary-gonadal axis can lead to diminished production of gonadal and adrenal androgens, contributing to the development of ED.¹⁶ Low levels of hormones such as testosterone, dehydroepiandrosterone (DHEA), pregnenolone, and thyroid hormones likewise may contribute to ED.^{7,17-20}

Finally, medications may contribute to organic erectile dysfunction. Prescription medications for treating high blood pressure (beta-blockers), depression (Prozac®, Zoloft®), insomnia (Ambien®), heart disease (statins), prostate enlargement (Proscar®) or cancer (Zoladex®), and other conditions have side effects that may include inducing ED.^{5-7,21} Excessive alcohol consumption can likewise negatively affect sexual function, especially with aging.¹

DIAGNOSIS

A diagnosis of erectile dysfunction can be based on general medical history, sexual history, physical examination, and laboratory testing.

Medical history is important in detecting the presence of concomitant health conditions such as heart disease, diabetes mellitus, hypertension (high blood pressure), endocrine disorders, depression, and insomnia, as well as in assessing possible contributing factors such as smoking, alcohol consumption, and prescription drugs. Use of over-the-counter medications and nutritional and herbal remedies must also be evaluated.

The physical examination and laboratory assessment should include measurement of body weight, height, pulse rate, blood pressure, complete blood cell count, glucose, lipid profile, prostate-specific antigen (PSA), and urine analysis. While a physical examination may reveal signs of an androgen deficiency, it is crucial to test for levels of hormones such as pregnenolone, DHEA-sulfate, testosterone (total and free), estradiol, and progesterone. Additional testing may include Doppler ultrasound of the penile blood vessels and the nocturnal penile tumescence study for assessing erection during sleep. Physical examination and other testing should be performed before initiating therapy.

TREATMENT OPTIONS

There are many options for treating erectile dysfunction. Managing ED may involve psychological, medical (oral, transdermal, or injected drugs), nutritional (supplements), and surgical therapies. To correct ED, it is essential to address any underlying chronic conditions and modify lifestyle factors such as obesity, smoking, alcohol consumption, and lack of exercise. Psychological therapy such as counseling and behavioral therapy can be effective if psychological factors are contributing to erectile dysfunction. Because ED can be a side effect of certain medications, it may be helpful to change drug regimens under a doctor's care. Finally, it is important for men to remain physically and sexually active for as long as possible.

Today, aging men are exposed to information and advertisements touting a wide variety of drugs and supplements that may help restore sexual function. The most popular option is a class of drugs called phosphodiesterase type 5 inhibitors such as Viagra® and Levitra®. These drugs dilate blood vessels in the genital region, leading to an erection; unfortunately, however, they do very little to increase libido (sexual desire). While these medications are valuable tools in the symptomatic treatment of erectile dysfunction, they may produce multiple side effects such as headaches, changes in blood pressure, irregular heart rhythm, flushing, nasal congestion, and others, and their long-term risks are unknown.²²

Men whose blood tests indicate hormonal deficiencies or imbalances can use bioidentical hormones to help manage ED. Replacement of androgens can be crucial in restoring normal sexual function. While testosterone is available by prescription only, over-the-counter hormones such as DHEA and pregnenolone may help boost testosterone levels and thus improve erectile dysfunction.

Owing to a lack of research in this area, the efficacy of some supplements in managing ED is considered moderate to uncertain. The benefits of most of the products available have been described through cultural experience and anecdotal reports. Many herbal "aphrodisiacs" have a positive influence on erectile dysfunction, and some have an effect on hormonal output as well.

Emerging evidence and case reports suggest that naturally occurring agents such as L-arginine,^{2,23} Korean red ginseng,²⁴ zinc,²⁵

DHEA,²⁶⁻³¹ maca root,^{2,32} and Tribulus terrestris³³ may help improve sexual function and thus ED. A naturally occurring alkaloid called yohimbine, derived from the African tree, *Pausinystalia yohimbe*, has been used for over 70 years as a pharmacological agent in treating ED.^{2,34,35} Other herbs that have been reported to improve ED include horny goat weed, oat straw (*Avena sativa*), damiana, muira puama, and ashwagandha. Studies of these herbal plants have often yielded inconsistent results, and clinical evidence to support herbal agents in managing ED is still minimal.

