Erectile dysfunction and testosterone deficiency syndrome: the "portal to men's health"

Michael B. Greenspan, MD,[1] Jack Barkin, MD[2]

[1]Department of Surgery (Urology), McMaster University, Hamilton, Ontario, Canada

[2]Department of Surgery, University of Toronto, Humber River Regional Hospital, Toronto, Ontario, Canada

GREENSPAN MB, BARKIN J. Erectile dysfunction and testosterone deficiency syndrome: the "portal to men's health". *Can J Urol* 2012;19(Suppl 1):18-27.

Erectile dysfunction (ED) and testosterone deficiency syndrome (TDS) are closely related. In addition to affecting men's sexual health, both conditions also affect other male health issues. Screening for ED, especially in younger men, should become standard clinical practice for the primary care physician. Possible systemic effects and associated effects of TDS are now well documented. Testosterone replacement therapy (TRT) is very safe and effective in the right man.

Key Words: erectile dysfunction, testosterone deficiency syndrome, testosterone replacement therapy

Introduction

Men's sexual health is an important part of their overall health and quality of life, and it also affects their partners. In 1994, the Massachusetts Male Aging Study (MMAS) reported that 52% of men between the ages of 40 and 70 had some degree of erectile dysfunction (ED).[1] In 2000, a study estimated that the worldwide incidence of ED will increase from 152 million cases in 1995 to 322 million cases by the year 2025.[2]

ED and testosterone deficiency syndrome (TDS) commonly occur along with other comorbidities, and may be markers for other comorbidities. A study published in 2000 estimated that in Canada, 25% of men aged 40 to 82 had TDS.[3] Similarly, the Hypogonadism in Males Study (HIM) reported that 38.7% of men over age 45 had TDS.[4]

Address correspondence to Dr. Michael Greenspan, 414 Victoria Avenue North, Suite M11, Hamilton, Ontario L8L 5G8 Canada

Erectile dysfunction

Risk factors and link to coronary artery disease

An erection is a complex event that requires an intact arterial and venous system, normal innervation, normal hormonal factors, and functioning erectile tissue (endothelium). Abnormalities in one or more of these factors can lead to ED.

Well-established risk factors for ED include hypertension, hyperlipidemia, diabetes, smoking, low testosterone, alcohol and drug abuse, anemia, trauma to/surgery of the pelvis or spine, coronary artery disease (CAD), peripheral vascular disease, Peyronie's disease, and depression.

It is well-established that ED is linked to cardiovascular disease. According to a landmark study published in 2009, ED, especially in younger men, can be an early warning sign for imminent cardiovascular disease.[5] Compared to men with no ED, men with ED who were age 40 to 49 at baseline had a 50-fold increase of CAD, including death from cardiovascular disease

within 10 years. Men aged 50 to 60 at baseline had a 5.4-fold increased risk, men aged 60 to 69 had a 2-fold increased risk, and men over age 70 had a 1.3-fold increased risk of this outcome. A 2003 study showed that 67% of men with angiographically proven CAD had experienced ED an average of 39 months prior to being diagnosed with CAD.[6] ED may accompany other undiagnosed diseases. In a United Kingdom study, among 178 men evaluated at an ED clinic, 65 men (37%) had hyperlipidemia, which was previously undiagnosed in 46 of the men (71%); 42 men (24%) had diabetes, which was previously undiagnosed in 6 of the men (14%); and 35 men (17%) had hypertension, which was previously undiagnosed in 11 of the men (31%).[7] Therefore, all physicians, especially primary care physicians who may have the initial contact with men with ED need to ask their male patients about sexual function as part of every routine, yearly physical check up. The take-home message is that "a man with ED and no cardiac symptoms is a cardiac (or vascular) patient until proven otherwise."[8]

Treatments for ED

Treatments for ED have evolved. Fifty years ago men were desperate for any improvement in sexual function, whereas now they can expect to have a return to a normal sex life. Left untreated, ED can cause emotional distress for the patient and his partner. Feelings that may result from undiagnosed or untreated ED include emasculation, depression, low self-confidence, embarrassment, and guilt or anxiety.[9] ED is one of the most bothersome sexual symptoms. The Danish Prostate Symptom Score (DAN-PSS) sex questionnaire[10] examined the "bothersomeness" of sexual symptoms in men and reported that the most bothersome sexual symptoms were pain or discomfort on ejaculation (89%), reduced or absent erections (78%), and reduced or absent ejaculation (59%).

