Evaluation and Management of Erectile Dysfunction in Clinical Practice

Case Study and Commentary, William O. Brant, MD, Tom F. Lue, MD, and James F. Smith, MD, MS

Erectile dysfunction (ED), defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance [1], is a common disorder that may affect 18 million men in the United States [2,3]. A meta-analysis of prevalence studies has demonstrated heterogeneous findings due to problems in reporting age categories, severity, and nomenclature [4]. Consistent with these findings, other studies have shown that prevalence rates vary by country or origin and ethnic group [5–9]. In the population-based National Health and Nutrition Examination Study (NHANES), almost 20% of all males and 75% of men older than 75 years reported ED [10]. This constitutes a significant psychological and public health burden. In 1998, almost 3400 out of 100,000 office visits by Medicare beneficiaries were related to ED [11]. Furthermore, annual expenditures in the United States for ED excluding pharmaceutical costs were $330 million in 2000; oral medication sales in 2005 amounted to $1.6 billion for sildenafil, $747 million for tadalafil, and $327 million for vardenafil [11]. Beyond the financial and social impact, studies have clearly demonstrated the negative impact of ED on health-related quality of life [12,13].

**CASE STUDY**

**Initial Presentation**

A 55-year-old man presents to his primary care physician with a chief complaint of poor erections.

**History**

For the last 5 years, the patient has noticed a gradual diminution in both the quality of his erections as well as his ability to maintain them. His libido and penile sensation are good, and he is capable of orgasm and ejaculation. He denies any history of trauma or significant lower urinary tract symptoms. Statin therapy and nonspecific β-blocker medication control his dyslipidemia and essential hypertension, respectively. He denies a history of diabetes, heart disease, or vascular disease.

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ERECTILE DYSFUNCTION

and has not undergone abdominal or pelvic surgery. His wife of 25 years is supportive and also interested in improving his sexual function. The patient has a 20 pack-year history of tobacco use but quit smoking 15 years ago. He uses alcohol in moderation and denies the use of other recreational drugs. He exercises infrequently but tries to eat a healthful diet and has not suffered from obesity or weight gain. He has not been previously evaluated for ED or tried any treatments.

Physical Examination

The patient’s height is 67 in and he weighs 150 lb. He appears healthy, his heart rate is 71 bpm, and his blood pressure is 120/70 mm Hg. Examination of the head, eyes, ears, nose, throat, neck, chest, and abdomen are unremarkable. He has no evidence of neurologic deficits or peripheral vascular disease. His testes are bilaterally descended, with symmetric normal size and texture. His penis is circumcised and free of any plaques. Digital rectal examination reveals a 25-g gland without nodules or induration.

- What causes ED?

Penile erection is a neurovascular event modulated by psychological and hormonal status (Figure 1 and Figure 2) [14].

The penis is innervated by autonomic and somatic nerves. The cavernous nerves regulate the blood flow during erection and detumescence. Sexual stimulation causes a release of neurotransmitters from the cavernous nerve terminals and relaxing factors from the endothelial cells in the penis, resulting in relaxation of smooth muscle in the arteries and arterioles supplying the erectile tissue. With this relaxation, there is a several-fold increase in blood flow. Additionally, venous outflow channels are compressed and thus the blood is trapped; additional muscle contractions serve to increase intracavernous pressures.

The principal neurotransmitter for penile erection is nitric oxide, which is released from nonadrenergic-noncholinergic neurotransmission of the cavernous nerves and the endothelium [15]. The pathway is regulated by cyclic guanosine monophosphate (cGMP), and the end result is a drop in cytosolic calcium and smooth muscle relaxation/erection. During the return to the flaccid state, cGMP is hydrolyzed to guanosine monophosphate by phosphodiesterase type 5 (PDE5) (Figure 3).

Sexual function progressively declines as men age. The latent period between sexual stimulation and erection increases, erections are less turgid, ejaculation is less forceful, ejaculatory volume decreases, and the refractory period between erections lengthens. There is also a decrease in penile sensitivity to tactile stimulation, a decrease in serum testosterone concentration, and an increase in cavernous muscle tone [16–18].