Those who do not benefit from drugs, supplements, or psychological treatment may see improvement with intracavernosal injection (such as prostaglandin and papaverine plus phentolamine),³⁶ vacuum/constrictive devices, penile prostheses, or vascular surgery.

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PREVENTION

Although the prevalence of erectile dysfunction increases with advancing age, it is not an inevitable consequence of aging. Men can do many things to reduce their risk for ED. Knowledge of the possible causes of this condition can help aging men and their physicians create prevention strategies. Maintaining normal levels of cholesterol, blood pressure, and blood glucose, as well as youthful levels of hormones, can help men avoid problems with sexual function. In addition, successfully managing stress, quitting cigarette smoking, avoiding heavy alcohol consumption, and eating a healthy diet can help promote overall health and well-being. Because certain drugs have been associated with ED, discuss their possible side effects with your doctor before using any prescriptions. Your doctor may choose to prescribe certain antihypertensive, antidepressant, or antipsychotic drugs that are associated with a reduced risk of ED.

The following case report details a patient with chronic, severe erectile dysfunction and an integrative approach that effectively corrected this pathology.

BACKGROUND

A 54-year-old white male presented in August 2000 with a long history of severe impotence. During his first visit to the clinic, the patient complained of severe erectile dysfunction—no libido, severe difficulty achieving erection, and very poor sex drive. He had had sex only four times in the previous eight months. He also complained of severe fatigue, depression, impaired short-term memory recall, muscle and joint pain, leg cramps, tingling and pain in the feet, and poor sleep. His vital signs were as follows: height, 5'9"; weight, 182 pounds; pulse, 76 beats per minute; blood pressure, 130/80 mmHg.

The patient had experienced erectile dysfunction since the age of 39, when his sex life began to deteriorate. Prior to that, he had been in good health and had never taken medications. His physician could find no obvious cause of or reason for a sexual disorder. For the past 15 years, the patient had been under a urologist's medical care for his ED. His doctor had prescribed different testosterone replacement therapy drugs available for erectile dysfunction (Testred® capsules, testosterone cypionate, Androderm®, etc.) as well as different delivery systems (pills, gels, injections, and patches). The patient had also used penile injections and Viagra®, but without success. The urologist requested that we evaluate the patient from an anti-aging perspective, as conventional treatment approaches had failed to resolve his problem.



DIAGNOSIS AND TREATMENT

During the patient's first visit, we took a lipid profile. His total cholesterol was very high at 330 mg/dL (optimal is less than 200). As described in our previous publications,^{37,38} our experience suggests that elevated total cholesterol can serve as a good marker for a deficiency of basic steroid hormones. After reviewing the lipid profile, we told the patient that we expected that hormone restoration therapy would have a very good chance of resolving his erectile dysfunction. Because of his long history and treatment failures with different medications, he was both surprised and skeptical.

We explained that our approach is distinctly different from his previous treatments, and that we would follow his cholesterol level as a surrogate biomarker to help evaluate the treatment program's effectiveness. We expected that with improvement in his cholesterol level, his ED symptoms would improve as well. We performed additional blood tests—for pregnenolone, DHEA-sulfate, total testosterone, estradiol, progesterone, and cortisol—and compared the patient's hormone levels to those found in healthy men in their twenties, which we consider to represent optimal levels for conferring anti-aging benefits.

We found that the patient's total testosterone, DHEA-sulfate, and cortisol were significantly below the desirable ranges. Lab results were as follows:

- total testosterone: 186 ng/dL (optimal: 241-827)
- DHEA-sulfate: 93 ug/dL (optimal: 280-640)
- morning cortisol: 0.9 ug/dL (optimal: 4.3-22.4).
- Progesterone and pregnenolone levels were on the low side of normal, at 0.3 ng/mL (optimal: 0.3-1.2) and 24 ng/dL

(optimal: 10-200), respectively.

- estradiol was high at 56 pg/mL (optimal: 0-53), and PSA level was normal at 0.89 ng/mL (optimal: 0.0-4.0).

