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Integrative Management of Erectile Dysfunction

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Definition

Erectile dysfunction (ED) is defined as a consistent or recurrent inability to achieve or maintain penile erection sufficient for satisfactory sexual function.

Epidemiology

A common disorder for men of all ages and ethnic and cultural groups, ED affects an estimated 152 million men worldwide[1] and 50% of men aged 40-70 in the United States.[2]

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]

Physiology of Normal Erection (cont.)

- There are inputs to penis function from the central and autonomic (both the sympathetic and parasympathetic) nervous systems.

- Stimulation of parasympathetic activity can lead to a release of nitric oxide from the terminal end of axons

- Nitric oxide then diffuses into the smooth muscle of the penile arteries. These arteries relax or dilate, and blood flow into the organ increases.

Physiology of Normal Erection (cont.)

- 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]

Physiology of Normal Erection (cont.)

- 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]

Causes of Psychological ED

- depression, anxiety, psychiatric diseases, marital or relationship problems, or financial difficulties.[7]

- ED attributable to psychological factors most frequently occurs at a younger age.

Causes of Organic ED

Organic ED can have numerous causes:

- Age appears to be a strong risk factor.
- 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.

Causes of Organic ED (cont.)

- 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]

Causes of Organic ED (cont.)

- Organic erectile dysfunction can also have neural causes.

- Disorders such as stroke, Parkinson's disease, multiple sclerosis, 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.

Causes of Organic ED (cont.)

- **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]**

Causes of Organic ED (cont.)

- 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.

Diagnosis (cont.)

- **Medical history is important in detecting the presence of concomitant health conditions such as heart disease, diabetes mellitus, hypertension, 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.**

Diagnosis (cont.)

- The physical examination should include measurement of body weight, height, pulse rate, and blood pressure.

- A physical examination may reveal signs of an androgen deficiency.

Diagnosis (cont.)

Diagnosis (cont.)

- The laboratory assessment should include complete blood cell count, glucose, lipid profile, prostate-specific antigen (PSA), and urine analysis.

- It is crucial to test for levels of hormones such as pregnenolone, DHEA-sulfate, testosterone, cortisol, total estrogen, and progesterone.

Diagnosis (cont.)

- 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

- 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.

Treatment Options (cont.)

- 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.

Treatment Options (cont.)

- 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).

Treatment Options (cont.)

- These medications are valuable tools in the symptomatic treatment of erectile dysfunction.

- But…. 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

Treatment Options (cont.)

- 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.

Treatment Options (cont.)

- 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.

Treatment Options (cont.)

- 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 terrestris[33] 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]

Treatment Options (cont.)

- 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.

Treatment Options (cont.)

- 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.

Prevention

- 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.

- Successfully managing stress, quitting cigarette smoking, avoiding heavy alcohol consumption, and eating a healthy diet can help promote overall health and well-being.

Prevention (cont.)

- 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.

Case study

Patient E. 54 yr, male

Diagnosis: hypercholesterolemia, *impotence*, depression, insomnia.

Complaints: severe ED (since age 39), hypercholesterolemia, severe fatigue, depression, short-term memory problems, muscle and joint pain, leg cramps, tingling and pain in the feet and poor sleep.

Height 5’ 9”. Weight 182 lb.

	TC	TRG	HDL	LDL	VLDL	TC/HDL
08/31/00	330	216	54	233	43	6.1

	DHEAS	Pregn	Estradiol	Progest	Test	Cortisol
(nl - age 20-29)	(280-640)	(10-200)	(0-53)	(0.3-1.2)	(280-830)	(4.3-22.4)
08/31/00	93	24	56	0.3	186	0.9

Case study (cont.)

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.**

Case study (cont.)

In addition, we suggested:

- vitamin E: 1000 IU in the morning
- vitamin C: 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
- 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
- MetaRest® (containing 3 mg of melatonin, 250 mg of kava root extract, and 10 mg of vitamin B6 per capsule): one capsule at bedtime.

Case study (cont.)