Pharmaceutical therapies for ED, such as oral phosphodiesterase-type 5 (PDE-5) inhibitors aim to increase the production of two key biochemical mediators involved in achieving an erection: nitric oxide and cyclic GMP. PDE-5 inhibitors prevent the breakdown of cGMP and increase nitric oxide and cGMP levels. A relatively normal testosterone level is necessary as an upstream biochemical precursor for the production of nitric oxide. Testosterone replacement therapy, for the hypogonadal man who is not responding to PDE-5 inhibitors, has been shown to salvage a response in a significant number of men.[11] By increasing nitric oxide levels, PDE-5 inhibitors may serve as "endothelial protectors" or endothelial stimulators.

To determine the best treatment option for a patient with ED, it is important for the physician to take an adequate patient history and to identify the onset time and duration of ED. The physician also needs to obtain answers to the following questions. Was the onset of ED gradual or abrupt? Is the ED global or situational? Did the patient have illness, surgery, or trauma that may have precipitated the ED? What is the role and attitude of the patient's partner(s)? Does the patient have any associated risk factors for ED such as diabetes, hypertension, or cardiovascular disease? Patients and physicians may not distinguish ED associated with premature ejaculation (PME) versus PME as a separate entity.

PDE-5 inhibitors

Since the PDE-5 inhibitor sildenafil (Viagra) became available in 1998, these oral agents have become the first-line, most common treatments for ED, Table 1. The three original available agents—sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis)—are all well established now. An oral, dissolvable form of vardenafil, Staxyn, has been recently released. Avanafil (Stendra), another oral PDE-5 inhibitor, has been approved by the FDA. Its "claim to fame" appears to be rapid onset of action.

On-demand therapy—that is, a PDE-5 inhibitor taken 30 to 60 minutes before sex—continues to be the most popular ED treatment method chosen by patients. Tadalafil has achieved notoriety because if it is effective for a patient, the average window of opportunity for sex or repeat sex is up to 36 hours. This is because tadalafil has a long half-life. Tadalafil is currently available in a daily, low-dose form (2.5 mg-5 mg). Once-daily administration may benefit patients who did not respond to or had unwanted side effects from on-demand tadalafil, or desire more spontaneity, or have performance anxiety, or were using an on-demand PDE-5 inhibitor more than twice a week (which is more costly).

Daily Cialis has been recently approved for treatment of ED and the signs and symptoms of benign prostatic hyperplasia (ED/BPH/LUTS) which are common and seen frequently as co-problems in a significant number of middle-aged men—see "Emerging Therapies" article by Barkin in this supplement.[12]

Among men with "classical" ED, 30% to 50% of those who do not initially respond to PDE-5 inhibitors may respond after they and their partners receive behavioral counseling about potential reasons for lack of a response.[13] Potential reasons for a lack of response to ED therapy include:

TABLE 1. **Oral phosphodiesterase-5 (PDE-5) inhibitors for erectile dysfunction (ED)**

