The field of erectile dysfunction continues to evolve. Updated AUA Erectile Dysfunction Guidelines and the second Princeton Consensus Panel Guidelines, as well as updates regarding the oral PDE-5 inhibitors, are the focus of this article.

Key Words: Erectile dysfunction (ED), male sexual dysfunction, cardiovascular risk, oral PDE-5 inhibitors, sildenafil (Viagra®), vardenafil (Levitra®), tadalafil (Cialis®), intraurethral suppositories, the vacuum constriction device (VCD), intracavernous injection, penile prosthesis.
Prevalence

Epidemiologic studies demonstrated that 35% of men aged 40 to 70 years suffer from moderate or severe ED, and an additional 25% have milder forms of ED (Feldman, Goldstein, Hatzichristou, Krane, & McKinlay, 1994). ED affects approximately 1 in 10 men worldwide (Benet & Melman, 1995). The risk of erectile dysfunction increases with age. As the population continues to grow and age, the prevalence is expected to continue to increase, with an estimate that there will be 322 million men worldwide with ED by the year 2025 (Aytta, McKinlay, & Krane, 1999). Although awareness of erectile dysfunction has increased with the advent of oral therapies, a significant number of men remain undiagnosed and untreated.

Etiology of Erectile Dysfunction

Historically, ED was believed to primarily have a psychogenic origin; however, the majority of individuals are currently identified to have organic ED due to an underlying physiologic cause. The most common cause of ED is atherosclerosis and is associated with disease states such as diabetes mellitus, hypertension, smoking, and dyslipidemia. These risk factors cause oxidative stress and damage to the endothelial cells (Azadzoi et al., 1998; Saenz de Tajada, Goldstein, Azadzoi, Krane, & Cohen, 1989; Sullivan et al., 2001; Solomon et al., 2002; Greenstein et al., 1997; Kawanishi et al., 2001; Solomon et al., 2002; Solomon, Man, Wierzbicki, & Jackson, 2003).

The presence of ED is a good predictor of occult coronary artery disease, particularly if the erectile dysfunction is severe. ED in men with coronary artery disease is a predictor of occult peripheral vascular disease (Solomon, Martin, & Jackson, 2002). In a study assessing cardiovascular disease in 50 men aged 40 to 60 years with organic ED and who were asymptomatic for coronary artery disease, up to 40% had significant coronary artery disease on cardiac evaluation (Pritzker, 1999). Peripheral vascular disease elsewhere in the body also correlates with the severity of ED (Gensini, 1983; Greenstein et al., 1997; Kawanishi et al., 2001; Solomon et al., 2002; Solomon, Man, Wierzbicki, & Jackson, 2003).

The normal erectile process is a neurovascular event that is triggered by cognitive or tactile stimulation. Psychogenic and hormonal factors may also play a role in the erectile process (Meredith, 1995). Disease states and medications that can affect arousal, hormones, and the normal function of nerves, arteries, and veins may have an impact on erectile function (see Table 1).

### Table 1.
Common Disease States and Medications That May Affect Erectile Function

| Cardiovascular Diseases                                    | Atherosclerosis, hypertension, peripheral vascular disease |
| Medical Conditions                                         | Diabetes mellitus, renal failure, chronic disease states |
| Neurologic Disorders                                        | Diabetes mellitus, cerebrovascular accidents, Parkinson’s disease, spinal cord injury |
| Endocrine Disorders                                         | Multiple sclerosis hypogonadism, pituitary adenoma, hyperthyroidism, hypothyroidism |
| Surgical Causes                                             | Pelvic surgery, including radical prostatectomy, low anterior resection, abdominal perineal resection, retropitoneal surgery |
| Radiation Causes                                            | Pelvic irradiation for genitourinary and colonic malignancies |
| Medications                                                  | Antihypertensive agents – Beta-blockers, thiazide diuretics, clonidine, methylxypine, reserpine, and spironolactone |
| Penile Abnormalities                                         | Central nervous system agents – Phenothiazines, butyrophenones, tricyclic antidepressants, antipsychotics, and selective serotonin reuptake inhibitors |
| Other                                                        | Medications that may have endocrine effects – Antiandrogens, gonadotropin-releasing hormone agonists and antagonists, cimetidine, metoclopramide, alcohol, and marijuana |
|                                                            | Peyronie’s disease, prior history of priapism, history of penile fracture, pelvic fracture |

### Physiology of Erection

Sexual stimulation is required for an erection. As a result of sexual stimulation, neural impulses are conveyed through the spinal cord to the pelvic parasympathetic preganglionic nerves, which form the pelvic plexus. Acetylcholine released from the pelvic nerve terminals stimulates
the cavernosal nerves, which enter the cavernosal bodies within the penis. Stimulation of the cavernosal nerves leads to the release of the neurotransmitter, nitric oxide. Nitric oxide activates the enzyme guanylate cyclase, which catalyzes the formation of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP). cGMP stimulates cGMP-specific protein kinase, which blocks calcium influx by inhibiting calcium channels. The decreased cytosolic calcium concentration leads to relaxation of the cavernosal smooth muscle, and a resultant inflow of blood into the cavernosal bodies and rapid distention of the sinusoids. The distended sinusoids compress peripheral venules against the tunica albuginea, a fibroelastic covering that surrounds the corporal bodies, thus preventing venous outflow. The combination of increased arterial inflow and diminished venous outflow yields intracavernosal pressures that approximate systolic pressure, and the penis achieves sufficient rigidity for vaginal penetration (Vickers & Wright, 2004). Cavernosal smooth muscle relaxation is also regulated by cyclic adenosine monophosphate, which causes relaxation of the trabecular smooth muscle in the corpus cavernosa (Walsh, Retik, Vaughan, & Wein, 2002).