After one month on the program:

	TC
08/31/00	330
10/01/00	243

	DHEAS	Pregn	Estradiol	Progest	Test	Cortisol
(nl - age 20-29)	(280-640)	(10-200)	(0-53)	(0.3-1.2)	(280-830)	(4.3-22.4)
08/31/00	93	24	56	0.3	186	0.9
10/01/00	340	43	31	0.8	396	16.2

Case study (cont.)

After one month on the program:

- 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).

Case study (cont.)

After six months on the program:

- **total cholesterol was down to 209 mg/dL**
- **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)**

Case study (cont.)

After one year of treatment:

- **total cholesterol had dropped to 187 mg/dL**
- **weight was down to 171, two pounds lower than his normal weight at the age of 35**
- **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."

Case study (cont.)

After three years on the program:

	TC	TRG	HDL	LDL	VLDL	TC/HDL
08/31/00	330	216	54	233	43	6.1
09/09/03	187	138	40	119	28	4.7

	DHEAS	Pregn	Estradiol	Progest	Test	Cortisol
(nl - age 20-29)	(280-640)	(10-200)	(0-53)	(0.3-1.2)	(280-830)	(4.3-22.4)
08/31/00	93	24	56	0.3	186	0.9
09/09/03	540	159	30	1.3	496	15.6

follow up 09/09/03 – no complaints

Commentary

- The age-related changes in men that occur after the age of 40 have generated worldwide interest in hormone supplementation.

- 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 ED, that occur in aging men.

Commentary(cont.)

- **Aging is associated with:**
- **diminished total and bioavailable testosterone**
- **a lower ratio of testosterone to estradiol**
- **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]**

Commentary(cont.)

- 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.

Commentary(cont.)

- 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.

Commentary(cont.)

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.**

- **Second, we wanted to restore youthful physiology by supporting the regulation of cholesterol metabolic pathways.**

Commentary(cont.)

- 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.

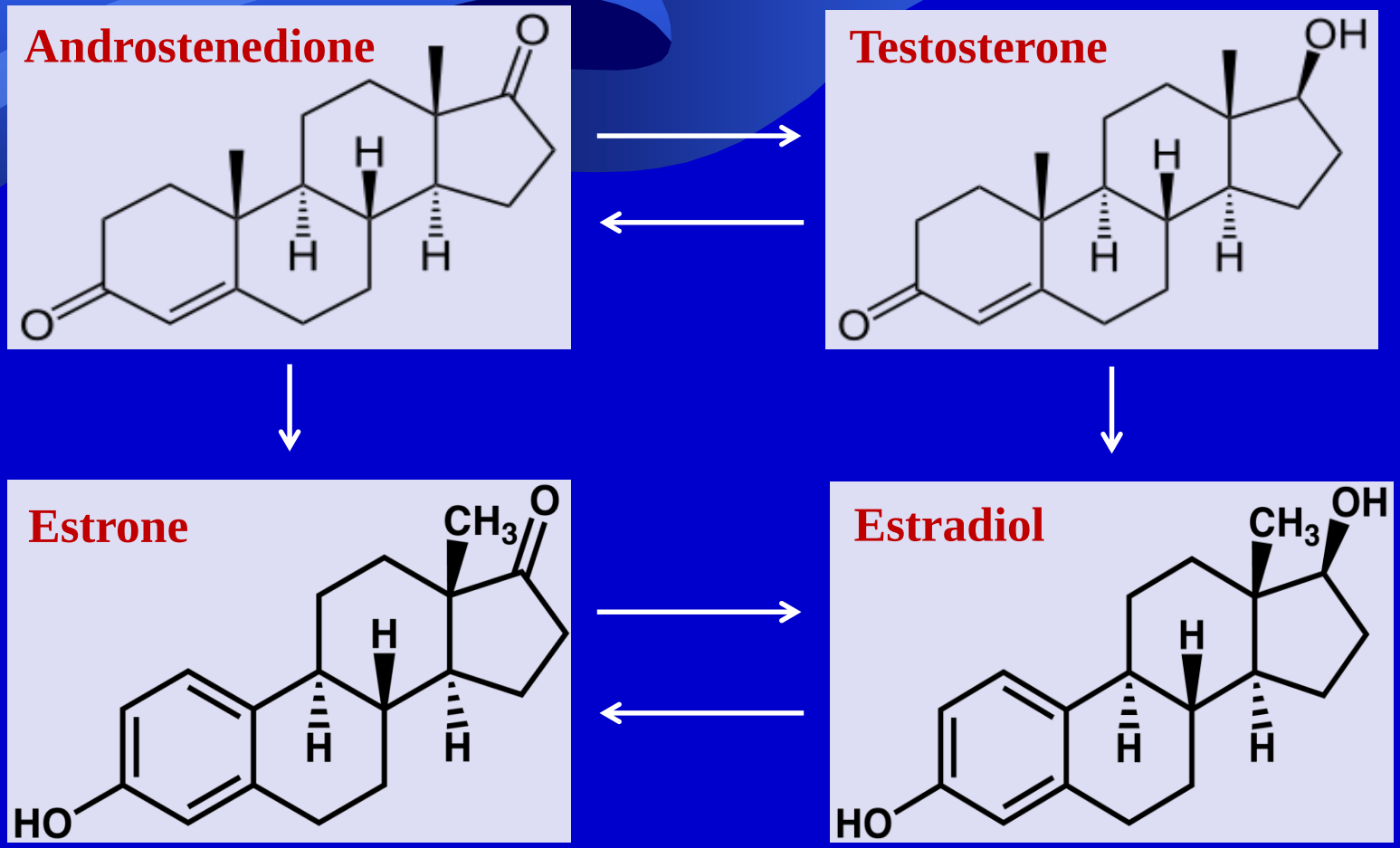
Commentary(cont.)