Many common medical conditions may induce ED. Common risk factors associated with generalized penile arterial insufficiency include hypertension, hyperlipidemia, cigarette smoking, diabetes mellitus, and pelvic irradiation [19–21]. In some cases, ED may predate cardiovascular disease and may serve as an important marker for its presence [22]. Psychogenic ED can be caused by performance anxiety, strained relationship, lack of sexual arousability, and overt psychiatric disorders such as depression and schizophrenia. Several studies have confirmed the strong relationship between depression and sexual dysfunction [23,24]. Many classes of medications, including antihypertensive agents, may cause ED via a variety of mechanisms as can use of alcohol, cigarettes, and cocaine. Cigarette smoking may induce vasoconstriction and penile venous leakage because of its contractile effect on the cavernous smooth muscle [25]; more importantly, chronic use may accelerate atherosclerotic changes in penile microvasculature. Alcohol in small amounts may improve erections and increases libido because of its vasodilatory effect and the suppression of anxiety; however, large amounts of alcohol can cause central sedation, decreased libido, and transient ED. Chronic alcoholism may cause hypogonadism and polyneuropathy, which may affect penile nerve function [26].
• What should be included in the evaluation of ED?

ED may be the first manifestation of many diseases, including diabetes mellitus, coronary artery disease, hyperlipidemia, hypertension, spinal cord compression, pituitary tumors, and pelvic malignancies (Table 1). The evaluation of a patient with ED requires a thorough medical, sexual, and psychosocial history; physical examination; and appropriate laboratory tests (eg, serum creatinine, fasting glucose, lipid profile, testosterone) aimed at detecting these diseases. If the patient’s total testosterone concentration is low, serum free (or bioavailable) testosterone, prolactin, and lutenizing hormone should be further investigated. Objective physiologic tests are never a substitute for self-reported patient symptoms in order to establish the diagnosis.

After assessing the needs and goals of the patient and his partner, further diagnostic and treatment options should be contemplated. Consideration must be made of the patient’s physical and mental health as well as his motivation and needs. The patient’s performance status and cardiovascular health also should be evaluated, in consultation with a cardiologist if necessary, in order to assess the patient’s ability to tolerate sexual activity. Occasionally, a change in lifestyle or medications may be all that is needed to restore potency.

Some men may benefit from a referral for further testing and treatment (Table 2); however, many urologists have largely adopted goal-oriented evaluation and treatment, and these additional tests are not commonly used. The indications for specialty referral include complex gonadal or other endocrine disorders, neurologic deficit suggestive of brain or spinal cord disease, deep-seated psychological or psychiatric problems, Peyronie’s disease, posttraumatic or primary ED, and active cardiovascular disease, especially if the patient wishes to take PDE5 inhibitors. Historically, androgens were thought to enhance male sexual function; however, androgen therapy should be used only in hypogonadal men. Testosterone therapy in men with normal hormonal levels may temporarily increase libido and desire but does not affect ED [27].

Initial Assessment

The patient has several risk factors for ED, including use of antihypertensive medications, mild systemic vascular disease, and a history of tobacco use. Testosterone (including levels of unbound testosterone), lipid profile, fasting glucose, and serum creatinine were found to be normal.

• What are initial treatment options for ED?

PDE5 inhibitors act to slow the breakdown of cGMP. As such, they act as amplifiers of the normal erectile physiology and are dependent on intact libido, sexual stimulation, sensory pathways, and other myriad factors that must be present in normal erectile function. Because of their ease of use, PDE5 inhibitors are used as first-line treatment for ED (Table 3). Currently, there are 3 PDE5 inhibitors approved by the U.S. Food and Drug Administration (FDA): sildenafil (approved in 1998), tadalafil, and vardenafil (both approved in 2003). Although each medication is relatively specific for PDE type 5, there are crossover effects on other PDE5 isoforms; these effects are partially responsible for the specific side effects seen with each medication. For example, sildenafil and to a lesser...
Extent vardenafil have cross-reactivity with PDE6 found in the eye, which is responsible for the sensitivity to light and other ocular disturbances that are seen with these medications. Tadalafil does not demonstrate significant cross-reactivity to PDE6 but does affect PDE11, which is found in disparate organs such as the testis and heart, although the clinical implications are not clear [28]. Although the PDE5 inhibitors act via a common pathway and thus share many similarities, there are pharmacologic and therapeutic differences, particularly with regard to timing of the clinical effect.