**Evaluation of Erectile Dysfunction**

In 1996, the American Urological Association (AUA) Erectile Dysfunction Clinical Guideline Panel published the *Report on the Treatment of Organic Erectile Dysfunction*, an evidence-based guideline for the diagnosis and treatment of erectile dysfunction (Montague et al., 1996). Since that time, an Erectile Dysfunction Guideline Update Panel (the Panel) was appointed by the AUA Practice Guidelines Committee in 2000 to update the 1996 guidelines. The following recommendations are in accordance with these guidelines (Montague et al., 2005). The male presenting with a complaint of ED should be evaluated with sexual, medical-surgical, and psychosocial histories; a focused physical examination; and laboratory tests thorough enough to identify co-morbid conditions that may predispose the individual to ED and may have an impact on the treatment choice (see Figure 1).

**Assessment of Cardiovascular Risk**

Cardiovascular risk stratification has become an essential component of the evaluation of men presenting with ED. Questions pertaining to exercise capabilities, history of cardiovascular disease, and current/past medications can help assess whether or not an individual is at risk for cardiovascular disease. Guidelines have been established to assist in stratification of an individual’s cardiovascular risk. Concerns regarding cardiovascular safety and the risk of drug-drug interactions have led to two Princeton Consensus conferences, one in 1999 and the other in 2004, that focused on sexual dysfunction and cardiac risk.

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**Figure 1.**

**Evaluation of a Patient Presenting with Complaints of Erectile Dysfunction**

<table>
<thead>
<tr>
<th><strong>History</strong></th>
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<tbody>
<tr>
<td>• Sexual – Assess for other coexisting sexual dysfunctions, such as ejaculatory and/or orgasmic dysfunction and decreased libido.</td>
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<tr>
<td>• Medical-surgical – Evaluate for co-morbidities, including cardiovascular disease, neurologic conditions, prior pelvic surgery or radiation, recreational drug use (including alcohol, tobacco, and other illicit drugs). Assess the individual’s cardiovascular risks related to resuming sexual activity.</td>
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<tr>
<td>• Psychologic – Assess for relationship problems, depression, and stressors.</td>
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<tr>
<td>• Other – Ask questions about penile curvature, pain with erections, and prior history of significant penile or penile trauma, as well as history and duration of bicycle riding.</td>
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<tr>
<th><strong>Physical Examination</strong></th>
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<tr>
<td>• Varies depending on whether the patient is a new patient, but typically focuses on abdomen and genital examination (presence, size, consistency, and location of the testes); examine penis for palpable plaques.</td>
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<td>• Focused neurologic examination.</td>
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<tr>
<td>• Assess for secondary sex characteristics.</td>
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<tr>
<td>• Check peripheral pulses – Check for symptoms of claudication.</td>
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<tr>
<td>• Digital rectal examination with AUA prostate-specific antigen (PSA) – Best practice policy on early detection of prostate cancer suggests that a digital rectal examination of the prostate and a serum PSA should be offered annually to all men over 50 years of age with an estimated life expectancy of greater than 10 years (Carroll et al., 2001).</td>
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<tr>
<th><strong>Laboratory Evaluation</strong></th>
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<tr>
<td>• Laboratory testing should be performed to evaluate those disease processes that may be suspect by the history and physical examination.</td>
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<tr>
<td>• Testosterone level measurements may be indicated in select patients.</td>
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<tr>
<th><strong>Other Tests</strong></th>
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<tr>
<td>• Additional testing, such as vascular and/or neurological assessment, and monitoring of nocturnal erections may be indicated in select patients including:</td>
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A risk stratification algorithm was developed by the First Princeton Consensus Panel to evaluate the degree of cardiovascular risk associated with sexual activity in men with varying degrees of cardiovascular disease (DeBusk et al., 2000). The consensus study from the Second Princeton Consensus Conference corroborated and clarified the algorithm and emphasized the importance of risk factor evaluation and management for all patients with ED.

Cardiovascular risk was divided into 3 groups: patients who were considered at low risk, intermediate or indeterminant risk, and high risk (see Table 2). Patients who are at intermediate or indeterminant risk are those with uncertain cardiac conditions and who may also have multiple risk factors. It is recommended that these individuals undergo further evaluation/testing before resuming sexual activity. Based on results of further evaluation, these individuals may be re-stratified as high or low risk for cardiovascular complications related to sexual activity. Patients in the high-risk group are deemed to have a potentially significant risk associated with sexual activity, and thus, sexual activity should be deferred until the patient’s cardiologist and/or primary care provider indicates that it is safe to participate in sexual activity.

Management of Erectile Dysfunction

The advent of oral therapy has revolutionized the management of ED. Although the vast majority of men presenting with ED have underlying organic causes, many men suffer from a combination of problems, including psychogenic and relationship issues that may be the result of or precede the ED. These factors must be identified and treated by appropriate individuals to achieve a satisfactory outcome. While ED therapy is designed to restore erections, it may or may not improve psychogenic and relationship problems.