Name (Brand name)	Dose	Time to maximum plasma concentration	Serum half life	Affected by food	Side effects/Notes*
Sildenafil (Viagra)	25 mg-100 mg 30-60 minutes before sexual activity, Max 1x day	60 minutes	4 hrs	Yes; delays onset	Visual disturbances ("blue haze")
Vardenafil (Levitra)	5 mg-20 mg 25-60 minutes before sexual activity Max 1x day	60 minutes	4 hrs	Yes; delays onset	Increases QT interval; avoid use with other medications which have similar side effect
Vardenafil (Staxyn)	10 mg oral disintegrating tablet (ODT) 45-90 minutes before sexual activity. Absorbed on the tongue (not under) without water	60 minutes	4 hrs	Yes; delays onset	Same as Levitra
Tadalafil (Cialis)	10 mg-20 mg 30 min before sexual activity Max 1x day Daily dosing: 2.5 mg-5 mg daily	120 minutes	17.5 hrs	No	Myalgia, back pain
Avanafil (Stendra [US only])	100 mg (50 mg-200 mg) 30 minutes before sexual activity Max 1x day	30 minutes	3 hrs	No	Back pain

*Class side effects include: headache, flushing, rhinitis, dyspepsia

- Inadequate dose of ED therapy: maximal dosages should and can be used safely to initiate therapy
- Inadequate patient arousal or stimulation
- Inadequate timing between therapy and attempted intercourse
- Not enough trials with a particular ED agent: four attempts with one agent may be needed
- The effect of ED therapy may be outweighed by multiple factors that affect erections, such as stress, fatigue, alcohol, smoking, obesity, diabetes, and vascular insufficiency
- Wrong diagnosis: the patient may have primary PME as opposed to ED
- Low testosterone levels: in a recent trial,[14] in 162 patients treated with a PDE-5 inhibitor, the odds ratio for lack of response to a PDE-5 inhibitor in patients with hypogonadism versus patients with normal testosterone levels was 1.89 (p = 0.0012).

PDE-5 inhibitors and nitrates: Patients using a PDE-5 inhibitor should never take a nitrate. The duration of action of a PDE-5 inhibitor (hours versus days) is irrelevant, if intercourse activity may produce angina that may require nitroglycerin in any form (pill, patch, spray, or sublingual). Studies have shown that in 8% of men, the combination of a nitrate and a PDE-5 inhibitor can cause a precipitous drop in blood pressure, as much as 40 mm Hg, which could cause sudden cardiac death or other signs of vascular insufficiency. The problem is that we cannot predict which men will be in the 8% that experience this effect, so the contraindication is firm and the same for all of the PDE-5 inhibitors.[15-17]

Counterfeiting of PDE-5 inhibitors: A discussion of PDE-5 inhibitors should not ignore the rampant counterfeit market and its potential dangers.[18] There are several reports of "natural therapies" that contain unlabelled quantities of PDE-5 inhibitors. This is a

concern, since patients may unknowingly be taking a PDE-5 inhibitor, placing those with contraindications at risk of a serious adverse event.

In 2010, it was estimated that the global illicit drug market was a $75 billion industry.[19] PDE-5 inhibitors are prime targets for counterfeiters.[20] It is estimated that between 4500 and 15000 websites offer online ordering of PDE-5 inhibitors and other substances purported to treat ED. These sites receive 13 million visitors a month and sell about 2.3 million tablets a month. More than 80% of these purchases were conducted without the patient providing a prescription or any medical history. About 10% of these medications contain toxins such as boric acid, highway paint (that contains lead), floor polish, heavy metals, nickel, arsenic, and brick dust.[21] Patients need to be discouraged from seeking treatments from these websites. This is a good reason to initiate a discussion about sexual dysfunction with patients, so that diagnosis and treatment of ED occurs under proper medical supervision.

Topical prostaglandin

The topical prostaglandin cream, Vitaros (alprostadil) was approved by Health Canada and is under review by the FDA for the treatment of ED. Vitaros is applied directly to the penis and is quickly absorbed through the skin, resulting in a faster onset of action than the oral ED therapies. The topical application of Vitaros may be associated with a lower risk of side effects, making it a treatment alternative for men who are unable to use or tolerate PDE-5 inhibitors. Penile burning sensation has been reported as a side effect in some of the clinical trials. It is not officially launched in Canada yet.