[Editor's note: Free testosterone is also a very important test and frequently used by Life Extension members to help diagnose testosterone deficiency and monitor the proper dose of testosterone replacement therapy.]

The initial treatment for the restoration of all deficient steroid hormones included:

- pregnenolone: 300 mg in the morning
- DHEA: 150 mg in the morning and 50 mg at noon
- micronized testosterone gel (50 mg/ml): 1 ml in the morning
- micronized progesterone (50 mg/ml): 0.3 ml in the morning
- androstenedione: 300 mg in the morning.

In addition, we suggested:

- vitamin E: 1000 IU in the morning
- vitamin C (as sodium ascorbate): 2000 mg in the evening
- selenium: 200 mcg in the morning
- saw palmetto (320 mg) with nettle root (240 mg) in the morning
- Pygeum africanum: 150 mg in the morning
- zinc: 30 mg at bedtime
- Life Extension Natural Sex for Men (containing extracts of oats, yohimbe, Siberian ginseng, and nettle, as well as mineral and glandular extracts): two tablets twice daily, in the morning and evening
- Nutribiotic® MetaRest® (containing 3 mg of melatonin, 250 mg of kava root extract, and 10 mg of vitamin B6 per capsule): one capsule at bedtime.

We asked the patient to return to the clinic in two weeks. At the follow-up visit, the patient reported that his sex life had improved dramatically in the previous two weeks. He noted that his sexual function had improved markedly within the first five days of treatment, his energy level had likewise improved greatly, and he no longer had muscle aches or pain.

After one month on the program, the patient's total cholesterol level had decreased to 243 mg/dL, estradiol had fallen to 31 pg/mL, pregnenolone had risen to 43 ng/dL, DHEA-S had increased to 340 ug/dL, total testosterone was up to 396 ng/dL, and cortisol had climbed to 16.2 ug/dL. The patient reported no difficulties with erection or sex drive; the joint pain and tingling in his feet were improved; his sleep had normalized; and his depression was improved. His short-term memory, however, was still problematic. We increased his daily dose of pregnenolone to 400 mg and of DHEA to 250 mg (150 mg in the morning and 100 mg at noon). We also added to his regimen:

- phosphatidylserine capsules: 200 mg in the morning
- glucosamine sulfate: 2250 mg in the morning
- omega-3 fatty acids: 3000 mg in the evening
- chromium: 200 mcg in the morning
- B-complex: 1 tablet in the morning.

After six months of treatment, the patient's total cholesterol was down to 209 mg/dL, while his quality of life had continued to improve. We decreased the dose of micronized progesterone to 0.1 ml (50 mg/ml) daily and added 7-Keto DHEA (50 mg in the morning).

After one year of treatment, his total cholesterol had dropped to 187 mg/dL and his weight was down to 171, two pounds lower than his normal weight at the age of 35. His depression had resolved, and he had no complaints other than minor joint pain. The patient noted during his last follow-up visit that his erectile dysfunction "nightmare" was gone, adding, "I am so much better than I was when I came here that I hate to complain about anything."

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COMMENTARY

The age-related changes in men that occur after the age of 40 have generated worldwide interest in hormone supplementation. In cases of endocrine deficiencies, traditional endocrinology aims to replace the missing hormone or hormones. Interventions such as hormone replacement therapy may favorably influence some of the pathological conditions, such as erectile dysfunction, that occur in aging men. Aging is associated with diminished total and bioavailable testosterone concentrations, a lower ratio of testosterone to estradiol, and decreased levels of DHEA, DHEA-sulfate, thyroid hormones, growth hormone, and melatonin. Additionally, sex hormone binding globulin (SHBG) increases with age, resulting in a decreased concentration of free testosterone.^{7,19} Testosterone deficiency is likely to be a primary contributor to sexual dysfunction in many cases of erectile dysfunction.³⁹

Upon interviewing this patient during his initial visit, we realized that conventional ED treatment had little chance of successfully resolving his condition. Because of the patient's very high serum cholesterol level, we suspected that he might have several hormonal deficiencies. Conventional testosterone replacement therapy had stopped working for this patient several years ago, and his serum testosterone level was low, despite being treated with a larger dose of testosterone every year.

