

# Erectile Dysfunction



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## KEYWORDS

• Erectile dysfunction • Impotence • Sexual dysfunction • PDE-5 inhibitors

## KEY POINTS

- Erectile dysfunction (ED), although recognized as a pathologic condition for thousands of years, was not clearly defined until 1992, thus overcoming one of many barriers to treatment.
- ED is defined as the inability to achieve and/or maintain erection of sufficient rigidity and duration to permit satisfactory sexual performance.
- Causes of ED are psychogenic, vasculogenic, neurogenic, endocrinologic, cavernosal smooth muscle dysfunction, iatrogenic, or pharmacologic; for many patients the cause may be any combination of these.
- Diagnosis and evaluation of ED can be as simple as using a questionnaire but can also involve complex testing and imaging modalities, with varying degrees of reliability and clinical utility.
- Treatment of ED usually follows a stepwise progression, from noninvasive strategies, such as lifestyle modifications and oral medications, all the way to surgical placement of penile prostheses for severe refractory disease.

## HISTORY

Although recognized as a pathologic condition for several millennia, the systematic and evidence-based investigation of erectile dysfunction (ED) is a relatively recent phenomenon in modern medicine. For as long as humans have been studying their sexuality, they have also been documenting the affliction of sexual dysfunction. By 1150 BCE, the ancient Egyptians had described 12 different sexual positions with explicit papyrus drawings that were passed down, studied, annotated, and preserved throughout the centuries. Predating these drawings by several hundred years, the Ebers papyrus contains, among many other remedies, prescriptions for “weakness of the male member” (1700 BCE).<sup>1</sup> Yet it was not until 1992 that the National Institutes of Health held a multidisciplinary consensus conference on impotence and officially defined ED as the inability to achieve and/or maintain erection of sufficient rigidity and duration to permit satisfactory sexual performance.<sup>2</sup> This marked a turning point

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Physician Assist Clin 3 (2018) 113–127

<http://dx.doi.org/10.1016/j.cpha.2017.08.011>

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for physicians and patients, making it easier to identify, diagnose, and address ED in common medical practice.

## EPIDEMIOLOGY AND RISK FACTORS

The Massachusetts Male Aging Study (MMAS) was the first cross-sectional population study for prevalence of ED, taking a random sample of men in Boston, ages 40 to 70, and using a self-administered sexual activity questionnaire to stratify mild, moderate, and complete ED. Overall prevalence of ED, regardless of type and severity, was 52% in this cohort, and prevalence of complete ED increased from 5.1% in men age 40% to 15% in the 70-year-old group. The probability of moderate ED increased from 17% to 34% with age, and the prevalence of mild ED stayed at 17% regardless of age.<sup>3</sup> More recent data from the Boston Area Community Health Survey, 2005 to 2006, revealed 10% of men in their 30s compared with 59% of men in their 70s had ED.<sup>4</sup> Worldwide prevalence of ED was estimated at 5% to 28% based on the Global Survey of Sexual Attitudes and Behaviors, which included men and women ages 40 to 80 from 29 different countries.<sup>5</sup> The MMAS data from 1987 to 1989 was later compared with new data collected from 1995 to 1997, representing the first reported longitudinal data set for establishing incidence of ED. The study concluded risk of ED was approximately 26 new cases per 1000 men annually. There was a higher incidence in older men (46.4/1000 in men 60–69) and in men with cardiovascular disease (58.3/1000), hypertension (42.5/1000), and diabetes (50.7/1000). Other independent risk factors for ED include smoking, obesity, depressive symptoms, metabolic syndrome, hyperlipidemia, sedentary lifestyle, spinal cord injury, certain medications, neurodegenerative diseases, renal insufficiency, prostate cancer treatments, blunt perineal or pelvic trauma, and bicycle riding.<sup>6–12</sup>

## ERECTILE PHYSIOLOGY

Normally, blood supply to the penis arises from the internal pudendal artery, which branches from the internal iliac artery, although there is often collateral circulation with accessory pudendal branches arising from other pelvic arteries, such as the external iliac, obturator, vesical, and femoral arteries.<sup>13</sup> The internal pudendal artery eventually becomes the common penile artery, which then branches into dorsal, bulbourethral, and cavernous arteries. The dorsal artery supplies the glans, and the cavernous artery is responsible for erection as it supplies the corpora cavernosa filling all of the branching helicine arteries, trabecular erectile tissue, and the sinusoids housed as a matrix of elastic erectile tissue within the cylindrical bilayered tunica albuginea. The outer layer of the tunica consists of collagen and elastin fibers arranged in a longitudinal fashion and the inner layer of circular-running fibers. On the periphery of the cavernosal sinusoids, there are subtunical venous plexuses, which drain venous blood and give rise to the emissary veins that penetrate through the tunical layers out to the larger return vessels.<sup>14</sup>

At baseline, the trabecular smooth muscle matrix of the corpus cavernosum is in a state of moderate tonic contraction, thus limiting arterial inflow and maintaining flaccidity. When the smooth muscle is further contracted, as in cold temperatures, the blood flow is further limited, resulting in shrinkage of the phallus. During erection, sexual stimulation via both somatic and autonomic pathways causes release of several neurotransmitters, including dopamine, serotonin, oxytocin, and, most importantly, nitric oxide (NO).<sup>15</sup> NO is responsible for binding and activating guanylyl cyclase, the enzyme that catalyzes the transition of guanosine 5'-triphosphate (GTP) to cyclic guanine monophosphate (cGMP), which relaxes cavernous smooth muscle.

NO released by neurons is responsible for initiation of erection through this mechanism; however, maintenance of the erection is mediated primarily by NO synthesized by the vascular endothelial cells.<sup>16</sup> With smooth muscle relaxation, the trabecular erectile tissue and sinusoids fill with blood causing increased rigidity.<sup>17</sup> Compression of the subtunical venous plexuses limits outflow, and the emissary veins traversing through the tunical layers are essentially pinched off as the hemodynamic pressure increases, further inhibiting detumescence.<sup>14</sup>

Erection is maintained until cGMP is degraded by phosphodiesterase enzyme (PDE) and the smooth muscle regains its tone. Inhibiting PDE has, therefore, become a major target for pharmacologic therapy for ED.