Other treatment options

Patients who do not respond to oral therapy or cannot use PDE-5 inhibitors (e.g., due to concomitant use of nitroglycerin) still have other viable options. They may respond to transurethral or intracavernosal therapies for ED, see Table 2.

TABLE 2. **Transurethral (TU) and intracavernosal (IC) therapy for erectile dysfunction (ED)**

Name (Brand name)	Dosage	Mechanism of action	Side effects/Notes
Alprostadil TU (MUSE)	250 mcg-1000 mcg Max 2 administrations per 24 hrs	Synthetic PGE1 stimulates increased levels of cAMP	Painful erection; urethral pain; bleeding; priapism (rare)
Alprostadil cream (Vitaros [approved in Canada])		Synthetic PGE1 stimulates increased levels of cAMP	Penile burning sensation
Alprostadil IC (Caverject, Edex†)	2.5 mcg-20 mcg* Max 1x daily and 3x weekly	Same as above	Penile pain, fibrosis hematoma; priapism (rare)
Papaverine IC‡	15 mg-60 mg (monotherapy) 5 mg-20 mg (combination therapy)	Non-selective PDEi increases cAMP and cGMP	Priapism; fibrosis
Phentolamine IC‡	0.5 mg-1 mg (combination therapy with papaverine)	Alpha blocker inhibiting sympathetic tone to penis	Hypotension; reflex tachycardia
Bimix (papaverine and phentolamine)	Papaverine 30 mg/mL + phentolamine 1 mg/mL in a 1:1 ratio		Less penile pain compared to monotherapy with alprostadil. More potent than monotherapy with alprostadil
Trimix (papaverine, phentolamine, and alprostadil)	Papaverine 30 mg/mL + phentolamine 1 mg/mL + alprostadil 20 mcg/mL in a 1:1:1 ratio		Less penile pain than alprostadil monotherapy. More potent than bimix

*Neurogenic ED may require lower starting dose. Severe vascular ED may require higher doses
†Not available in Canada; ‡Not approved by Health Canada for this use

Transurethral drugs

MUSE or the "Medicated Urethral System for Erections" has been available for many years as a transurethral installation of an absorbable pellet containing prostaglandin. It can also stimulate the rapid onset of an erection in a segment of men. Because it is a direct effect, it can be safely used in men taking nitroglycerin agents. There is sometimes a complaint of urethral burning.[22]

Intracorporeal injection therapy. This modality has been available since 1983. Patients inject the medication into the side of the penis 15 minutes before they would like to have an erection. Trimix, a custom-made mixture of papaverine, phentolamine, and prostaglandin E1 (PGE1 or alprostadil), is the most widely used injection therapy for ED. Other injection therapies include a bimix (papaverine, phentolamine), which also must be custom compounded by specialized pharmacies or alprostadil alone (Caverject, Edex [US]). Potential complications of penile injection therapy include prolonged erections and penile fibrosis.

Vacuum pump therapy. A mechanical device (a plastic cylinder with a rubber flange-attached to either a manual or electric pump) is placed over the penis. When the pump is activated, it creates a vacuum that draws blood into the penis, which results in penile engorgement. A ring must then be placed over the base of the penis to hold the blood in. Complaints of penile pain and ejaculatory interference from the ring are common. If a patient chooses this method, he needs to be counseled about how to use the device, to maximize his chance of success. Merely telling a patient to buy the device and watch the accompanying video is not recommended.