Sildenafil has onset of action within 30 to 60 minutes and lasts from 4 to 8 hours, as assessed by Rigiscan measurements [29], although it may act as quickly as 14 minutes in over one third of users [30]. Vardenafil acts somewhat more rapidly at 25 minutes and also lasts for 4 to 8 hours [31,32]. In contrast, tadalafil acts quickly, 45 minutes as assessed by Rigiscan measurements and as little as 16 minutes as assessed by patient-controlled stopwatch, but lasts much longer with efficacy continuing up to 36 hours [33]. However, the subtle differences in time of onset may be of only minor clinical import. A population-based study from the United Kingdom examined the time course of intercourse (from a man considering it, to agreeing with his partner, to actually beginning it) and found that it was 53 minutes on average between the initial thought and the beginning of intercourse, whether or not the patient had ED [34]. Therefore, all of the available PDE5 inhibitors likely have appropriate onset of action. In hypogonadal men with ED, transdermal and intramuscular testosterone therapy are considered more efficacious than oral testosterone preparations [34,35].

- How efficacious are PDE5 inhibitors for ED? What side effects are seen? Are there any contraindications to treatment with PDE5 inhibitors?
Table 1. Classification and Common Causes of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Class</th>
<th>Common Disorders</th>
<th>Pathophysiology</th>
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<tbody>
<tr>
<td>Neurogenic</td>
<td>Stroke or Alzheimer's disease</td>
<td>Interrupted neuronal transmission, failure to initiate nerve impulse</td>
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<td>Spinal cord injury</td>
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<td></td>
<td>Radical pelvic surgeries</td>
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<td></td>
<td>Diabetic neuropathy</td>
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<td></td>
<td>Pelvic injury</td>
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<tr>
<td>Psychogenic</td>
<td>Depression</td>
<td>Impaired nitric oxide (NO) release, overinhibin of NO release, loss of libido</td>
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<td></td>
<td>Psychological stress</td>
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<td></td>
<td>Performance anxiety</td>
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<td></td>
<td>Relationship problems</td>
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<tr>
<td>Hormonal</td>
<td>Hypogonadism</td>
<td>Loss of libido, inadequate NO release</td>
</tr>
<tr>
<td>Vasculargenic (arterial and cavernosal)</td>
<td>Hypertension</td>
<td>Impaired venooclusion, inadequate arterial inflow</td>
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<td></td>
<td>Atherosclerosis</td>
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<td></td>
<td>Diabetes mellitus</td>
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<td></td>
<td>Trauma</td>
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<td></td>
<td>Peyronie's disease</td>
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<tr>
<td>Drug-induced</td>
<td>Antihypertensive agents</td>
<td>Central suppression, decreased libido, alcoholic neuropathy, vascular insufficiency</td>
</tr>
<tr>
<td></td>
<td>Antidirogen medications</td>
<td></td>
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<tr>
<td></td>
<td>Antidepressants</td>
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<tr>
<td></td>
<td>Alcohol abuse</td>
<td></td>
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<tr>
<td></td>
<td>Cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>Systemic diseases</td>
<td>Old age</td>
<td>Multifactorial, neuronal and vascular dysfunction</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td></td>
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<tr>
<td></td>
<td>Chronic renal failure</td>
<td></td>
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<tr>
<td></td>
<td>Coronary heart disease</td>
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In short-term (12-week) studies, sildenafil was found to lead to a 65% successful intercourse rate in general ED populations as compared with a 20% success rate with placebo [35]. These trends are borne out when the ED population is stratified in terms of duration of ED, severity (mild/moderate vs. severe), and origin (organic vs. psychogenic vs. mixed) [35]. Longer-term data are also available. In an open-label 4-year extension study, over 95% of patients continued to be satisfied with the effect of sildenafil on erections, with a cumulative dropout rate of 6.3% for insufficient response and 1.2% for adverse events [36]. Vardenafil showed similar efficacy, with greater than 70% of patients experiencing successful intercourse during a 12-week period [37] and greater than 85% of patients having success at 2 years [38]. The efficacy of tadalafil is also similar, with greater than 60% and 70% of patients having successful intercourse with 10-mg and 20-mg doses, respectively [33].

Side effects of PDE5 inhibitors are generally mild and well tolerated. For sildenafil, side effects include headache (16%), flushing (10%), dyspepsia (7%), and nasal congestion (4%), although as previously noted, a much smaller percentage of men discontinue the medications as a result of these side effects [39]. Vardenafil has a similar side effect profile, with the FDA Web site listing headache (15%), flushing (11%), dyspepsia (9%), and rhinitis (4%) as side effects occurring appreciably more than in patients taking placebo. Tadalafil has somewhat less flushing (3%) than the other PDE5 inhibitors but uniquely has significant rates of pain at different sites, including back (6%), myalgia (3%), and limb pain (3%).