## ETIOLOGIES AND ASSOCIATED CONDITIONS

The causes of ED can be broadly categorized as either organic, psychogenic, or mixed. Etiologies of organic ED are subdivided into vasculogenic, neurogenic, endocrinologic, and cavernosal smooth muscle dysfunction. Additionally, ED is also a result of iatrogenic trauma and medications.

Psychogenic ED stems from the release of adrenaline associated with psychologic stress. Many psychologic conditions have been implicated in ED, including depression, generalized anxiety, guilt, performance anxiety, relationship discord, and internal conflict about sexuality.<sup>18</sup> Sympathetic stress response stimulates catecholamine release, resulting in a shunting of blood flow away from the genitals and out to skeletal muscles in preparation for a fight-or-flight response, thus inhibiting penile tumescence. This adrenaline-mediated mechanism is particularly useful in explaining to patients why the excitement and anxiety experienced with a new sexual partner may result in premature loss of erection. It is also likely responsible for compounding the severity of ED in men with only mild vasculogenic or neurogenic pathology or in men who have lost an erection even 1 time who then experience sudden and severe ED in subsequent attempts despite no acute change in any other risk factors.<sup>19</sup>

Vasculogenic ED has been widely recognized as an early warning sign for underlying subclinical cardiovascular disease because both processes typically result from endothelial injury and dysfunction, which then progress to arterial insufficiency and vascular occlusive disease. Therefore, the independent risk factors commonly listed for coronary artery disease (CAD) are the same as for ED: blood pressure greater than 130/85, triglycerides greater than 150 mg/dL, high-density lipoprotein less than 40 mg/dL, diabetes, body mass index (BMI) over 30, waist circumference greater than 40 inches, tobacco use, and sedentary lifestyle.<sup>6–12</sup> Another important factor in vasculogenic ED is the reduced availability of endothelial NO seen with aging and in certain disease states, such as diabetes and sickle cell disease. This mechanism is the focus of many new and ongoing studies.<sup>20–23</sup>

Neurogenic ED is a broad category encompassing any insult to the nervous system, resulting in ED from chronic neurodegenerative conditions, such as Alzheimer disease, multiple sclerosis, acute injuries from spinal cord trauma, and stroke. Strokes involving the right occipitoparietal and thalamic areas may interfere with visual and somatosensory processing; and lesions involving the left insular and adjacent parietotemporal areas may disrupt the ability to generate visceral arousal states. These types of strokes have been shown to significantly reduce erectile function independent of age, stroke severity, infarct volume, brain volume, and independent CAD risk factors.<sup>24</sup> Spinal injury affecting the S2–4 nerve roots or downstream injury to the cavernous nerve often lead to ED. These injuries may be insidious from diabetic neuropathy or aging but often are acute injuries as a result of pelvic surgery, most

commonly radical prostatectomy, although this is far less common with newer nerve-sparing techniques. Diabetes also commonly affects autonomic nerve function by progressive demyelination of peripheral nerves, including the cavernosal nerve. Denervation of the corpora cavernosa induces remodeling of the cavernosal sinusoids and smooth muscle complex, resulting in irreversible fibrosis and loss of compliance and elasticity needed for penile tumescence and rigidity.

Endocrinologic ED primarily refers to hypogonadism or testosterone deficiency. When testosterone levels are below an average threshold of 12 nmol/L (346 ng/dL), testosterone replacement was shown to significantly increase libido and desire, the number of nocturnal erections, frequency of penetrative sex, International Index of Erectile Function (IIEF) scores, and overall sexual satisfaction in a 2005 meta-analysis. In men with ED and normal serum testosterone levels, however, there was no improvement in erectile function with testosterone therapy.<sup>25</sup> Other studies have shown contradictory data indicating that even eugonadal men may experience better erectile function with androgen therapy, thus calling into question the relationship between hypogonadism and ED.<sup>26</sup> Hyperprolactinemia is associated with sexual dysfunction and often ED, but this is likely a result of luteinizing hormone (LH) suppression and secondary hypogonadism. Hypothyroidism may also suppress LH secretion. Hyperthyroidism is associated with increased levels of serum estrogens. There is much debate and many ongoing investigations into the interplay between testosterone levels and erectile function.<sup>27</sup> Diabetes is a major cause of ED, not because of the short-term effects of impaired insulin secretion and hyperglycemia but because of the long-term damage to nerves and microvasculature; therefore, it is more accurately implicated in neurogenic and vasculogenic ED.

More than 200 medications, including entire drug classes, have been associated with ED. Approximately 25% of patients presenting with ED are taking offending medications, but often the underlying diseases treated by these medications are also associated with ED.<sup>28</sup> Antihypertensive agents are widely associated with ED, the most common offenders include  $\beta$ -blockers, clonidine, thiazide diuretics, angiotensin-converting enzyme inhibitors, and spironolactone. Essentially all classes of antidepressants (tricyclics, heterocyclics, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors) are notorious for their sexual side effects. Other psychiatric drugs associated with ED include benzodiazepines, antipsychotics, and phenytoin.<sup>29</sup> Risperidone and other typical antipsychotics like haloperidol and amisulpride block D<sub>2</sub> dopamine receptors and have a prolactin-elevating effect.<sup>30</sup> Other agents that may cause ED by lowering circulating testosterone levels include LH-releasing hormone agonists/antagonists, antiandrogens, and 5 $\alpha$ -reductase inhibitors. Antiulcer drugs, opiates, and cytotoxic agents have also been associated with ED (Table 1).