We therefore decided on a new strategy. First, we needed to restore youthful levels of all the steroid hormones, not just testosterone. Second, we needed to block enzymes (5-alpha reductase and aromatase) responsible for the "leakage," or conversion, of testosterone to the less desirable hormones, dihydrotestosterone (DHT) and estradiol. Third, we needed to increase the level of free testosterone by preventing the binding of testosterone to sex hormone binding globulin (SHBG) through the use of supplements such as nettle root.

Our approach with this patient differed from standard management of erectile dysfunction. First, we tried to restore the normal feedback mechanism of the neuroendocrinological system, which is important for maintaining the homeostasis, or dynamic equilibrium, of steroid hormones. Furthermore, we wanted to restore youthful physiology by supporting the regulation of cholesterol metabolic pathways. Decreased DHEA and DHEA-sulfate production with age can contribute to diminished testosterone formation.⁴⁰ We suggested a high dose of DHEA in this case to restore optimal levels of DHEA and DHEA-sulfate.

Additionally, we sought to encourage the conversion of DHEA to androstenedione, androstenediol, and testosterone. DHEA was a very important element of restoring the patient's testosterone level, allowing us to use a smaller dose of testosterone than would have been required using testosterone replacement therapy alone.

In this case, blood testing was very helpful in detecting suboptimal levels of several hormones in addition to low testosterone.

Furthermore, we believe that cholesterol was a very important biomarker for baseline evaluation, as well as a means to monitor the treatment plan's effectiveness.

Normally, testosterone can convert to dihydrotestosterone (DHT), androstenediol, and estradiol. With age, the conversion of testosterone to DHT and estradiol increases, as does the production of sex hormone binding globulin (SHBG). These factors contribute to a reduced amount of free testosterone in the body. To help restore youthful physiology, we aimed to prevent the conversion of testosterone to DHT by using supplements that block the 5-alpha reductase enzyme. Furthermore, we used the natural aromatase inhibitors progesterone and zinc to help prevent the conversion of testosterone to estradiol.^{41,42} Additionally, we used an herbal extract that inhibits the binding of testosterone to SHBG. Through these interventions, we sought to achieve a higher level of endogenous testosterone.

The following supplements have some potential use for testosterone metabolism:

- saw palmetto: 5-alpha reductase inhibitor in the prostate gland^{43,44}
- nettle root: 5-alpha reductase inhibitor; inhibits the binding of testosterone and SHBG⁴⁵⁻⁴⁷
- *Pygeum africanum*: has an inhibitory effect on prostate cell proliferation^{48,49}
- zinc: aromatase inhibitor⁴¹

As noted previously, stimulation of the parasympathetic nervous system can lead to a release of nitric oxide from the terminal end of axons, leading to vasodilation. That is why we recommended two agents that increase activity of the parasympathetic system: progesterone and MetaRest® (melatonin, kava root, and vitamin B6). In addition to parasympathetic stimulation, MetaRest® can help promote a vasodilating effect because of kava root's effect of being a mild calcium channel blocker.⁵¹

In this patient, blood tests indicated a low-normal level of progesterone, but we opted to elevate that level to the high side of normal to support the parasympathetic system and further inhibit the aromatase enzyme. Progesterone is vital for good health, in men as well as in women. In men, progesterone is made by the adrenal glands and the testes. It is the precursor of the adrenal cortical hormones and androgens. All men over 40 should consider natural progesterone replacement therapy. Progesterone can be considered as a physiological suppressor of aromatase induction in adipose tissue.⁴² Also, progesterone can inhibit 5-alpha reductase's conversion of testosterone to DHT.⁵⁰ Through these effects, progesterone promotes higher levels of endogenous testosterone.

This case report stresses the importance of restoring youthful hormone levels and physiology in a man who suffered from erectile dysfunction. Restoration of all of the important steroid hormones—not just testosterone—helped to normalize this man's high cholesterol level in addition to resolving his chronic erectile dysfunction.

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