Priapism, a pathologic erection that lasts more than 4 hours despite lack of sexual stimulation, is extremely uncommon, with isolated case reports in the literature [40,41]. Nonarteritic ischemic optic neuropathy is a very rare complication that may be associated with PDE5 inhibitor use [42]. Due to the risk of profound and dangerous hypotension that may result from the use of PDE5 inhibitors and nitrate-containing medication, regular or intermittent use of nitrates (eg, nitroglycerin, isosorbide dinitrate) is an absolute contraindication to PDE5 inhibitor use. Amyl nitrate inhalers (“poppers”) are occasionally used as a drug of abuse, and the practitioner should ask about their use prior to prescribing PDE5 inhibitors. Taken alone, sildenafil causes only mild (<10 mm Hg) and transient effects on systolic and diastolic blood pressure [43].

Table 2. Tests That May be Used in the Urologic Workup of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Test</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined injection and stimulation test (injection of intracavernous medication followed by penile stimulation)</td>
<td>Assess penile vascular function, therapeutic test in men who choose intracavernous therapy</td>
</tr>
<tr>
<td>Duplex (color) ultrasonography</td>
<td>Assess vascular function and Peyronie’s disease</td>
</tr>
<tr>
<td>Cavernosography</td>
<td>Young men with congenital or traumatic venous leakage</td>
</tr>
<tr>
<td>Pelvic arteriography</td>
<td>Young men with traumatic arterial insufficiency</td>
</tr>
<tr>
<td>Ambulatory nocturnal penile tumescence and rigidity</td>
<td>Differentiate psychogenic from organic erectile dysfunction</td>
</tr>
</tbody>
</table>

Controlled and postmarketing studies of the 3 available PDE5 inhibitors have not demonstrated any increase in rates of myocardial infarction or death; this was true in double-blind, placebo-controlled trials as well as in open-label studies (when compared with expected rates in the study populations) [44]. In patients with known coronary artery disease or heart failure, use of PDE5 inhibitors did not lead to worsening ischemia, coronary vasoconstriction, or worsening hemodynamics on exercise testing or cardiac events.

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catheterization. PDE5 inhibitors have a minimal effect on QTc interval [45]. However, vardenafil is not recommended in patients who take type 1A (eg, quinidine, procainamide) or type 3 antiarrhythmic agents (eg, sotalol, amiodarone) or in patients with congenital prolonged QT syndrome.

Due to a lack of controlled clinical data, PDE5 inhibitors should be used with caution, if at all, in patients with recent serious cardiovascular events, uncontrolled hypertension, unstable angina, or retinitis pigmentosa. One proposed rule of thumb is that patients with cardiovascular disease may be stratified into high, intermediate (which may be further stratified depending on subsequent testing), and low risk; low-risk patients may be treated with first-line agents while those at high risk (eg, patients with unstable angina, uncontrolled hypertension, or a myocardial infarct or stroke within the last 2 weeks) should have their cardiovascular status stabilized prior to resuming sexual activity [46].

**Initial Management**

Because this patient does not have any signs or symptoms that would require more extensive testing, the choice is made to initially change his antihypertensive medication to an angiotensin-converting enzyme inhibitor. The angiotensin-converting enzyme inhibitor continues to control the patient’s blood pressure but does not alleviate his symptoms of ED. He is begun empirically on a PDE5 inhibitor and given thorough instructions on its use. After trying the medication on several occasions, he has found it to be somewhat helpful but finds the side effects (headaches and flushing) to be intolerable. He has the same symptoms on each of the 3 medications.