Table 1 The A-list quick reference for some common causes of erectile dysfunction	
Psychogenic As	Anxiety, anhedonia (depression), adjustment disorder, adrenaline
Vasculogenic As	Arteriolosclerosis, arterial insufficiency, hemoglobin A <sub>1c</sub>
Neurogenic As	Alzheimer, aging, hemoglobin A <sub>1c</sub> , cvA, msA, acute trauma/infection
Endocrinologic As	Androgen deficiency, agonadal, hemoglobin A <sub>1c</sub>
Pharmacologic As	Antidepressants, antihypertensives, anxiolytics, antipsychotics, antiandrogens, antiulcer, 5 $\alpha$ -reductase inhibitors, alcohol, analgesic narcotics

Abbreviations: cvA, cerebrovascular accident; msA, multiple system atrophy.

## EVALUATION: HISTORY

There are numerous reasons given by patients and clinicians alike for not discussing sexual history during an office visit. Patients often cite shame, embarrassment, lack of opportunity, and pessimism about the outcome of such a discussion as well as uncertainty about what is appropriate to address and with which doctor or specialty it should be addressed.<sup>31</sup> Clinicians are often concerned with time constraints, reimbursement, lack of knowledge/training, lack of available treatments, fear of offending patients, and discomfort in discussing sexual issues with those younger than 18, older than 65, or patients of the opposite gender.<sup>31</sup> In a survey of more than 27,000 patients, approximately half of the sexually active respondents, reported having at least 1 sexual problem, yet only 18% of those men attempted to seek medical help for these issues. Only 9% reported they had been asked about sexual health by a provider during a routine visit in the preceding 3 years.<sup>32</sup> It is universally acknowledged that sexual dysfunction, in particular ED, goes undiagnosed and undiscussed for a majority of men suffering its course. ED is not something that must be addressed at every clinical encounter, but it may be poignant to screen for sexual issues during annual visits, wellness checks, and when patients present with other neurologic, vascular, endocrine, or psychological symptoms. Certainly, if the topic is broached by the patient, even as an aside to the primary complaint, it warrants evaluation because it may weigh more heavily on the patient than he indicates and may be difficult for him to bring up again if it goes unaddressed.

First and foremost, before treating ED, a patient's cardiac risk should be assessed to ensure the heart is healthy enough to tolerate sexual activity. If considered high cardiac risk, then cardiology consultation should be pursued prior to treating ED. If at intermediate cardiac risk, then a cardiac stress test should be considered to better stratify into low risk versus high risk.<sup>33</sup> Patients who are asymptomatic with fewer than 3 major risk factors (hypertension, diabetes mellitus, cigarette smoking, dyslipidemia, sedentary lifestyle, and family history of premature coronary artery disease) are considered low risk and should proceed to comprehensive sexual history and treatment as indicated. Any modifiable risk factors identified in this process should be reviewed with the patient. Encouraging smoking cessation, control of blood sugar and blood pressure, increasing activity, and any other steps to optimize vascular health may improve erectile function and slow the inevitable age-related deterioration of erectile function as well as increase overall longevity.<sup>34</sup> The threat of complete and permanent loss of erectile function is often highly motivational for patients to improve their overall cardiovascular health and control diabetes.<sup>35</sup> In a survey asking impotent men with diabetes how much they would be willing to spend on treating complications from their diabetes, ED was ranked third behind renal failure and blindness.<sup>35</sup>

Once it is recognized that a patient self-identifies as having ED, it is first important to distinguish between ED and other common sexual dysfunctions, such as premature ejaculation, anejaculation, delayed orgasm, painful orgasm (dysorgasmia), lack of libido, Peyronie disease, and other penile deformities.<sup>31</sup> The formal definition of ED is fairly subjective: the inability to achieve and/or maintain erection of sufficient rigidity and duration to permit satisfactory sexual performance. Therefore, making a diagnosis is fairly straightforward based on a reliable patient history alone. A complete history should include onset, duration, rigidity with a partner, rigidity with masturbation, ability to penetrate, ability to sustain the erection, presence and quality of nocturnal erections, and prior ED treatments used and their efficacies.<sup>31</sup> A thorough surgical history, specifically asking about any previous abdominal, pelvic, penile, or scrotal surgeries, should identify patients at risk of vascular insufficiency secondary to surgical trauma

as well as patients who may have corporal denervation after radical prostatectomy, cystectomy, colorectal surgery, or exenteration of other pelvic organs.<sup>36–38</sup> Teasing out the specific subtype of ED for each patient can be difficult if not impossible, because many patients have a multifactorial etiology, as previously discussed. In the end, determining the exact cause of a patient’s ED may be helpful for treating underlying conditions and for guiding more advanced treatments but is usually unnecessary before initiating first-line therapies because nearly all types of ED are treated similarly and in a stepwise fashion.

In determining the presence and degree of ED and monitoring progress and effectiveness of treatment, it is often helpful to have a patient fill out a self-reported survey. There are several validated questionnaires used in sexual medicine practice to identify and quantify the degree of ED.<sup>39</sup> The IIEF, introduced in 1997, was originally developed for use in the clinical trials evaluating sildenafil as a treatment of ED. It is now recognized as the gold standard instrument for measuring efficacy in clinical trials for ED interventions.<sup>40</sup> The IIEF has been validated in 32 languages and consists of 15 self-administered questions addressing the domains of male sexual function, including erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.<sup>41</sup> An abridged version, known as the IIEF-5, takes only 5 questions from the IIEF and has become the preferred tool for evaluating ED for many providers for its ease of administration and validated specificity for ED. Each question is scored on a scale from 1 to 5, with a score of 5 generally indicating optimal performance and 1 indicating the highest degree of dysfunction. The sum of the 5 scores then stratifies a patient’s level of ED from “severe ED” to “no ED” (Table 2).