### Table 2. Erectile Dysfunction and Cardiac Risk

<table>
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<tr>
<th>Risk Level</th>
<th>Indicators</th>
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</table>
| I – Low risk | • Asymptomatic, < 3 cardiovascular risk factors (age, male gender, hypertension, diabetes mellitus, cigarette smoking, dyslipidemia, sedentary lifestyle, family history of premature coronary artery disease).  
• Controlled hypertension – Well-controlled hypertension with 1 or more medications.  
• Mild, stable angina pectoris – Noninvasive evaluation to rule out serious underlying cardiovascular disease before treating their ED.  
• Post-revascularization – Exercise stress test may help determine the extent and severity of residual ischemia.  
• Post-myocardial infarction (> 6-8 weeks) – Individuals with past MIs who are asymptomatic, do not have treadmill-induced ischemia, or who have undergone coronary revascularization are at low risk.  
• Mild valvular disease – Mild mitral valvular disease, no increased risk; same may be true for mild aortic stenosis.  
• Left ventricular dysfunction (New York Heart Association [NYHA] Class I) – Most are not at increased risk, especially if treated medically.  
• Other cardiovascular conditions – Pericarditis, mitral valve prolapse, or atrial fibrillation with controlled ventricular response are not at increased risk, if treated individually. |
| II – Intermediate or Indeterminant Risk | • Asymptomatic, > 3 risk factors for coronary artery disease.  
• Moderate, stable angina pectoris.  
• History of MI (> 2 weeks, < 6 weeks).  
• Left ventricular dysfunction (ejection fraction < 40%) or congestive heart failure (NYHA Class II).  
• Patients with non-cardiac sequelae of atherosclerotic disease, peripheral vascular disease, history of stroke, or transient ischemic attack. |
| III – High Risk | • Uncontrolled or refractory angina – Includes new onset, severe acceleration, refractory angina, or that which occurs at rest.  
• Uncontrolled hypertension – Untreated, poorly controlled, accelerated, or malignant hypertension.  
• Congestive heart failure (NYHA Class III or IV).  
• Recent MI (< 2 weeks).  
• High-risk arrhythmia – Ventricular arrhythmias at increased risk, if a pacemaker or defibrillator is placed, risk is decreased.  
• Obstructive hypertrophic cardiomyopathy.  
• Moderate to severe valve disease including aortic stenosis. |

Source: Kostis et al., 2005.

### First-Line Therapies for ED

**Oral PDE-5 Inhibitors**

Oral PDE-5 inhibitors remain the first-line therapy for the treatment of ED in men with no contraindications to their use. Since the development of sildenafil (Viagra®) and its approval by the FDA in 1998, there have been two additional PDE-5 inhibitors approved for use in the treatment of ED; these are vardenafil (Levitra®) and tadalafil (Cialis®). All three agents are similar in their mechanism of action and efficacy; however, subtle differences exist between these agents.
(see Table 3). In January 2008, the FDA approved the use of once-daily tadalafil (Cialis) at doses of 2.5 mg and 5.0 mg for men who anticipate more frequent sexual activity, such as twice per week. The daily regimen is not recommended for men with severe renal failure or severe hepatic failure.

There are no well-designed, head-to-head trials comparing oral PDE-5 inhibitors. Efficacy has been demonstrated for all in the general population as well as special populations, such as men with diabetes mellitus, spinal cord injury, post-radical prostatectomy, multiple sclerosis, post-radiation therapy for prostate cancer, and depression. A variety of factors may account for oral PDE-5 inhibitor failure, including physician, patient, and partner-related causes, as well as disease and drug-related causes. Proper use of the medication, dose optimization, and follow up are essential to successful therapy. In individuals who fail initial trials with oral PDE-5 inhibitors, re-education and a re-challenge result in success rates ranging from 40% to 55% in prior non-responders (Atiemo, Szostak, & Sklar, 2003; McCullough, Barada, Fawzy, Guay, Hatzichristou, 2002). Similarly, individuals who have failed to respond to one PDE-5 inhibitor may respond differently to another (Carson et al., 2004b).

Visual and hearing loss have been reported since the approval of these medications. Although causality has not been established, the FDA recommends that patients and providers be aware of these adverse effects. Hearing loss, both with and without accompanying symptoms of