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**Table 3. Treatment Options for Erectile Dysfunction**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosexual therapy</td>
<td>$50–$150/session</td>
<td>Noninvasive, partner involved, curative for psychogenic ED</td>
<td>Time consuming</td>
<td>If patient resistant to medication, first-line treatment; may be combined with other treatments</td>
</tr>
<tr>
<td>Oral PDE5 inhibitor (ie, sildenafil, tadalafil, vardenafil)</td>
<td>$10/dose</td>
<td>Effective 1-hour wait, up to 24-hour action (tadalafil)</td>
<td>Contraindicated in men with severe cardiovascular disease and men on nitrates; side effects common</td>
<td>First-line treatment</td>
</tr>
<tr>
<td>Vacuum constriction device</td>
<td>$150–$450/device, least expensive</td>
<td>No systemic side effects</td>
<td>Unnatural erection, discreet &amp; traps ejaculation, causes petechiae and numbness</td>
<td>Second-line treatment</td>
</tr>
<tr>
<td>Transurethral injection (MUSE*)</td>
<td>$25/dose</td>
<td>Local therapy, few systemic side effects</td>
<td>Moderately effective, requires training, causes penile pain</td>
<td>Second-line treatment</td>
</tr>
<tr>
<td>Penile injection (alprostadil for injection or mixtures†)</td>
<td>$5–$25/dose</td>
<td>Highly effective (up to 90%), few systemic side effects</td>
<td>Requires injection, causes penile pain, high dropout rate, risk of priapism or fibrosis</td>
<td>Second-line treatment</td>
</tr>
<tr>
<td>Prosthesis (all types)</td>
<td>$8000–$15,000</td>
<td>Very successful, normal spontaneity, most control over length of intercourse</td>
<td>Infection, requires surgery and replacement at product end of life, penile shortening</td>
<td>Men dissatisfied with medical management</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>$10,000–$15,000</td>
<td>Potentially curative</td>
<td>Requires surgery, poor results in older men with generalized disease, mixed results even in selected populations</td>
<td>Young men with congenital or traumatic ED</td>
</tr>
</tbody>
</table>

ED = erectile dysfunction; PDE5 = phosphodiesterase type 5.

*MUSE is Medicated Urethral System for Erection and contains alprostadil pellet.

†Drug mixtures contain 2 or 3 of the following drugs: papaverine, phentolamine, and alprostadil.

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**What can be done for patients who cannot take oral medications or find them unsatisfying?**

Prior to moving on to second-line treatments, several strategies may be undertaken when a patient complains that their new medication is not having the desired effect. An important first step is re-education on the correct use of the medications. Many patients need to be reminded that these medications are reliant on central mechanisms and that they will not work well without erotic stimulation. Up to 55% of patients who initially do not respond to sildenafil will respond after education [47,48]. Dose titration may be necessary.
Additionally, sildenafil may not work as well after a high-fat meal, although vardenafil and tadalafil seem to be less dependent on timing with regard to meals [49,50]. Another step that can be taken is to check hormonal levels, as these medications are at least partially androgen-dependent [51]. There is also evidence that erectile function may improve with chronic use [52,53], both in animal models as well as in selected human populations [54–56].

- Are there any other alternative medications?

Yohimbine is a centrally acting α2-adrenergic receptor antagonist produced from the bark of the yohimbe tree. Its effect on erectile function is at best marginal and is therefore not recommended in patients with organic ED. A meta-analysis of several placebo-controlled studies of 419 men with predominantly nonorganic ED has shown some benefit with yohimbine over placebo [57]. Side effects include gastrointestinal intolerance, headache, palpitation, fine tremor, elevation of blood pressure, and anxiety. Oral phentolamine has been reported to improve erectile function compared with placebo [58,59]. Side effects of the medication include headache, facial flushing, and nasal congestion. Oral phentolamine has not been approved by the FDA, but it is available in several South American countries.

Apomorphine is a sublingual dopaminergic agonist that is available for use in Europe. Apomorphine is a potent emetic that acts on central dopaminergic (D1/D2) receptors. When injected subcutaneously, it induces erections in rats and humans, but the side effects (notably nausea) limit its clinical usefulness [60]. Sublingual apomorphine has not received FDA approval.

Bremelanotide (formally known as PT-141) is a melanocortin agonist that acts centrally and has been investigated in subcutaneous and intranasal administration. These studies reported statistically significant improvements in erections compared with placebo in both healthy men and those who did not respond well to sildenafil [61,62]. Common side effects include flushing and nausea. The medication has not been approved by the FDA, as phase 3 trials are not yet completed.

**Urologist Evaluation**

The patient is referred for evaluation by a urologist. The urologist confirms the history and previous examination/laboratory testing, including the patient’s intolerance of oral medication. After assessing the patient’s and partner’s goals and expectations, the urologist performs a combined injection and stimulation test using alprostadil [63]. This results in a rigid erection that lasts for 30 minutes in clinic and does not require additional maneuvers to treat priapism. After appropriate training, the patient receives a prescription for alprostadil and begins to use the injections at home.

- What are available second-line treatments for ED?