The Sexual Health Inventory for Men (SHIM) is often referred to interchangeably as the IIEF-5. The only difference between the 2 is that some versions of the SHIM questionnaire allow for a score of 0 on 4 of the questions to indicate either “no sexual activity” or “did not attempt intercourse” resulting in the severe ED category expanded to a range of 1 to 7.<sup>42</sup> To further simplify the process, it has been suggested that a single-question screening tool may be useful in identifying patients with ED. A subset of 137 male patients ages 55 to 85 from the MMAS were screened with the single question, asking them to characterize their ability to “get and keep an erection good enough for sexual intercourse” as either “always,” “usually,” “sometimes,” or “never.” Patients were then evaluated with a full urologic examination, developed by the Process of Care Consensus Panel for ED,<sup>43</sup> to obtain a clinical diagnosis of ED. The 75.2% of patients identified as having ED by the single-question method was nearly identical to the 75.9% determined to have ED by urologic examination. The stratification of ED into severity categories was not as strongly correlated, but by using “minimal” as the cut-point for self-reported ED, the researchers found the single-question tool to have a sensitivity of 91% and specificity of approximately 76%, making the diagnosis of clinical ED with “reasonable accuracy.”<sup>44</sup>

Table 2 International index of erectile function –5 questionnaire	
Score on International Index of Erectile Function –5 Questionnaire	Degree of Erectile Dysfunction
22–25	No ED
17–21	Mild ED
12–16	Mild to moderate ED
8–11	Moderate ED
5–7	Severe ED

The Erection Hardness Score is another single-item Likert scale that was also developed to evaluate effectiveness of sildenafil but has since been applied to and validated for<sup>45</sup> other treatments as well, including intracavernosal prostaglandins (Table 3).<sup>46</sup>

### EVALUATION: PHYSICAL EXAMINATION

A patient's vital signs may be the first indicator of a precipitating condition in an ED patient. Look for evidence of hypertension, cardiac arrhythmia, weak pulse, tachycardia, or bradycardia. If suspicious features are noted, a more complete vascular examination may be warranted, including palpation of abdominal aorta for aneurysm and palpation of peripheral pulses.<sup>47</sup> Waist circumference and BMI, both independent risk factors for ED, should be measured and addressed.<sup>48</sup> Look for signs of androgen deficiency: gynecomastia, beard growth, pubic hair, testicular size and location, phallus length, and girth. The genitourinary examination should also include thorough palpation of the entire length of penile shaft for deformities, scars, Peyronie plaques, and location of the urethral meatus. Size and character of the prostate and seminal vesicles may be evaluated with digital rectal examination because concomitant prostate pathology is often noted in patients presenting with ED. Ultimately, the physical examination may not elucidate the exact cause of the ED, but it should help identify any underlying sexual or urologic abnormalities, and it may lead to the diagnosis of other urgent or even life-threatening comorbidities.<sup>47</sup>

### EVALUATION: LABORATORY VALUES AND OTHER TESTS

Laboratory testing is not necessary in every patient with ED, although it may reveal underlying pathology associated with ED, especially in patients who have not been followed regularly by a primary care provider. To look for underlying cardiovascular risk, serum fasting lipids and fasting glucose or hemoglobin A<sub>1c</sub> are helpful. Testosterone levels may be checked for those men with ED and low libido, decreased energy, increased fatigability, or other signs/symptoms of hypogonadism. Serum testosterone is typically checked in the early morning because it tends to be highest at this time and decrease throughout the day at least in younger men. When testosterone is found to be low, a prolactin level is helpful in differentiating between primary hypogonadism and testosterone suppression secondary to a prolactin-secreting pituitary microadenoma. PSA testing may be discussed with patients over age 40 to 45 particularly if a patient will be receiving supplemental testosterone. Thyroid testing is another consideration depending on patient presentation and clinical picture.<sup>47</sup>

In addition to serum testing, there are several investigational studies that can be conducted to help determine ED etiology. Most of these investigations have limited utility in clinical practice because there is little evidence to suggest they alter patient management. Biothesiometry is an assessment of penile vibratory sensation where a stimulator is first applied at very low intensity and then gradually increased until

**Table 3**  
Erection hardness score

Erection Hardness Scale	Patient Response
0	Penis does not enlarge
1	Penis is larger but not hard
2	Penis is hard but not hard enough for penetration
3	Penis is hard enough for penetration but not completely hard
4	Penis is completely hard and fully rigid



the patient reports the first sensation. The lower this threshold for sensation, the greater the neural integrity is thought to be. If the penile threshold is significantly lower than for other areas of the body, this is considered a positive screen for penile neuropathy.<sup>49</sup> Pudendal somatosensory evoked potentials, performed by neurologists or other specialists, aim to evaluate afferent sensory spinal pathways by measuring latency time of electrical stimulus from penis to brain.<sup>50</sup>

Vascular testing for ED can be used to assess the vascular integrity of the corpora cavernosa and to potentially identify patients with inadequate veno-occlusive function, termed *venous leak*. One simple test, often performed as part of an injection therapy teaching visit, is to inject the corpora with a vasoactive agent, such as alprostadil, papaverine, or other erectogenic drug. If an adequate erection is achieved after approximately 10 minutes, then vascular insufficiency is unlikely. If the erection is maintained, then venous leak is not a factor. Inability to achieve an erection or early loss of the erection after injection, however, is not diagnostic of vascular insufficiency or venous leakage. Penile duplex Doppler ultrasound (DDUS) can be performed after injection of vasoactive erectogenic drugs to measure intracavernosal peak systolic velocity at maximal erection as well as end-diastolic velocity. Peak systolic velocity less than 30 cm/s supports a diagnosis of arterial insufficiency, and end-diastolic velocity greater than 5 cm/s suggests venous leak. DDUS does not necessarily change the treatment plan, but it may be useful to rule out organic pathology in patients with purely psychogenic ED, and it may encourage other men to seek definitive surgical management with penile prosthesis if it confirms that even with maximal pharmacotherapy, the penile vasculature simply will not support satisfactory rigidity.<sup>51</sup> More invasive studies, such as cavernosometry and cavernosography, are more accurate in diagnosing venous leak but are rarely used in the modern era. Pudendal angiography may be used in patients who have diagnosed arterial insufficiency by DDUS or cavernosometry and plan to undergo revascularization surgery.<sup>52</sup>