### Table 3. Oral PDE-5 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset of Action</th>
<th>t1/2</th>
<th>Dose</th>
<th>Metabolism</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
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<tbody>
<tr>
<td>Sildenafil</td>
<td>• Tmax 30 to 120 minutes • Median 60 minutes • Duration 4 hours • High-fat meal decreases absorption, and delays peak plasma concentration • ETOH may affect efficacy</td>
<td>2 to 5 hours</td>
<td>2.5 mg to 100 mg • Starting dose is 50 mg • Flexible dose study • 75% preferred 100 mg</td>
<td>• CytoP 450 3A4 • 2C9 patients with hepatic dysfunction • &gt;65 years or taking 3A4 or 2C9 inhibitors have increased levels • Potent 3A4 and 2C9 inhibitors include grapefruit, cimetidine, ketoconazole, and erythromycin • Patients taking ritonavir should use only 25 mg Q 48 hours • Severe renal insufficiency associated with increased levels</td>
<td>• Headache 15.0% • Flushing 10.5% • Dyspepsia 6.5% • Nasal congestion 4.5% • Altered vision 2.7% • NAOIN and hearing loss – This applies to all PDE-5 inhibitors</td>
<td>• Nitrates • Post-release labeling caution use in patients not studied, including men with MI, stroke, life-threatening arrhythmia within 6 months • Resting BP &lt;30/50 or &gt; 170/110 mm Hg • Cardiac failure • Unstable angina • Retinitis pigmentosa – Applies to all PDE-5 inhibitors • Must be on stable dose of alpha-blocker before concomitant use</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>• Tmax 30 to 120 minutes • Duration 4 to 5 hours • High-fat meals decrease maximum concentration by 18% to 50% • ETOH may affect efficacy</td>
<td>t1/2 4.5 hours</td>
<td>5 mg, 10 mg</td>
<td>• Metabolized by cytoP450, 3A4, and 2C9 • Same restrictions as sildenafil • Patients taking ritonavir or indinavir should not use more than 5 mg Q 48 hours</td>
<td>• Headache 8% to 10% • Flushing 6% to 13% • Rhinitis 1% to 8% • Dyspepsia 2% to 6%</td>
<td>• As above with sildenafil • Associated with minor 2Q prolongation of QT interval avoid in patients with congenital prolonged QT interval • Those on Class I (quinidine, procainamide) or Class II (amiodarone, sotalol) anti-arrhythmics</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>• Tmax 30 to 60 minutes • Median 120 minutes • Duration 12 to 36 hours • Plasma concentration not affected by food or ETOH</td>
<td>t1/2 17.5 hours</td>
<td>10 mg, 20 mg 2.5 or 5.0 mg for once daily use</td>
<td>• Metabolized by cytoP450, 3A4, and 2C9 • Same restrictions as sildenafil • Severe renal insufficiency • Antivirals start with 5 mg and not to exceed 10 mg Q 72 hours</td>
<td>• Headache 11% to 15% • Dyspepsia 4% to 10% • Backpain 5% to 6% • Nasal congestion 3% • Myalgia 3% to 4%</td>
<td>• As above with sildenafil</td>
</tr>
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</table>
None of the three FDA-approved PDE-5 inhibitors can be taken in conjunction with any form of nitrate, whether oral, topical, or intravenous.

condition that has been reported after the use of all 3 PDE-5 inhibitors and is felt to be unrelated to PDE-6 inhibition. NAION presents as acute monocular/binocular visual loss. Spontaneous NAION is the most common acute optic neuropathy in patients over the age of 50 years and occurs in approximately 1,500 to 6,000 people each year (Hattenhauer, Leavitt, Hodge, Grill, & Grady, 1997; Johnson & Arnold, 1994). One in four of these individuals will develop NAION in the other eye. NAION is felt to be the result of vascular injury at the optic head, which may be more frequently identified in individuals with certain anatomic characteristics, such as small cup to disc ratio. Risk factors for NAION include age greater than 50 years, diabetes mellitus, hypertension, coronary artery disease, hyperlipidemia, and smoking, which are the same risk factors as with ED (Ischemic Optic Neuropathy Decompression Trial Research Group, 1996; Rucker, Bioisse, & Newman, 2004). As of May 2005, there were 43 cases of NAION reported to the FDA after the use of PDE-5 inhibitors, including 38 associated with sildenafil, 4 with tadalafil, and 1 with vardenafil. Visual loss was noted in 36 patients, and it was permanent in 26 of 36 patients. A temporal relationship to PDE-5 inhibitor use was noted in 19 patients taking sildenafil, 4 taking tadalafil, and 1 taking vardenafil. The FDA noted that most, but not all, of the individuals had underlying anatomic or vascular risk factors for the development of NAION (FDA, 2007a). The role of PDE-5 inhibitors in the occurrence of NAION is unclear. At present, the FDA concluded that there is insufficient data to establish a causal effect; however, patients need to be appropriately counseled and recommends:

- Physicians/prescribers should advise patients to stop use of all PDE-5 inhibitors and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of NAION, a cause of decreased vision, which can result in permanent loss of vision.
- Physicians/prescribers should discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by the use of vasodilators, such as PDE-5 inhibitors.

Cardiac Safety with Oral PDE-5 Inhibitors

Controlled and post-marketing surveillance studies of the FDA-approved PDE-5 inhibitors demonstrated no increase in myocardial infarction or death rates in men who received oral PDE-5 inhibitors as part of either double-blind, placebo-controlled trials or open-label studies, compared to expected rates. In addition, patients with known coronary artery disease or heart failure who received PDE-5 inhibitors did not experience worsening of their ischemia, coronary vasoconstriction, or worsening hemodynamics on exercise testing or cardiac catheterization (Emmick, Stuewe, & Mitchell, 2002; Shakir, Wilton, Boshier, Layton, & Heeley, 2001; Wysocki, Farinas, & Swartz, 2002; Zusman, Morales, Glasser, & Osterloh, 1999). Vardenafil (Levitra) is not recommended for use in patients who are taking type IA antiarrhythmics (procainamide or quinidine) or type 3 antiarrhythmics (sotalol or amiodarone), or in patients with congenitally prolonged QT intervals due to its effect on the QT interval. Sildenafil (Viagra) and tadalafil (Cialis) are not associated with statistically significant changes in QT interval.