Penile-implant surgery. This is the "final frontier" in the treatment of ED. It actually has the highest patient/ partner satisfaction rate of any ED treatment, approaching 90% in most series. Success rates are higher and infection rates lower (< 2%) when done in specialized implant centers.[23]

Measuring response to ED treatment

At regular patient check ups, primary care physicians need to measure blood glucose and cholesterol levels and blood pressure, etc. Patients may volunteer information about their success and satisfaction with ED treatment. However, to objectively measure a patient's response to ED treatment, to facilitate dialogue and diagnosis, and to evaluate treatment changes, patients can be asked to fill in a questionnaire such as the International Index of Erectile Function (IIEF) questionnaire,[24] the Sexual Health Inventory for Men (SHIM) questionnaire,[25] or the Erection Hardness Scale (EHS) questionnaire.[26,27]

The IIEF is a 15-item, validated questionnaire addressing erectile function, orgasm, sexual desire, intercourse satisfaction, and overall satisfaction. Each modality can be measured separately. The SHIM consists of the five questions from the IIEF questionnaire that deal with erectile function. Each question is scored from 1 to 5. A total score of 22 to 25 indicates normal erectile function, whereas a score of 21 or lower indicates some degree of ED.

The EHS describes four types of erectile quality: penis larger but not hard; penis hard but not hard enough for penetration; penis hard enough for penetration but not completely hard; and penis completely hard and fully rigid.

Erectile hardness appears to be a very important part of ED treatment and patient satisfaction, such that the greater a patient's satisfaction with erection hardness, the greater his satisfaction with sexual life, love and romance, and overall health.[28.] The EHS is a very simple way to discuss ED treatment goals and responses with patients.

Testosterone deficiency syndrome

What it is

In 2000, physician experts at the First Annual Andropause Consensus Meeting recognized that "as men age, a majority have testosterone levels that are below the normal range for a young population. This decrease has clinical implications for the aging male population: these implications include changes in bone density, body composition, mood and sexual function and possibly the cardiovascular system."

There is a lack of large, blinded, placebo-controlled studies for treating below-normal levels of testosterone. The clinical condition that physicians recognize and treat has had many names in the past, which is confusing. The most appropriate name is testosterone deficiency syndrome (TDS).

As John Kenneth Galbraith said, "The conventional view saves us from the painful job of thinking." This statement can apply to physicians' views about the indications, risks, benefits, and potential complications of therapy for TDS.

The barriers to proper diagnosis and management of TDS include a lack of physician awareness about how TDS is associated with other diseases (such as metabolic syndrome, diabetes, and CVD), a lack of physician awareness of the ability of testosterone replacement therapy (TRT) to reduce disease symptoms, and controversy about the effect of TDS on prostate health.

It is generally accepted that TDS is characterized by below-normal serum testosterone levels. TDS may involve changes in testosterone-receptor sensitivity to

androgens, and research is underway to try to develop selective androgen receptor modulators (SARMs).

In men, testosterone is produced by the Leydig cells in the testis. In the blood, only 2% of testosterone is free, up to 40% is bound to albumin, and the rest is bound to sex-hormone-binding globulin (SHBG). Bioavailable testosterone (BT) is the sum of free testosterone and albumin-bound testosterone.[29]

Testosterone is metabolized into inactive products in the liver, and, in fat tissue it can be metabolized and converted to estradiol via aromatization. Therefore, an obese individual may develop gynecomastia as one of the sequelae of raising or changing the estrogen/testosterone ratio through increased aromatization.[30]

Testosterone targets the following organs and has the following effects:

- Skin (hair growth balding, sebum production)
- Muscle (strength, volume, energy, reduction in visceral fat)
- Male sexual organs (penile growth, spermatogenesis, erections, prostate growth and function)
- Bone marrow (stimulation of stem cells)
- Brain (libido, mood, cognition)
- Heart (cardiovascular health)
- Liver (protein synthesis)
- Kidney (stimulation of erythropoietin production)
- Bone (strength and density)

As suggested by the many target organs for testosterone, the clinical manifestations of TDS are considerable.[31,32] These can include decreased libido, decreased vitality, fatigue, mood changes, insomnia, anemia, ejaculatory disturbance, erectile dysfunction, hot flushes, decreased muscle mass, increased visceral body fat, testicular atrophy, weakness, osteopenia/osteoporosis, and loss of facial, axillary, and pubic hair.