## MANAGEMENT

ED is typically treated in a stepwise fashion, often irrespective of etiology. In terms of preventing further or progressive blood flow impedance and/or neurologic damage, however, it is of utmost importance to identify and treat modifiable risk factors and comorbidities, such as diabetes, hypertension, hyperlipidemia, CAD, systemic inflammatory disorders, and so forth. The MMAS data suggest that lifestyle changes targeting modifiable risk factors, such as smoking, heavy alcohol consumption, sedentary lifestyle, and obesity, are most effective when started before age 50.<sup>53</sup> First-line medical therapy usually consists of a trial of oral phosphodiesterase type 5 inhibitors (PDE5Is). Failure of a PDE5I usually precedes a trial of another PDE5I because some patients may respond better to one agent over another or may find the dosing and timing requirements easier to follow for a particular drug. Second-line therapies include intracavernosal injection therapy, intraurethral suppositories, and vacuum erection devices (VEDs). Third-line management involves surgical intervention.

### ***Phosphodiesterase Type 5 Inhibitors***

PDE is the enzyme that degrades cGMP and leads to increased smooth muscle tone and decreased cavernosal blood flow. PDE5Is, therefore, prolong the action of cGMP created during sexual stimulation leading to more rigidity and longer duration of erections. Of these agents, sildenafil has the longest history of utilization in ED and is also the most widely studied. Other agents have been developed to alter the time of onset, duration of action and other pharmacokinetic factors. Sildenafil is dosed



approximately 1 hour prior to sexual activity, has an oral bioavailability of 41%, has elimination half-life of 4 hours, and has better absorption on an empty stomach because the effect of food may delay time to maximum plasma concentration ( $T_{\max}$ ) by 60 minutes and reduce maximum serum concentration by 29% (Micromedex). It is supplied in 25-mg, 50-mg, and 100-mg tablets. Tadalafil reaches  $T_{\max}$  at 2 to 4 hours and absorption is not affected by food. Elimination half-life is much longer at 15 hours to 35 hours and, therefore, is many times preferred by patients who desire more spontaneity or have a harder time planning their sexual activity. Tadalafil may be dosed as 10 mg to 20 mg on demand like sildenafil, or it may be taken as a 2.5-mg to 5-mg daily dose to achieve a reasonable steady-state concentration allowing for maximum spontaneity. A systematic review and meta-analysis published in 2013 concluded that PDE5 inhibitors, in recommended doses, are more effective than placebo for ED, and that PDE5Is are generally safe and well tolerated without any major differences in safety profiles.<sup>54</sup> PDE5Is are contraindicated in patients who take daily nitrates and should be used with extreme caution in any patients who have access to nitrates but do not use them regularly, such as nitroglycerin for angina. Combining PDE5Is with nitrates may lead to sudden and life-threatening hypotension. Extra attention should be given to patients who take  $\alpha$ -blockers for hypertension or BPH because there is some evidence this may worsen orthostatic symptoms, and it is generally suggested to start at the lowest dose before titrating up as tolerated. Vardenafil should be avoided in patients with congenital QT syndrome and in those taking type 1A or type 3 antiarrhythmics. PDE5I are metabolized via the cytochrome CYP3A4 pathway. Other drugs also metabolized by CYP3A4 include antiretroviral protease inhibitors, azole antifungals, and macrolide antibiotics.<sup>55</sup> Common adverse effects of PDE5Is include headache, flushing, nasal congestion, heartburn, muscle aches, and vision changes.<sup>54</sup> Patients should always be cautioned about priapism and instructed to seek medical attention for erections lasting longer than 4 hours, although there are only a handful of reported cases of priapism from PDE5Is alone in patients without any underlying conditions predisposing them to priapism (sickle cell disease or trait, thrombocytopenia, multiple myeloma, and polycythemia) (Table 4).<sup>56</sup>

**Table 4**  
**Phosphodiesterase type 5 inhibitors dosing**

Phosphodiesterase Type 5 Inhibitors	Trade Name and Date Approved	Doses Supplied	Timing Relative to Intercourse	Onset	Half-Life	Meal Timing
Sildenafil	Viagra, 1998	25 mg, 50 mg, 100 mg	60 min	14–60 min	4 h	Take on empty stomach
Tadalafil	Cialis, 2003	2.5 mg, 5 mg, 10 mg, 20 mg	1–12 h	16–45 min	17.5 h	Not affected by meals
Vardenafil	Levitra, 2003	5 mg, 10 mg, 20 mg	60 min	25 min	4–5 h	Decreased effect
Vardenafil ODT	Staxyn, 2010	10 mg	90 min	—	4–6 h	Decreased effect
Avanafil	Stendra, 2012	100 mg, 200 mg	30 min	30–45 min	5 h	Decreased effect

From Smith-Harrison LI, Patel A, Smith RP. The devil is in the details: an analysis of the subtleties between phosphodiesterase inhibitors for erectile dysfunction. *Transl Androl Urol* 2016;5(2):181–6.

### ***Vacuum Erection Device***

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A VED is considered second-line therapy for ED after failure of PDE5I or when up-stream damage to the cGMP/NO pathway from damage to the cavernosal nerve (radical prostatectomy or autonomic diabetic neuropathy) renders PDE5I ineffective. Although there are many different models of VED, the set-up generally includes a cylinder that can be placed over the shaft of the penis and held to form an air-tight seal against the body; a pump mechanism evacuates air from the cylinder, thus creating a negative pressure around the penile shaft, promoting cavernosal filling with venous blood; and a constriction band that can be slipped off of the proximal end of the cylinder onto the base of the penis to maintain penile tumescence after the cylinder is removed. The band should be removed within 30 minutes to avoid ecchymosis and skin necrosis. Barriers to patient use may include inability to make an adequate seal against the skin, painful ejaculation secondary to urethral compression from the constriction band, a darker/cooler erection from venous filling rather than arterial, and poor manual dexterity. Many of the medical-grade devices come with helpful instruction manuals and videos for teaching and often the companies offer one-on-one teaching with a device representative who may meet with patients in a physician's office setting when allowed.<sup>57,58</sup>

### ***Intraurethral Suppositories***

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Prostaglandin E1 (PGE1) is a direct stimulator of intracellular cAMP in smooth muscle, initiating a cascade that leads to sequestration of intracellular calcium resulting in cavernosal smooth muscle relaxation and penile erection.<sup>59</sup> PGE1 can be delivered as a small suppository inserted into the urethra through the meatus. The penile shaft is then massaged and rolled between the hands to promote dissolving and absorption of the suppository across the corpus spongiosum and into the corpora cavernosa through collateral vessels. Penile pain is a common side effect along with urethral burning. Priapism is a rare but documented risk. A test dose is typically administered under medical supervision to ensure the patient will tolerate the medication and to look for symptomatic hypotension seen in as high as 2% of patients at maximum dosage.