None of the three FDA-approved PDE-5 inhibitors can be taken in conjunction with any form of nitrate, whether oral, topical, or intravenous. Patients who develop chest pain after taking a short-acting PDE-5 inhibitor (sildenafil and vardenafil) cannot take nitroglycerin for more than 24 hours (Cheitlin et al., 1999), whereas those taking a tadalafil, a long-acting PDE-5 inhibitor, cannot take nitroglycerin for 48 hours. The FDA no longer considers concomitant use of alpha-blockers a contraindication to use of oral PDE-5 inhibitors. However, individuals on alpha-blockers must be on a stable dose of alpha-blocker prior to using an oral PDE-5 inhibitor.

Second-Line Therapies for ED

Second-line agents for the treatment of ED include intracavernous injection. Intracavernosal Alprostadil (MUSE) Intracavernosal alprostadil (250 ug to 1,000 ug) initially provided an alternative to intracavernous injection therapy; however, with the advent of oral therapy, its use has decreased. Currently, it is being used as a first-line therapy in those who have contraindica-
tions to the use of the oral PDE-5 inhibitors or those who fail oral therapy and who are reluctant to try intracavernous therapy. Success rates with intraurethral alprostadil were initially reported to be 49.2% to 65.9%, but further studies have demonstrated success rates of only 30% with intraurethral alprostadil (Hellstrom et al., 1996; Fulgham et al., 1998; Guay, Perez, Velasquez, Newton, & Jacobson, 2000; Mulhall, Jahoda, Ahmed, & Parker, 2001; Padma-Nathan et al., 1997). Improved results have been noted with the use of a constricting band, the ACTIS adjustable constriction loop, placed at the base of the penis to prevent venous outflow (Lewis, Weldon, Nemo, & the MUSE ACTIS Study Group, 1998). The most commonly reported side effect of intraurethral alprostadil is pain, occurring in 29% to 41% of patients, followed by dizziness in 1.9% to 14%. Hypotension has been noted in 3% of men with initial test dosing, and thus, test dosing in the office setting is recommended (Padma-Nathan et al., 1997).

**Vacuum Constriction Device**

The vacuum constriction device (VCD) remains an option for individuals who fail or who have contraindications to oral therapy and/or intracavernous/intraurethral therapies. Vacuum devices provide passive engorgement of the corpora cavernosa in conjunction with a constricting band placed at the base of the penis to retain blood within the corpora cavernosa. Efficacy in terms of satisfactory rigidity for intercourse is as high as 90% (Soderahl, Petroski, Mode, Schwartz, & Thrasher, 1997; Witherington, 1989), but satisfaction rates range between 27% to 94% (Turner et al., 1991; Vrijhof & Delaere, 1994). Contraindications to the use of VCDs include bleeding disorders or anticoagulant therapy. Patients, particularly patients with spinal cord injury, must be instructed to remove the constricting band 30 minutes after placement to prevent penile ischemia. More common side effects include pain, ejaculatory troubles, petechiae, bruising, and numbness (Lewis & Witherington, 1997). VCDs may be more effective than intracavernous injection therapy in men with severe veno-occlusive dysfunction. In older patients with other co-morbidities who do not participate in frequent sexual activity and who desire a non-invasive, drug-free form of ED therapy, the VCD may be the treatment of choice (Hatzimouratidis & Hatzichristou, 2005). Patients must be counseled to use only a VCD, which contains a vacuum limiter, preventing extremely high negative pressures that may injure the penis (Montague et al., 2005).

**Intracavernous Therapy**

Despite intracavernous therapy being used for more than 20 years, alprostadil (5 ug to 40 ug) is the first and only drug approved worldwide for this use (Leungwattanakij, Flynn, & Hellstrom, 2001; Linet & Ogirc, 1996; Porst, Buvat, Meuleman, Michal, & Wagner, 1998). Other forms of injection therapy, including papaverine (Pavabid®) (20 mg to 80 mg), papaverine (7.5 mg to 45 mg) plus phentolamine (0.25 mg to 1.5 mg) (Bimix®), and papaverine (8 mg to 16 mg) plus phentolamine (0.2 mg to 0.4 mg) plus alprostadil (10 ug to 20 ug) (Trimix®), have been used in the management of ED, but often require acquisition through multiple pharmacies. Trimix is associated with the highest efficacy rate, but also has the highest risk of priapism and corporal fibrosis. Intracavernous therapy is associated with treatment satisfaction rates of 87% to 93.5% in patients and 86% to 90.3% in their partners (Heaton et al., 2001). High discontinuation rates have been noted with intracavernous therapies, ranging from 40.7% to 68% (Flynn & Williams, 1996; Pagliarulo, Ludovico, Cirillo-Marucco, Corvasce, & Pagliarulo, 1996; Sundaram et al., 1997).

Intracavernous therapy is associated with the risk of priapism, and thus, all patients should be started on a low dose of therapy and the dose titrated according to response. The starting dose varies with the individual's underlying medical problem(s). Patients who have a spinal cord injury are often test-dosed, with doses as low as 5 ug of alprostadil, whereas individuals with diabetes mellitus are often test-dosed at 10 ug and frequently require 20 ug to 40 ug to achieve a satisfactory erection. Injection of intraurethral alprostadil has been associated with hypotension, and individuals should always be test-dosed in the office prior to starting therapy at home. Fibrosis of the tunica albuginea, related to repetitive trauma for the injections, is possible, and patients are instructed to alternate sides to prevent penile curvature.