Clinical disorders associated with TDS

Low levels of serum testosterone are quite common in many clinical disorders/conditions including type 2 diabetes, metabolic syndrome, HIV-associated weight loss, treatment with opioids, glucocorticoids or ketoconazole, osteoporosis or low-trauma fracture at a young age, end-stage-renal-disease and maintenance hemodialysis, chronic obstructive pulmonary disease (COPD), and infertility.[33] Patients with these clinical disorders/conditions are considered to be at high risk for TDS and should be screened for this disorder.[34]

Among men with diabetes, about 30% to 40% have low testosterone[35] and 40% to 50% have ED.[36] Men with higher levels of testosterone (15.6 nmol/L to 21.0 nmol/L) have a 42% lower risk of developing diabetes compared to men with normal levels of testosterone.[37]

A study found that 74% of men with chronic pain who take sustained-action oral opioids have low levels of testosterone.[34] This opioid-induced androgen depression (OPIAD) has a marked negative effect on male sexual function.

A study using data from the Male Massachusetts Aging Study,[38] found that in 17 years of follow up, compared with men whose total serum testosterone was 14 nmol/L to 18 nmol/L, men whose total serum testosterone was less than 7 nmol/L had a 2-fold higher risk of death, a 3-fold higher risk of cancer, and a 2-fold higher risk of cardiovascular death.[39] Shores and Matsumoto[40] used data from the Veteran's Affairs clinical database to assess how low testosterone is linked with all-cause mortality. Of 858 men over age 40, 166 men (19%) had a low serum testosterone level; these men had a mean age of 63.6. During 4.3 years of follow up, 34.9% of men in the low-testosterone cohort died versus 20.1% of men in the normal-testosterone cohort.

Testosterone and the prostate

Concerns about testosterone administration and its effect on the prostate is a leading cause of reluctance to treat patients with TDS.

In 2006, Morgentaler[41] performed a comprehensive review of testosterone and the prostate. He found no increase in prostate cancer in clinical trials of testosterone supplementation in normal men or even in men at increased risk for prostate cancer, such as those with previously diagnosed high grade prostatic intraepithelial neoplasia (PIN), possibly a pre-malignant lesion. He also reported that there was no link between prostate cancer and testosterone levels in multiple longitudinal studies. As men aged, testosterone levels dropped, but the incidence of prostate cancer increased. Men with more aggressive prostate cancer had lower levels of testosterone.

Prostate volume increases with age in normal men but not in untreated hypogonadal men. When hypogonadal men are treated with testosterone, their prostate volumes may increase, but only to the size of eugonadal men. Placebo-controlled studies showed that the differences between men receiving TRT and those receiving placebo were insignificant in terms of prostate volume, PSA, and LUTS. However, the belief that testosterone can promote the growth of an established prostate cancer is well-established.

Diagnosing TDS

In 2010, two comprehensive publications outlining practice guidelines for TDS were published: an American

article, "Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline"[41] and a Canadian article, "A practical guide to diagnosis, management and treatment of testosterone deficiency for Canadian physicians."[34] Both articles provide extensive evidence-based information about TDS.

To diagnose TDS, the authors recommend that first, total testosterone levels should be determined in two different early-morning serum samples. When results of these tests establish that the patient has low testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels should be determined. Before a patient receives TRT, he should have a baseline complete blood count (CBC) test and he MUST have a prostate-specific antigen (PSA) test. More sophisticated testing to determine bioavailable testosterone and/or calculated free testosterone can be done when TDS is suspected. Total testosterone measurements alone are non-diagnostic or equivocal. However, free testosterone, which may be offered in many labs, should not be requested, since it is generally inaccurate and imprecise.

As well as undergoing these blood tests, patients with suspected TDS can be asked to fill in the Androgen Deficiency in Ageing Males (ADAM) screening questionnaire.[3] This is a ten-item survey with yes/no answers. Answering "Yes" to questions 1 and 7, or any 3 other questions is suggestive of TDS.