### ***Intracavernosal Injections***

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Intracavernosal injections (ICIs) for ED actually predate use of oral PDE5I yet are still widely regarded as one of the safest and most effective treatments for ED.<sup>60</sup> Similar to intraurethral suppositories, PGE1 is the most common agent used in ICI therapy. There are proprietary forms of injectable PGE1 available at various concentrations in both prefilled syringes and in vials of powder for reconstitution. Alternatively, sterile compounding pharmacies often formulate their own compounded PGE1 for injection and have the ability to combine it with other erectogenic agents, such as papaverine and phentolamine, to create what is commonly known as bimix or trimix. Papaverine inhibits PDEs nonspecifically to increase intracellular concentrations of both cAMP and cGMP and promote smooth muscle relaxation. Phentolamine inhibits  $\alpha_1$ -adren-ergic receptors effectively blocking vasoconstriction by reducing sympathetic tone. Although there are no specific guidelines as to which doses and concentrations are to be used, it is generally best to start with a low dose and slowly titrate up over several days or weeks until an optimal erection is achieved. A test dose in the office is helpful to teach patients how to select and draw up their dose, how to locate the corpora

cavernosa, and how to inject intracavernosally while avoiding important structures, such as the urethra, the dorsal veins and nerves, and any prominent superficial veins that may cause bruising or hematoma.<sup>61</sup> Optimally, a patient injects the dorsolateral aspect of the base to midpenile shaft on one side, and the site of injection is varied with each dose to prevent scarring. It is not recommended to exceed 1 dose in 24 hours or to dose more frequently than 3 times per week because more frequent dosing may theoretically increase risk of priapism or scarring and fibrosis. Barriers to patient compliance with ICIs include anxiety, fear of needles, stinging at the injection site, and pain or aching from the erectogenic drugs, most commonly PGE1, with up to 50% of men reporting some degree of discomfort, especially those with a history of pelvic surgery.<sup>62</sup> Patients may increase their injected volumes and report back progress. If a large volume fails to produce an adequate erection, then a new formulation with a higher concentration and/or addition of other agents may be prescribed. If a high-volume of high-concentration trimix fails to produce an erection, then it is often time to consider surgical management of ED.

### ***Penile Implant Surgery***

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Third-line therapy for ED involves surgical placement of a penile prosthesis. Penile implants are broadly categorized into noninflatable implants, 2-piece inflatable implants, and 3-piece inflatable implants.<sup>63</sup>

Noninflatable or malleable implants are flexible rods inserted into each corporal body. The cylindrical rods can then be bent downward when not in use or bent upward to straighten the penile shaft and simulate an erection. There is no flaccid state with a malleable implant, so more caution must be exercised in patients with loss of sensation to ensure the constant pressure of the device does not result in erosion through the distal glans.

A 2-piece inflatable penile prosthesis (IPP) includes 2 inflatable cylinders within the corpora connected to a small pump hidden in the scrotum. When in the flaccid state, the fluid resides in the more proximal base of the cylinders. The scrotal pump is then depressed multiple times to transfer fluid from the proximal reservoir into the decompressed distal portion of the cylinders. The IPP is deflated by bending the cylinders to a 90° angle, which then transfers fluid back to the proximal reservoir. The 2-piece IPP is primarily used in patients for whom placement of a separate fluid reservoir intra-abdominally is difficult, dangerous, or impossible.

A 3-piece IPP consists also of 2 inflatable cylinders in the corpora. The pump in the scrotum has a compressible end for inflation as well as a button or separate mechanism to open a valve allowing flow of fluid from the cylinders back to the reservoir for deflation. In the 3-piece IPP, the reservoir is a separate balloon that is traditionally placed intra-abdominally through the inguinal ring in the space of Retzius; however, more modern techniques have demonstrated safe placement of the reservoir in ectopic locations, such as in a submuscular tunnel developed between the peritoneum and transversalis fascia, deep to the rectus abdominis.

Candidates for IPP should have good manual dexterity and sensation to allow for locating the pump among the other scrotal contents and to ensure ability to squeeze the pump with adequate force while stabilizing the pump to prevent it slipping painfully out of grip.

Although mechanical failure is always a possibility (5%–10% after 10 years),<sup>64</sup> the most severe and devastating complication is infection, because the device must be completely explanted, with tissue washout and systemic antibiotics, and traditionally a 3-month waiting period before another implant can be attempted. Infections are

more common with longer surgical times or less-experienced implanters and in patients with diabetes, especially poorly controlled (hemoglobin A<sub>1c</sub> >8).

It is important to manage patient expectations before implant surgery. No matter how much care is taken to maximize length and ensure that cylinders fit the native corporal size, there nearly always is some perception of loss of length and/or girth with erection and a decrease or absence of the natural lengthening of the shaft some men experience during tumescence. Ideally the device provides excellent rigidity for reliable on-demand erections, but it will certainly not look and feel as natural as patients remember from their youth.