**Vacuum Erection Devices**

A variety of vacuum erection devices (VEDs) are available. In all cases, medical grade VEDs work by applying negative pressure to the penile shaft and glans, which provokes ingress and storage of blood in the sinusoidal tissue. An elastic band is then applied to the base of the penis, which prevents egress of the trapped blood. There are several advantages to VEDs. Despite an initial expense, overall they are the most economical therapy for men who fail first-line treatments for ED. Further, there are very few contraindications, no systemic side effects, and are highly effective [64]. Despite these advantages, VEDs require manual dexterity and a supportive partner, are cumbersome, and give an unnatural erection. Side effects include petechiae, pain, numbness or coldness, delayed ejaculation, and a sense of trapped ejaculation. Because of these factors, satisfaction rates for VEDs are approximately 55% even though erections are achieved in almost every man [65]. Younger and single patients are rarely willing to continue using VEDs, and this type of therapy is preferred for older patients in stable relationships.

**Intracavernosal Injections**

There are several available intracavernosal medications available, the most popular of which are alprostadil (prostaglandin E1), papaverine, and phentolamine; these may used individually or in combination. In general, intracavernosal injection (ICI) therapy has the advantage of provoking a rapid, predictable, and reliable erection once the patient has had proper instructions and training. Men (and preferably their partners) must receive appropriate training and education by medical personnel before beginning home injections. The goal is to achieve an erection that is adequate for sexual intercourse but does not last for more than 1 hour. In contrast to VEDs, ICI results in a much more natural erection, does not use bulky equipment, requires minimal manual dexterity, and does not obstruct ejaculation.

Alprostadil has the highest efficacy of any of the individual agents, results in erections in more than 70% of treated men [66], and is the only FDA-approved agent for ICI. Administration of alprostadil leads to increased intracellular cyclic adenosine monophosphate levels, decreased intracellular calcium, and intracavernosal smooth muscle relaxation, resulting in increased penile erection [14]. The usual dose of alprostadil ranges from 5 to 20 µg. The most frequent side effect is painful erections that occur in 17% to 34% of
men [66,67]. This hyperalgesic effect is most prominent in men with partial nerve injury, such as those with diabetic neuropathy and those who have undergone radical pelvic surgery. Alprostadil has a relatively low incidence of priapism (0.35%–4%) and fibrosis (1%–23%) [67–69].

Papaverine is a nonspecific PDE inhibitor that increases cyclic adenosine monophosphate and cGMP concentrations in penile erectile tissue [70]. The usual dose ranges from 15 to 60 mg. It is more effective in psychogenic and neurogenic ED (up to 80%) compared with vasculogenic ED (36%–50%). Its advantages include low cost and stability at room temperature, while the disadvantages include priapism (up to 35%), corporal fibrosis (up to 33%), and occasional increases in liver function tests [70].

Phentolamine is a competitive $\alpha_2$-adrenergic receptor antagonist and must be used in combination with papaverine to produce rigid erections (63%–87% success rates) [71,72]. Many urologists use a combination of papaverine 30 mg and phentolamine 0.5 to 1 mg. The side effects of phentolamine include hypotension and reflex tachycardia.

Although individual agents are used, the most effective ICI therapy used in the United States is a 3-drug mixture containing papaverine, phentolamine, and alprostadil. The usual dose of this 3-drug solution ranges from 0.1 to 0.5 mL, and the response rate is reportedly as high as 90% [73]. Although widely used in the United States, it is not approved by the FDA. Other combinations of medications such as papaverine and alprostadil [74], ketanserin and alprostadil [75], and phentolamine and alprostadil [76] have also been proven to be superior to single medications in efficacy of response.

Side Effects
Two important side effects of ICI are priapism and fibrosis (penile deviation, nodules, or plaque). In adults, ICI therapy with papaverine, phentolamine, alprostadil, or combinations of these agents is the most common cause of ischemic priapism [77]. Zorgniotti and Lefleur [78] first reported the use of a combination of papaverine 30 mg and phentolamine 0.5 mg for self-injection. Prolonged erection occurred in 1.6% of patients during titration and in 1 patient on home therapy. In a review of the literature, Linet and Neff [66] found that doses of 10 to 20 µg alprostadil led to prolonged erection/priapism in 1.3% of patients. The incidence was found to be about 5 times lower with alprostadil than with papaverine or papaverine/phenolamine (1.3% vs. 10% vs. 7%), a finding supported by an Australian study [79]. In the 1996 worldwide clinical trials conducted by the Alprostadil Study Group, prolonged erection (4–6 hours) was noted in 5% of patients and priapism (> 6 hours) in 1% [80]. In an Argentinean study, a much higher rate of priapism was reported for papaverine plus phentolamine (18%) and prostaglandin E1 (15%) [81]. These figures are substantially higher than those found in other studies, which is likely secondary to testing patients with neurologic or psychological impotence who are often sensitive to the medication. Priapism is largely preventable through in-office instruction and at-home careful dose titration.