Treatments for TDS

Prior to prescribing TRT for a patient, the physician needs to be aware of contraindications for this therapy. TRT is absolutely contraindicated in men who have been previously diagnosed with breast cancer or prostate cancer (untreated), and TRT may worsen erythrocytosis, untreated obstructive sleep apnea, and severe congestive heart failure. TRT should be used with caution in men who may become fathers, since it may lead to infertility.[34]

Alternatives to treatment with testosterone in this situation are off-label use of clomiphene, or use of human chorionic gonadotrophin (HCG).

The goals of treatment are symptom improvement and restoration of testosterone to physiological levels. The acronym ASTEP—which stands for Availability, Safety, Tolerability, Efficacy, and Preference—can be used to guide treatment choices.

Types of testosterone

Therapeutic forms of testosterone include injections, oral capsules (not available in the United States), transdermal patches, transdermal gels, and sustained release subcutaneous pellets, see Table 3.

Testosterone injections. There are two available forms: testosterone cypionate (Depo-testosterone) 100 mg/mL and testosterone enanthate (Delatestryl) 200 mg/mL. The usual dosage of injectable testosterone is 1 mL-2 mL every 2 weeks. If the response is good, the ultimate goal is to titrate the dosage so that the patient receives one injection per month. There are "peaks and valleys" with intramuscular (IM) administration with the possibility of "super-physiologic" levels occurring 2 to 4 days after injections. This may result in a slightly higher incidence of polycythemia compared to other forms of treatment. This is, by far, the cheapest method of TRT. "In our opinion, no patient can be considered a TRT failure unless they have tried injections."

Oral testosterone therapy. Testosterone undecanoate (Andriol) oral capsules have been available for over 20 years. Capsules are available in a 40 mg format. The suggested starting dosage is 80 mg, twice a day (160 mg/day). Subsequent dosing (40 mg/day-120 mg/day) should be based on response. The capsules must be taken with food (ideally a fatty food, because the drug is bound to long-chain fatty acids, and this will allow for better absorption) or absorption does not occur. With this therapy, blood levels of testosterone fluctuate and peak levels are often difficult to measure.

Transdermal testosterone patches. The testosterone patch (Androderm) is usually applied to the back, upper arms, thighs or abdomen. Skin irritation, pruritis or rash at the application sites is more commonly seen with the patch (than with gel formulations). It is important to rotate the application site with an interval of 7 days to reduce the risk of skin irritation.

Transdermal testosterone gels. There are several types. AndroGel 1% testosterone gel is available in a metered-pump bottle (1.25 g of gel per actuation) or in sachets containing 2.5 g or 5 g of gel (delivering 25 mg and 50 mg of testosterone, respectively). The usual starting dosage is 5 g daily. The gel is applied to the shoulders, upper arms or lower abdomen. The patient can expect to see stable, physiologic blood levels of testosterone within 4 weeks. The difference is that the Gel is absorbed and disappears. No visible evidence of the application is left. The patient is able to swim a few hours later if desired.

Testim 1% testosterone gel is supplied in 5 g tubes (delivering 50 mg of testosterone), and may be applied to the shoulders and/or upper arms. The starting dose is one tube (5 g) daily. The perception is that it is thicker than the gel and a little more odorous. It is not clear. Neither complaint is usually significant enough to instigate patient withdrawal from the medication.