## SUMMARY

Over the past 25 years, ED has gone from a vague, underdiagnosed, difficult-to-treat disease process to a clearly defined pathologic state with well described though complex etiologies, a variety of tools for screening and evaluation, and an explosion of treatment options that provide clinicians a logical, stepwise algorithm to help patients restore erectile function and reclaim their sexual health. As the taboo around sexual dysfunction has diminished, ED has been recognized by general practitioners and cardiologists as an important risk factor for microvascular disease and a potential harbinger of cardiovascular disease. As the field of ED treatment has expanded, new pharmacologic agents have continued to be developed, new strategies such as extracorporeal shockwave therapy have been explored, and surgical techniques and prosthetics have been constantly revised and refined. In essence the modern study and treatment of ED are still burgeoning frontiers in the fight against an ancient disease.

## REFERENCES

1. Shokeir AA, Hussein MI. Sexual life in pharaonic Egypt: towards a urological view. *Int J Impot Res* 2004;16(5):385–8.
2. Impotence. NIH Consensus Statement 1992;10(4):1–33.
3. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. *J Urol* 1994;151(1):54–61.
4. Brookes ST, Link CL, Donovan JL, et al. Relationship between lower urinary tract symptoms and erectile dysfunction: results from the Boston area community health survey. *J Urol* 2008;179(1):250–5 [discussion: 255].
5. Laumann EO, Nicolosi A, Glasser DB, et al. Sexual problems among women and men aged 40–80 y: prevalence and correlates identified in the global study of sexual attitudes and behaviors. *Int J Impotence Res* 2005;17(1):39–57.
6. Skrypnik D, Bogdanski P, Musialik K. Obesity—significant risk factor for erectile dysfunction in men. *Polski Merkurusz Lekarski* 2014;36(212):137–41 [in Polish].
7. Sommer F, Goldstein I, Korda JB. Bicycle riding and erectile dysfunction: a review. *J Sex Med* 2010;7(7):2346–58.
8. Bacon CG, Mittleman MA, Kawachi I, et al. A prospective study of risk factors for erectile dysfunction. *J Urol* 2006;176(1):217–21.
9. Jeon YJ, Yoon DW, Han DH, et al. Low quality of life and depressive symptoms as an independent risk factor for erectile dysfunction in patients with obstructive sleep apnea. *J Sex Med* 2015;12(11):2168–77.
10. Sanjay S, Bharti GS, Manish G, et al. Metabolic syndrome: an independent risk factor for erectile dysfunction. *Indian J Endocrinol Metab* 2015;19(2):277–82.

11. Kalka D, Domagala Z, Rakowska A, et al. Modifiable risk factors for erectile dysfunction: an assessment of the awareness of such factors in patients suffering from ischaemic heart disease. *Int J Impotence Res* 2016;28(1):14–9.
12. El-Assmy A, Harraz AM, Benhassan M, et al. Erectile dysfunction post-perineal anastomotic urethroplasty for traumatic urethral injuries: analysis of incidence and possibility of recovery. *Int Urol Nephrol* 2015;47(5):797–802.
13. Breza J, Aboseif SR, Orvis BR, et al. Detailed anatomy of penile neurovascular structures: surgical significance. *J Urol* 1989;141(2):437–43.
14. Lue TF, Tanagho EA. Physiology of erection and pharmacological management of impotence. *J Urol* 1987;137(5):829–36.
15. Yang CC, Jiang X. Clinical autonomic neurophysiology and the male sexual response: an overview. *J Sex Med* 2009;6(Suppl 3):221–8.
16. Prieto D. Physiological regulation of penile arteries and veins. *Int J Impotence Res* 2008;20(1):17–29.
17. Lue TF, Takamura T, Schmidt RA, et al. Hemodynamics of erection in the monkey. *J Urol* 1983;130(6):1237–41.
18. Melman A, Gingell JC. The epidemiology and pathophysiology of erectile dysfunction. *J Urol* 1999;161(1):5–11.
19. Trussell JC, Kunselman AR, Legro RS. Epinephrine is associated with both erectile dysfunction and lower urinary tract symptoms. *Fertil Sterility* 2010;93(3):837–42.
20. Liu C, Lu K, Tao T, et al. Endothelial nitric oxide synthase polymorphisms and erectile dysfunction: a meta-analysis. *J Sex Med* 2015;12(6):1319–28.
21. Muniz JJ, Lacchini R, Rinaldi TO, et al. Endothelial nitric oxide synthase genotypes and haplotypes modify the responses to sildenafil in patients with erectile dysfunction. *Pharmacogenomics J* Apr 2013;13(2):189–96.
22. Soni SD, Song W, West JL, et al. Nitric oxide-releasing polymeric microspheres improve diabetes-related erectile dysfunction. *J Sex Med* 2013;10(8):1915–25.
23. Burnett AL. The role of nitric oxide in erectile dysfunction: implications for medical therapy. *J Clin Hypertens* 2006;8(12 Suppl 4):53–62.
24. Winder K, Seifert F, Kohrmann M, et al. Lesion mapping of stroke-related erectile dysfunction. *Brain* 2017;140(6):1706–17.
25. Isidori AM, Giannetta E, Gianfrilli D, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. *Clin Endocrinol* 2005;63(4):381–94.
26. Buvat J, Lemaire A. Endocrine screening in 1,022 men with erectile dysfunction: clinical significance and cost-effective strategy. *J Urol* 1997;158(5):1764–7.
27. Bhasin S, Enzlin P, Coviello A, et al. Sexual dysfunction in men and women with endocrine disorders. *Lancet* 2007;369(9561):597–611.
28. Keene LC, Davies PH. Drug-related erectile dysfunction. *Adverse Drug React Toxicol Rev* 1999;18(1):5–24.
29. Francis ME, Kusek JW, Nyberg LM, et al. The contribution of common medical conditions and drug exposures to erectile dysfunction in adult males. *J Urol* 2007;178(2):591–6 [discussion: 596].
30. Park YW, Kim Y, Lee JH. Antipsychotic-induced sexual dysfunction and its management. *World J Mens Health* 2012;30(3):153–9.
31. Althof SE, Rosen RC, Perelman MA, et al. Standard operating procedures for taking a sexual history. *J Sex Med* 2013;10(1):26–35.
32. Moreira ED Jr, Brock G, Glasser DB, et al. Help-seeking behaviour for sexual problems: the global study of sexual attitudes and behaviors. *Int J Clin Pract* 2005;59(1):6–16.