To prevent fibrosis, we routinely instruct men to compress the injection site for 3 to 5 minutes (up to 10 minutes in men taking anticoagulants). ICI therapy is relatively contraindicated in men with sickle cell anemia and in those taking medication for schizophrenia or other severe psychiatric disorders due to the risk of priapism associated with ICI. Additionally, ICI therapy may be difficult to perform if patients are obese or have poor manual dexterity; teaching the partner to administer the injection may circumvent some of these barriers.

Although ICI therapy offers several advantages over VEDs, the drop out rate is still very high. In long-term studies, 38% to 80% of men withdrew from treatment [82,83]. For men unable or unwilling to perform penile injections, an intraurethral suppository with or without PDE5 inhibitors can be used. Alternatively, in men whom ICI therapy alone fails or is insufficient, we recommend the use of injection therapy in combination with a VED.

Transurethral and Transdermal Medications
Transurethral alprostadil (Medicated Urethral System for Erection [MUSE]) has been extensively studied in Europe and the United States and was found to be effective in 43% of men with ED of various organic causes. The most common side effects were penile pain (32%) and urethral pain or burning (12%) [84,85]. Using an adjustable constriction device (Actis, Vivus Corporation, Lakewood, NJ) placed at the base of the penis after transurethral alprostadil administration resulted in an increase in successful sexual intercourse in 69% of men [86]. Patients are initially started with a test dose of 500 µg in the office. Depending on the patient’s response, this dose can be titrated from 250 to 1000 µg. It is important to administer the test dose in the office due to the risks of urethral bleeding, vasovagal reflex, hypotension, and priapism (occurring < 0.1%) [87] that can occur with this medication.

No transdermal medication has been approved by the FDA for ED, and at this time there are no transdermal medications available for clinical use. Nitroglycerin cream or paste, alprostadil cream, and a cream containing aminophylline, isosorbide dinitrate, and cedoglocrine mesylate have been used in pilot studies in men with ED with varying results [88].

Surgical Treatment and Outcome
Two years after his initial assessment, the patient returns to the urologist. Although he is still using alprostadil successfully, he and his wife find it cumbersome and somewhat uncomfortable. After taking a new history and repeating the physical examination, he and his urologist decide to try placement of an inflatable penile prosthesis.
• What are the surgical interventions for ED?

Although some men who are unhappy with results of oral medications or who cannot take them proceed directly to surgical intervention, most men try 1 or several second-line therapies prior to embarking on an operative course of management.

Penile Prostheses

When there is lack of efficacy or dissatisfaction with other modalities, penile prostheses are often the best alternative for ED. Unlike the other modalities, prosthesis surgery is irreversible in that the corporal tissue is permanently altered such that physiologic erections are no longer possible. If the prosthesis has to be removed, there will be complete ED, although devices are readily replaced should mechanical failure occur. While a variety of exotic materials, flaps [89], and grafts have been used, most contemporary prostheses are hydraulic or semi-rigid/malleable. The malleable prostheses are made of silicone rubber with a central intertwined metallic core. Mechanical devices are also made of silicone rubber with interlocking rings in a column, which provide rigidity when the rings are lined up in a straight line and flaccidity when the penis is bent. The advantages of semi-rigid devices are that they are easy to implant, have few mechanical parts with minimal mechanical failure, and generally last longer than inflatable devices. The major disadvantage of the semi-rigid devices is that the penis is neither fully rigid nor fully flaccid. These devices may interfere with urination, are difficult to conceal, and have a higher likelihood of device erosion.

Currently available inflatable prostheses come in 2- or 3-component setups. Two-piece inflatable prostheses consist of a pair of cylinders attached to a scrotal pump. The prosthesis can be deflated by bending the penis at midshaft. When fully erect, 2-component prostheses are as rigid as the 3-piece device; however, in the flaccid state, they are not quite as flaccid as the 3-piece prosthesis. Finally, 3-piece inflatable prostheses consist of a pair of penile cylinders, a scrotal pump, and a suprapubic reservoir. Three-piece prostheses provide excellent rigidity when erect and a more natural appearance when flaccid. Of all the prosthesis types, hydraulic 3-piece implants have been the most popular, accounting for 85% of those used in the U.S. market. Approximately 15% of patients choose semi-rigid rod implants, and those with limited mental or manual dexterity are encouraged to have this type of device. In general, the semi-rigid devices last longer than the inflatable prostheses. Most devices will need replacement after 10 to 15 years. Repair or replacement rates of 5% to 20% in the first 5 years are realistic.