**Third-Line Therapies for ED**

Placement of a penile prosthesis is the primary therapeutic option for individuals who have failed or cannot tolerate prior therapies. Surgeries performed to limit venous outflow of the penis are not recommended by the AUA guidelines for management of ED. The AUA guidelines indicate that arterial reconstructive surgery is a treatment option only in healthy individuals with recently acquired ED secondary to a focal arterial occlusion and in the absence of any generalized vascular disease (Montague et al., 2005).

**Penile Prosthesis**

The penile prosthesis remains a surgical option for men who fail intracavernous therapy and/or in whom intracavernous therapy is not acceptable. There are essentially two types of penile prostheses – inflatable and semi-rigid rod. The semi-rigid prosthesis consists of malleable rods constructed of silicone elastomer, with central metal cables that allow for some degree of movement to the device. Mechanical malfunction with this device is rare; however, over the long term, microfractures of the internal metal cables can decrease penile rigidity (Cohan, Dunnick, & Carson, 1989).

There are two and three-piece inflatable prostheses. Two-piece inflatable prostheses contain two
inflatable cylinders that are implanted into each of the corpora and a pump that is placed into the scrotum. An erection is achieved by compressing the pump in the scrotum, which transfers fluid from the reservoir areas in the pump and proximal cylinders into the inflatable part of the cylinder to produce cylinder rigidity. A limitation of this device is the small amount of fluid that may be transferred, which compromises rigidity. The three-piece penile prosthesis is the prosthesis of choice of most patients because it provides a larger volume of fluid in the cylinders and better rigidity. The three-piece prosthesis differs from the two-piece in that there is a fluid-filled reservoir, and compression of the scrotal pump transfers fluid from the reservoir into the cylinders. Unlike other forms of therapy, the prosthesis provides rigidity by an increase in girth, but it is not associated with an increase in length. Furthermore, penile length may actually decrease slightly after placement of a penile prosthesis. One of the three-piece prostheses, the Ultrex™ cylinders produced by American Medical Systems, actually allows for an increase in length, up to 15% in addition to the increase in girth (Milbank, Montague, Angermeier, Lakin, & Worley, 2002).

To help decrease the risk of infection, the prostheses are available impregnated with antibiotics or with hydrophilic coatings that allow antibiotics to be topically placed onto the device for 24 to 72 hours. The AMS 700 CX InhibiZone™ model has a coating of rifampin and minocycline, which has been shown to decrease the infection rate from 2.07% to 1.06% at 1 year (Carson, 2004b). The Mentor Titan™ has a hydrophilic coating, Resist™, which is associated with a decreased infection rate from 1.6% to 0.68% at 180 days (Walter & Hellstrom, 2004). It also has a lockout valve on the prosthesis reservoir to decrease the chances of penile cylinder autoinflation.

Placement of a penile prosthesis, unlike the other forms of therapy for ED, is considered to be permanent. If the prosthesis is removed, other forms of therapy are rarely successful due to extensive penile scarring related to the prosthesis. Thus, prior to placement, patients must be properly counseled regarding the expectations and risks of penile prostheses. The most significant complication after placement of a penile prosthesis is infection. In most cases, penile prosthesis infections result in removal of the device and complete loss of erectile function. In select cases, a salvage procedure may be performed whereby the infected prosthesis is removed, the wound irrigated using a special regimen, and a new prosthesis is placed, with success rates of 85% (Mulcahy, 2003). Technical complications, such as urethral perforation, corporal perforation, or placement of an inadequate length cylinder leading to lack of glans support, occur infrequently. In patients who have been on intracavernous injection therapy, corporal fibrosis may occur, making placement of an inflatable prosthesis difficult; in such situations, a narrower cylinder may be useful.

Penile Arterial Reconstructive Surgery

Although surgical intervention for the treatment of vasculogenic ED has been performed by a variety of procedures for the past 30 years, there is little data on the long-term efficacy of the procedures. Most reported studies involve only small numbers of patients and lack objective outcome criteria. Four studies that included outcome data utilized either an anastomosis of the inferior epigastric artery to the dorsal penile artery (dorsal artery arterialization) or anastomosis of the inferior epigastric artery to the dorsal penile vein (dorsal vein arterialization). Satisfactory outcomes, measured by objective criteria, occurred in 36% to 91% of the 50 patients who participated in these four studies (Montague et al., 2005).

Combination Therapies for ED

Combination therapy has been used in the management of ED since the 1980s with the advent of various drug combinations for intracavernous injection therapy. Although investigational, a variety of combination therapies have been tried in small, open-label, short-term studies in men with ED refractory to various monotherapies. Although provocative, these studies provide limited information regarding the true efficacy and safety of such combinations and provide no long-term data regarding issues such as tolerance/tachyphylaxis. Patients considering combination therapy must be warned of the unknown risk of priapism, as well as the lack of long-term data regarding combination therapy.

Sildenafil Plus Intraurethral Prostaglandin E1

Raina, Nandipati et al. (2005) evaluated the use of intraurethral prostaglandin E1 (MUSE) in 23 men with post-radical retropubic prostatectomy (RRPX) ED refractory to 100 mg of sildenafil. Nineteen of the 23 (89%) men reported improvement in rigidity and sexual satisfaction. Nehra, Blute, Barrett, and Moreland (2002) evaluated 28 patients, 17 with post-RRPX ED and 11 with organic ED who had failed monotherapy with either 100 mg of sildenafil or 1,000 mcg of MUSE and who were then treated with the combination of the two agents. All 28 patients reported improvement in their erections and were able to achieve vaginal penetration with a mean of 3.6 intercourse
episodes per month. In addition, some individuals were able to decrease their dose of sildenafil to 50 mg.