33. Kostis JB, Jackson G, Rosen R, et al. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol* 2005;96(12B): 85M–93M.
34. Gupta BP, Murad MH, Clifton MM, et al. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med* 2011;171(20):1797–803.
35. Rance J, Phillips C, Davies S, et al. How much of a priority is treating erectile dysfunction? A study of patients' perceptions. *Diabetic Med* 2003;20(3):205–9.
36. Celentano V, Cohen R, Warusavitarne J, et al. Sexual dysfunction following rectal cancer surgery. *Int J Colorectal Dis* 2017. [Epub ahead of print].
37. Bratu O, Oprea I, Marcu D, et al. Erectile dysfunction post-radical prostatectomy - a challenge for both patient and physician. *J Med Life* 2017;10(1):13–8.
38. Nandipati KC, Raina R, Agarwal A, et al. Erectile dysfunction following radical retropubic prostatectomy: epidemiology, pathophysiology and pharmacological management. *Drugs Aging* 2006;23(2):101–17.
39. Giuliano F. Questionnaires in sexual medicine. *Prog Urol* 2013;23(9):811–21 [in French].
40. Rosen RC, Cappelleri JC, Gendrano N 3rd. The International Index of Erectile Function (IIEF): a state-of-the-science review. *Int J Impotence Res* 2002;14(4): 226–44.
41. Rosen RC, Riley A, Wagner G, et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49(6):822–30.
42. Cappelleri JC, Rosen RC. The Sexual Health Inventory for Men (SHIM): a 5-year review of research and clinical experience. *Int J impotence Res* 2005;17(4): 307–19.
43. The process of care model for evaluation and treatment of erectile dysfunction. The process of care consensus panel. *Int J Impotence Res* 1999;11(2):59–70 [discussion: 70–54].
44. O'Donnell AB, Araujo AB, Goldstein I, et al. The validity of a single-question self-report of erectile dysfunction. results from the Massachusetts male aging study. *J Gen Intern Med* 2005;20(6):515–9.
45. Mulhall JP, Goldstein I, Bushmakin AG, et al. Validation of the erection hardness score. *J Sex Med* 2007;4(6):1626–34.
46. Parisot J, Yiou R, Salomon L, et al. Erection hardness score for the evaluation of erectile dysfunction: further psychometric assessment in patients treated by intracavernous prostaglandins injections after radical prostatectomy. *J Sex Med* 2014;11(8):2109–18.
47. Ghanem HM, Salonia A, Martin-Morales A. SOP: physical examination and laboratory testing for men with erectile dysfunction. *J Sex Med* 2013;10(1):108–10.
48. Walls HL, Stevenson CE, Mannan HR, et al. Comparing trends in BMI and waist circumference. *Obesity* 2011;19(1):216–9.
49. Bemelmans BL, Hendriks LB, Koldewijn EL, et al. Comparison of biothesiometry and neuro-uropsychological investigations for the clinical evaluation of patients with erectile dysfunction. *J Urol* 1995;153(5):1483–6.
50. Giuliano F, Rowland DL. Standard operating procedures for neurophysiologic assessment of male sexual dysfunction. *J Sex Med* 2013;10(5):1205–11.
51. Sikka SC, Hellstrom WJ, Brock G, et al. Standardization of vascular assessment of erectile dysfunction: standard operating procedures for duplex ultrasound. *J Sex Med* 2013;10(1):120–9.

52. Spiliopoulos S, Shaida N, Katsanos K, et al. The role of interventional radiology in the diagnosis and management of male impotence. *Cardiovasc Interv Radiol* 2013;36(5):1204–12.
53. Derby CA, Mohr BA, Goldstein I, et al. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? *Urology* 2000;56(2):302–6.
54. Yuan J, Zhang R, Yang Z, et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. *Eur Urol* 2013;63(5):902–12.
55. Corona G, Razzoli E, Forti G, et al. The use of phosphodiesterase 5 inhibitors with concomitant medications. *J Endocrinological Invest* 2008;31(9):799–808.
56. McMahon CG. Priapism associated with concurrent use of phosphodiesterase inhibitor drugs and intracavernous injection therapy. *Int J Impotence Res* 2003;15(5):383–4.
57. Ganem JP, Lucey DT, Janosko EO, et al. Unusual complications of the vacuum erection device. *Urology* 1998;51(4):627–31.
58. Baltaci S, Aydos K, Kosar A, et al. Treating erectile dysfunction with a vacuum tumescence device: a retrospective analysis of acceptance and satisfaction. *Br J Urol* 1995;76(6):757–60.
59. Palmer LS, Valcic M, Melman A, et al. Characterization of cyclic AMP accumulation in cultured human corpus cavernosum smooth muscle cells. *J Urol* 1994;152(4):1308–14.
60. Shabsigh R, Padma-Nathan H, Gittleman M, et al. Intracavernous alprostadil al-fadex (EDEX/VIRIDAL) is effective and safe in patients with erectile dysfunction after failing sildenafil (Viagra). *Urology* 2000;55(4):477–80.
61. Hsiao W, Bennett N, Guhring P, et al. Satisfaction profiles in men using intracavernosal injection therapy. *J Sex Med* 2011;8(2):512–7.
62. Nelson CJ, Hsiao W, Balk E, et al. Injection anxiety and pain in men using intracavernosal injection therapy after radical pelvic surgery. *J Sex Med* 2013;10(10):2559–65.
63. Minervini A, Ralph DJ, Pryor JP. Outcome of penile prosthesis implantation for treating erectile dysfunction: experience with 504 procedures. *BJU Int* 2006;97(1):129–33.
64. Holloway FB, Farah RN. Intermediate term assessment of the reliability, function and patient satisfaction with the AMS700 ultrex penile prosthesis. *J Urol* 1997;157(5):1687–91.