Of all modalities for management of ED, prostheses have the highest satisfaction rates [90,91], with 2 large studies demonstrating greater than 95% satisfaction [92,93]. This extremely high satisfaction rate is likely due to multiple factors: prostheses allow for spontaneous, repeated, and reliable erections without external medications or devices. Also, many men undergoing prostheses have tried many first- and second-line treatments unsuccessfully or unsatisfactorily prior to choosing a penile prosthesis.

Infection remains the most devastating and feared complication of penile implants. Modern prostheses allow for antibiotic impregnation and elution, and infection rates are approximately 3% for a first-time prosthesis. Although some studies suggest that elevated glycosylated hemoglobin (HbA1c) levels may predict a higher rate of infections in diabetics undergoing penile prosthesis surgery [94], more recent studies refute this claim. A large study by Wilson et al [95] demonstrated that diabetic status or preoperative HbA1c levels were not risk factors for prosthesis infection. A more recent study [96] found that elevated HbA1c was not a risk factor for infection, while short-term glucose control (as defined by morning fasting glucose levels > 200 ng/mL) was a significant risk factor for infection. Penile shortening and eventual mechanical failure of the device are other common side effects.

Vascular Surgery

Since ED often has a vascular component, it stands to reason that practitioners who have tried to develop surgical methods to re-establish penile vascular integrity. In general, these methods have addressed either inflow (ie, increasing delivery of arterial flow to the corpora cavernosa) or outflow (ie, obstruction of pathologic leak of veins draining the corpora) problems. Unfortunately, despite the theoretical appeal of improving the underlying pathology, results of vascular reconstructive surgery, both venous and arterial, have been extremely disappointing unless patients are highly selected [97–100]. Optimal candidates for surgery are young men without any vascular comorbidities who have discrete, singular lesions; very few men with ED fall into this category, although occasional young men may have congenital anomalous venous leakage or perineal trauma–induced arterial or venous lesions [101].

Case Outcome

The patient has no apparent complications after his prosthetic surgery. He returns to clinic 6 weeks after the operation, and he and his wife are thoroughly instructed in the use of the prosthesis. Three months postoperatively, the patient and his wife report satisfying erections.

CONCLUSION

As our understanding of the basic mechanisms of erectile function continues to grow, new therapies will emerge in the treatment of ED, with the eventual goal of eliminating
the need for surgical treatment of the disease. Treatment options have progressed from psychosexual therapy and penile prostheses in the 1970s, through arterial revascularization, vacuum constriction devices, and ICI therapy in the 1980s, to transurethral and oral drug therapy in the 1990s and perhaps gene or growth factor therapy in the new millennium. A wide variety of medications, administrative techniques, and surgical interventions are available to patients with ED. These range from first-line oral agents to second-line injections or VEDs to third-line penile prosthesis implantation. Very few patients may be candidates for curative vascular reconstructive surgery. In the future, tissue-, cellular-, or genetic-based therapies, such as stem cell implantation or gene transfer, may allow truly curative therapies through the regeneration or growth of healthy vascular and neural tissue.

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CME EVALUATION: Evaluation and Management of Erectile Dysfunction in Clinical Practice

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. In the population-based National Health and Nutrition Examination Study (NHANES), what percentage of men over the age of 75 years reported erectile dysfunction (ED)?
   A. 25%
   B. 50%
   C. 75%
   D. 95%

2. Which of the following sexual function findings is commonly seen in the aging male?
   A. Decreased cavernous muscle tone
   B. Decreased penile sensitivity
   C. Increased ejaculatory volume
   D. Increased serum testosterone

3. Which of the following is NOT a risk factor for ED?
   A. Alcohol use (small amounts)
   B. Alcohol use (large amounts)
   C. Cocaine use
   D. Tobacco use

4. Which of the following is NOT a second-line therapy for treatment of ED?
   A. Inflatable penile prosthesis
   B. Intracavernous injection of vasoactive agent
   C. Intraurethral suppository of alprostadil
   D. Vacuum erection device

5. Which is the LEAST common side effect of phosphodiesterase type 5 inhibitors?
   A. Flushing
   B. Headache
   C. Nasal congestion
   D. Priapism
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