**Oral PDE-5 Inhibitors Plus Intracavernous Injection of Prostaglandin E1**

Mydlo, Volpe, and MacChia (2000) evaluated the combined use of intracavernosal prostaglandin E1 and oral PDE-5 inhibitors in 34 men with post-RRPX ED refractory to oral therapy. Eighteen men received 100 mg of sildenafil, and 16 received 20 mg of vardenafil and were then started on 15 to 20 mcg of intracavernous prostaglandin E1. Twenty-two of the 32 men who started on 15 to 20 mcg of intracavernous prostaglandin E1 and oral PDE-5 inhibitors in 34 men with post-RRPX ED refractory to oral therapy demonstrated improvement in erections, and some were able to lower the dose of intracavernous therapy with a sustained response.

**Sildenafil Combined with an Oral Alpha-Antagonist**

De Rose, Giglio, Traverso, Lantieri, and Carmignani (2002) randomized 28 patients who had failed to respond to sildenafil alone to sildenafil plus placebo (14) or sildenafil plus 4 mg doxazosin (14) for 30 days. Only 7.1% of the men on sildenafil plus placebo showed significant improvement in international index of erectile function (IIEF) scores, whereas 78.6% of those taking sildenafil plus doxazosin demonstrated a significant improvement in IIEF scores.

**Intracavernous Prostaglandin E1 Combined with Oral Alpha-Antagonist**

Kaplan, Reis, Kohn, Shabsigh, and Te (1998) evaluated the use of combination alpha-blocker therapy and intracavernous prostaglandin E1 in men who failed prior intracavernous prostaglandin E1. Thirty-eight males received daily doxazosin 4 mg and intracavernous prostaglandin E1 (10 to 20 ug) for 12 weeks. Combination therapy resulted in an overall 55.7% improvement on a global efficacy questionnaire. Fifty-eight percent of the men achieved a 60% increase in total IIEF score.

**Vacuum Device Combinations**

Chen, Sofer, Kaver, Matzkin, and Greenstein (2004) evaluated 10 males who had failed therapy with the vacuum device and intracavernous injection therapy for ED. The men were treated with either 60 mg papaverine or 30 ug of prostaglandin E1, followed by vacuum device. All 10 responded to combination therapy with satisfactory erections. Chen et al. (2004) also assessed the combination of vacuum device and sildenafil in men who were not satisfied with either treatment alone. All 41 men treated with combination therapy reported a greater level of satisfaction with results than with either treatment alone as assessed by the global assessment question.

Raina, Agarwal et al. (2005) evaluated the use of the combination of sildenafil plus the vacuum device in men who had failed initial early use with the vacuum device post-RRPX. Seventy-four patients started on early use of the vacuum device after catheter removal post-RRPX. Thirty-one (42%) were not satisfied with early use of the vacuum device after RRPX (mean f/up 4 to 5 months) and were started on sildenafil 100 mg 1 to 2 hours before use of the vacuum device for sexual intercourse. This combination was used for a total of 5 attempts before assessment with the sexual health inventory for men (SHIM, abbreviated IIEF, IIEF-5) and a visual analog scale to assess rigidity. Of the 31 patients who tried the combination therapy, 7 (22%) noted no improvement, whereas 24 (77%) had improvement in penile rigidity and sexual satisfaction. Seven (30%) reported return of natural erections at 18 months using combination therapy, with 5/7 reporting erections satisfactory for vaginal penetration.

**Testosterone Plus Sildenafil**

Shabsigh, Kaufman, Steidle, and Padma-Nathan (2004) compared the efficacy of adding testosterone gel to sildenafil therapy in patients with morning serum testosterone levels less than 400 ng/DL who had failed to respond to sildenafil alone. Patients were randomized to 1% testosterone gel or placebo plus 100 mg sildenafil. After 12 weeks, patients receiving testosterone plus sildenafil had a greater improvement in erectile function than those receiving placebo plus sildenafil.

**Current Concepts Regarding Testosterone Replacement Therapy**

Between 1993 and 2000, prescription sales for various testosterone formulations increased by 500% (Bhasin & Buckwalter, 2001). Despite this exponential increase in the use of testosterone replacement therapy (TRT), the role of testosterone in the physiology of erections is unclear, and thus, the role of testosterone therapy in the management of ED and androgen deficiency is controversial. Animal models have suggested a role for androgens in erectile function, but the role of androgens in the human erectile response is not well defined (Gore, Swerdloff, & Rajfer, 2005). The prevalence of hypogonadism increases from 7% in males 40 to 60 years of age to 20% in males 60 to 80 years of age (Araujo et al., 2004). Androgen deficiency in the aging male is associated with decrease in lean body mass, increase in body fat, osteoporosis, decreased libido, ED, and depression.