TABLE 3. **Testosterone replacement therapy (TRT) for male hypogonadism**

Name (Brand name)	Route	Dose	Notes*
Testosterone (Striant [US, not Canada])	Buccal tablets	30 mg buccal tablets BID	Apply to gum over incisor; do not chew or swallow
Testosterone cypionate (Depo-Testosterone)	IM injection	200 mg-400 mg every 3-4 weeks 100 mg-150 mg (up to 200 mg) every 2 weeks preferred	
Testosterone enanthate (Delatestryl)	IM injection	100 mg-400 mg every 4 weeks (100 mg-150 mg every 2 weeks preferred)	
Testosterone gel (AndroGel 1%)	Topical	5 g-10 g daily (max)	Apply to clean dry shoulder area, upper arm, or abdomen
Testosterone gel (Testim 1%)	Topical	5 g-10 g daily (max)	Apply to clean dry area on shoulder or upper arm
Testosterone gel (Fortesta 2% [US only])	Topical	10 mg-70 mg daily (max) Starting dose is 40 mg/day, then adjust accordingly.	Apply to inner thigh area only
Testosterone (Axiron)	Topical	30 mg-120 mg daily (max) Starting dose is 60 mg/day (30 mg/pump applied to each axilla)	Apply once daily to axillary region
Testosterone patch (Androderm)	Transdermal	2.5 mg-7.5 mg daily	Apply to clean dry area on back or arm; rotate site; remove for MRI as patch contains metal
Testosterone implant (Testopel [US, not Canada])	Implantable pellets 75 mg/each	150 mg-450 mg SC implant every 3-6 months 2 pellets for each 25 mg testosterone required weekly	Implant in upper buttock under local anesthesia
Testosterone undecanoate (Andriol [Canada, not US])	Oral	40 mg-160 mg daily, Divided in two doses	Take with food
Testosterone undecanoate (Nebido [US, not Canada])	IM injection	1000 mg every 6-12 weeks	

*Monitor levels of serum testosterone for all agents

An underarm topical testosterone (Axiron) will be available in Canada in 2013. It is applied like an underarm deodorant, once a day using an applicator.

A 2% testosterone gel (Fortesta- Endo Pharma) has been approved by the FDA. It is applied to the inner thighs. In the clinical trials it demonstrated efficacy in restoring normal testosterone labels. There was a report of 16.1% (24/149) incidence of skin reactions. It is unclear if this drug will be submitted for approval to Health Canada.

Monitoring patients on TRT

All patients on TRT should be monitored on a regular basis. Guidelines recommend measuring CBC, PSA and testosterone levels at 3, 6, and 12 months after patients commence therapy, and yearly thereafter. Serum testosterone levels are more difficult to interpret following injections or oral administration.

The time to clinical response to different symptoms can vary. Morales et al[34] suggested that enhanced libido, improved emotional well-being, increased

energy, and reduced ED should occur within 3 months. Increased strength, enhanced bone mineral density (BMD), improved cognition, enhanced cardiovascular health, decreased body fat, and improvement in some components of metabolic syndrome are more likely to be noticed between 6 and 12 months.

Non-response to treatment can occur secondary to compliance issues, malabsorption, insufficient dose, unsatisfactory formulation (seen with some compounded testosterone made in pharmacies), or because the patient's symptoms are not related to TDS.

Remember that for ED patients who are not responding to testosterone alone or PDE-5 inhibitors alone, physicians should strongly consider giving both therapies. Similarly, physicians should check the testosterone levels of "clinically depressed" male patients who are not responding to their antidepressant medications. If their testosterone levels are low, a significant number of these men will respond better to combined TRT and an antidepressant.[42]

Conclusion

ED and TDS are closely related. In addition to affecting sexual health, both conditions also affect other male health issues. Screening for ED, especially in younger men, should become standard clinical practice for the primary care physician. Possible systemic effects and associated effects of TDS are now well documented. TRT is very safe and effective in the right man.

Disclosure

Dr. Michael Greenspan serves/has served as advisor/consultant/speaker for: Pfizer, Eli Lilly, Bayer, Abbott, Solvay, Paladin, American Medical Systems, GlaxoSmithKline and Watson Pharma.
Dr. Jack Barkin has been a clinical investigator, speaker and medical advisory board member and consultant for Abbott, Lilly, Bayer, Paladin, Watson Pharma, Bayer, AstraZeneca , Astellas, Solvay, Pfizer and Triton. □

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