- Blood testing is very helpful in detecting suboptimal levels of several hormones in addition to low testosterone.
- Furthermore, we believe that cholesterol is a very important biomarker for baseline evaluation, as well as a means to monitor the treatment plan's effectiveness.

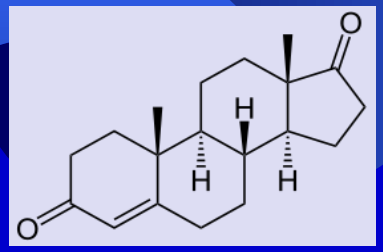
Commentary(cont.)

- Normally, testosterone can convert to dihydrotestosterone (DHT), androstanedione, 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.

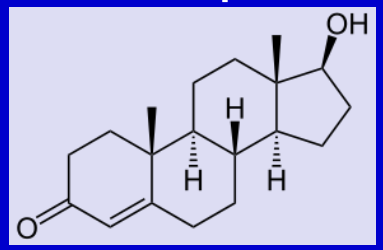
Androgen conversion to estrogen



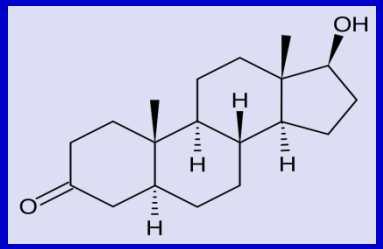
Metabolism of the major secreted androgens



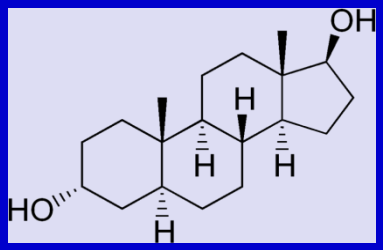
Androstenedione



Testosterone



Dihydrotestosterone (DHT)



3alpha-androstanediol

Commentary(cont.)

- 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.

Commentary(cont.)

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 SHBG[45-47]**
- **Pygeum africanum: has an inhibitory effect on prostate cell proliferation[48,49]**
- **zinc: aromatase inhibitor[41]**
- **progesterone: 5-alpha reductase inhibitor; aromatase inhibitor[42,50]**

Commentary(cont.)

- 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]

Commentary(cont.)

- 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.

Commentary(cont.)

- 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.

Commentary(cont.)

- 5 alpha-reductase inhibitors may only be useful in the short term. In the long run, they may be potentially harmful
- by blocking the conversion of testosterone to DHT, they force testosterone down to aromatase-estradiol pathway – thus shifting the hormonal balance in favor of estrogen
- DHT inhibits aromatase activity, potentially reducing the level of estradiol. This would tend to shift the estrogen:DHT ratio back in a safer direction[52]

Commentary(cont.)

- 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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