Testosterone secretion follows a circadian pattern, with peak testosterone levels in the early morning and a nadir in the late afternoon (Cooke, McIntosh, & McIntosh, 1993). This circadian pattern of testosterone secretion is lost in older men (Feldman et al., 2002). Testosterone exists in both an unbound and bound state. The bioavailable form of testosterone is the unbound testosterone and that which is bound to albumin. The inactive form of testosterone is that which is bound to sex hormone-binding globulin (SHBG). Beyond 40 years of age, the total serum testosterone level decreases at an average rate of 0.8% per year. In addition, the level of inactive testosterone, that bound to SHBG, increases with age at a rate of 1.5%.
Diagnosing Androgen Deficiency in the Aging Male

The diagnosis of hypogonadism is by hormonal evaluation. It is rarely identified by history and physical examination. Although testosterone positively affects libido, decreased libido may be related to other causes, such as depression and lack of interest due to underlying ED. Similarly, the presence of normal secondary sex characteristics on physical examination does not rule out a low testosterone level.

In most men, a morning total testosterone level is all that is necessary. In older and obese males, increased SHBG levels may aberrantly raise total serum testosterone levels; therefore, measurement of bioavailable testosterone, ideally via equilibrium dialysis assay, is more accurate. Although there are no clear-cut testosterone levels that define hyponadism, it is believed that levels less than 250ng/dL are low, levels greater than 350 ng/dL are normal, and levels between 250 ng/dL and 350 ng/dL are indeterminate. If the testosterone level is low, then it is appropriate to check LH, FSH, and serum prolactin levels.

Medications that may affect gonadal function include thiazide diuretics, long-acting oral opiates, antiepileptics, corticosteroids, and atypical antipsychotic (such as risperidone and olanzapine) (Lunenfeld, 2003). If the prolactin level is elevated, then further evaluation with an MRI is indicated to rule out a pituitary adenoma.

What Level of Serum Testosterone Level Warrants Treatment?

Current consensus recommendations suggest limiting use of TRT to men with a serum testosterone level of less than 200 ng/dL and symptoms of hyponadism, although evidence supporting this recommendation is lacking (The Practice Committee of the American Society for Reproductive Medicine, 2004). Studies have demonstrated that in individuals with low normal testosterone levels who have failed oral PDE-5 inhibitor therapy, an improvement in response to PDE-5 inhibitors with testosterone supplementation exists (Shabsigh et al., 2004). The use of TRT for other factors, such as bone density and body fat mass, remains controversial.

What Types of TRT Are Available?

The ideal testosterone preparation is that which allows for normalization of serum testosterone levels, mimics the normal
circadian pattern of testosterone production, produces normal levels of testosterone metabolites, and minimizes side effects. Therapies currently used in the United States include injectable, topical, and transbuccal testosterone. Oral testosterone therapy is not used in the United States due to the inability to achieve adequate systemic levels and the higher risk of adverse effects. Table 4 lists the available formulations of testosterone.

What Are the Potential Adverse Effects of TRT?

Side effects relative to the individual preparation are listed in Table 4. TRT may increase prostate size and cause lower urinary tract symptoms. In males on testosterone supplementation, the PSA may increase by 0.3 ng/ml/year, whereas older men may experience up to a 0.43 ng/ml/yr change in PSA when on TRT (Bhasin & Buckwalter, 2001). A baseline PSA should be obtained before starting TRT and a repeat PSA obtained 6 to 12 weeks after starting therapy and semi-annually thereafter. Polycythemia and sleep apnea are more commonly associated with the parenteral testosterone, and a baseline hematocrit is recommended in individuals starting TRT and periodically thereafter.

The impact of TRT on cardiovascular morbidity remains poorly defined. Physiologic doses of testosterone have either no effect or potentially beneficial effects on the cardiovascular system. Caution should be used in men with congestive heart failure, since testosterone therapy may lead to an increase in hematocrit levels (Kostis et al., 2005; Swerdloff & Wang, 2003). From a cardiovascular standpoint, higher serum testosterone levels may be cardioprotective, and changes in lipid profile are less relevant when the testosterone level is restored to physiologic levels (Liu et al., 2003).

Changes in anticoagulant activity may be seen with androgen use, and thus, individuals on anticoagulants should have regular laboratory testing. Concurrent use of oxyphenbutazone and androgens may lead to increased levels of oxyphenbutazone. In diabetic patients, the metabolic effects of androgens may lower the blood glucose and insulin requirements. Concurrent administration of testosterone with adrenocorticotropic hormone (ACTH) may enhance edema formation, and the combination should be used with caution, especially in patients with cardiovascular or hepatic disease.

Conclusion

ED is a highly prevalent condition that remains under-diagnosed and under-treated. Primary care physicians and nurse practitioners need to initiate the assessment of erectile function in patients who are considered high risk. A focused history, physical examination, and a limited laboratory evaluation are often helpful in identifying risk factors for ED. Due to the high incidence of underlying cardiovascular disease, all men with ED should be assessed for cardiovascular risk factors. Men with significant cardiovascular risk factors should undergo further evaluation and management prior to treating their ED. Oral PDE-5 inhibitors remain the first-line therapy in individuals with no contraindications to their use. Although causality has not been established for NAOIN and hearing loss, the FDA recommends that patients be educated regarding these conditions. Second-line therapies include the vacuum device, intraurethral alprostadil (MUSE), and intracavernous injection therapy. The most common third-line therapy is placement of a penile prosthesis. Penile arterial revascularization procedures should only be performed on certain individuals by select surgeons who are skilled in such procedures. Combination therapy may be considered in certain individuals after proper counseling. The role of TRT remains controversial, and individuals started on TRT should be followed carefully with periodic PSA determinations and serum hematocrits. The current approved therapies for erectile dysfunction and investigational combination therapies provide nearly every man with ED the opportunity for safe and efficacious treatment.

References


