# Treatment of male sexual dysfunction

**Author:** Mohit Khera, MD, MBA, MPH
**Section Editors:** Peter J Snyder, MD, Michael P O'Leary, MD, MPH
**Deputy Editor:** Kathryn A Martin, MD

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## INTRODUCTION

Three of the most common male sexual dysfunctions are decreased libido, erectile dysfunction (ED), and ejaculatory dysfunction (including premature ejaculation [PE] in men ages 18 to 59 years). One or more conditions can coexist in an individual. The inability to achieve and/or maintain an erection sufficient for satisfactory sexual intercourse is a distressing and common symptom, affecting up to one-third of adult men [1].

ED is common in men with systemic disorders such as hypertension, ischemic heart disease, and diabetes mellitus, and its prevalence increases with age ( figure 1). Although sexual dysfunction is more common in older men, it also affects younger men (ages 18 to 25 years) [2]. Health care professionals should therefore ask men of all ages about sexual dysfunction as part of their routine psychosocial assessment. ED can also be seen commonly in men who undergo radical prostatectomy for prostate cancer.

The nonsurgical management of male sexual dysfunction is reviewed here. The etiology and evaluation of sexual dysfunction, the surgical management of ED, and the management in men with cardiovascular disease are discussed in detail separately.

- (See "Epidemiology and etiologies of male sexual dysfunction" and "Evaluation of male sexual dysfunction".)
- (See "Surgical treatment of erectile dysfunction".)
- (See "Sexual activity in patients with cardiovascular disease", section on 'Treatment of sexual dysfunction'.)

## GENERAL PRINCIPLES

Therapy of men with sexual dysfunction is aimed at improving libido and addressing the two vital sexual functions: the capacity to acquire and sustain penile erections and treating premature ejaculation (PE).

Optimal treatment varies, depending upon the factor(s) that have reduced libido or caused erectile or ejaculatory dysfunction ( table 1 and table 2A-B).

With respect to erectile dysfunction (ED) therapy, oral phosphodiesterase-5 (PDE5) inhibitors, penile self-injections with vasoactive drugs, intraurethral suppositories, vacuum erection devices, or penile prostheses allow many men with vasculogenic, neurogenic, or psychogenic ED to treat their ED by acquiring and maintaining erections ( figure 2).

**Guidelines** — Guidelines from the American Urological Association (AUA) have been published for the treatment of ED [3], PE [4], and priapism [5]. The American College of Physicians (ACP) [6] and the American Association of Clinical Endocrinologists (AACE) have also issued treatment guidelines [7]. The Endocrine Society has published guidelines for the diagnosis and treatment of hypogonadism [8].

## DECREASED LIBIDO

The prevalence of reduced libido is estimated to be 5 to 10 percent in men [9]. It increases with age, and it frequently accompanies other types of sexual dysfunction. Men with erectile dysfunction (ED) may experience loss of libido as a secondary consequence of ED. This usually is ascertained from a detailed sexual history, including the chronology of the disorder. However, most patients who complain of ED do not complain of reduced libido or sexual desire. Low libido is often secondary to medications, depression, systemic illness, or testosterone deficiency, but it can also be due to psychogenic causes. Most of these conditions are potentially treatable. (See "Epidemiology and etiologies of male sexual dysfunction", section on 'Decreased libido'.)

The most common causes of decreased libido and their treatment include:

- Psychological, which is treated with formal or informal psychotherapy. (See 'Therapies for psychogenic ED' below.)
- Low testosterone, the most common hormone associated with low libido is treated with testosterone replacement therapy (see "Testosterone treatment of male hypogonadism").

Other hormones that should be assessed in men with low libido include serum prolactin, TSH, and estradiol.

- Medications, most commonly selective serotonin reuptake inhibitors (SSRIs) [10]. Treatment strategies for SSRI-associated sexual side effects are reviewed separately. (See "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management".)

- Sexual dysfunction is common in men who use opioids chronically [11]. These individuals usually have low testosterone levels. (See "Causes of secondary hypogonadism in males", section on 'Opioids'.)

- Partner interactions. (See "Epidemiology and etiologies of male sexual dysfunction", section on 'Decreased libido'.)

A small but significant percentage of men who use 5-alpha-reductase inhibitors (finasteride, dutasteride) to treat benign prostatic hyperplasia (BPH) or male-pattern baldness may experience a decrease in libido, ED, and/or ejaculatory dysfunction [12]. Depending upon the diagnosis, it may be possible to stop the drug to see if this improves the man's libido. In one report of men ages 18 to 45 years, persistent sexual dysfunction with finasteride therapy was associated with a possible increased risk of suicidal ideation. Further studies are underway to understand the pathophysiology associated with post-finasteride syndrome.

Alcoholism is also recognized to reduce libido. Studies have demonstrated that intake of 40 grams of alcohol per day (approximately three drinks) can lead to impaired testosterone production. Making the patient aware of this association may help to reduce or stop the excessive alcohol intake; however, professional counseling usually is required. Low libido may also be a function of partner issues. For example, marital strife, marital guilt, or a naturally or surgically induced postmenopausal female partner who has diminished or absent sexual interest can create low libido in the male partner. (See "Evaluation of male sexual dysfunction", section on 'Hormonal testing' and "Epidemiology and etiologies of male sexual dysfunction", section on 'Decreased libido'.)

## ERECTILE DYSFUNCTION

### Overview of management approach

- **Identify etiology** – Identifying the underlying etiology, including drugs such as antidepressants or antihypertensive agents that may be causing or contributing to the

erectile dysfunction (ED) ( table 3). Nonsteroidal antiinflammatory drug (NSAID) use has not been associated with ED risk [13]. (See "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management" and "Epidemiology and etiologies of male sexual dysfunction", section on 'Drugs'.)

- **Cardiovascular risk factors** – Identifying and treating cardiovascular risk factors such as smoking, obesity, hypertension, and dyslipidemia, as both lifestyle measures and pharmacotherapy for risk factor reduction, are sometimes effective for prevention and treatment of ED ( table 4). (See 'Lifestyle changes' below.)

- **Initiating medical therapy** – The 2018 American Urological Association (AUA) ED Guidelines no longer advocate first-, second-, or third-line therapy for erectile dysfunction. The principles of shared decision making are now recommended. A patient presenting with erectile dysfunction should be counseled about the risk, benefits, and alternatives to all the treatment options for ED and can then select whichever form of therapy best fits their needs ( figure 2). Despite the shared decision-making model, most clinicians still first recommend the phosphodiesterase-5 (PDE5) inhibitors because of their efficacy, ease of use, and favorable side-effect profile (see 'Phosphodiesterase-5 inhibitors' below). Sildenafil, vardenafil, tadalafil, and avanafil appear to be equally effective, but tadalafil has a longer duration of action. Avanafil and orodispersible (ODT) vardenafil have a more rapid onset [14,15]. (See 'Choice of drug' below.)

  PDE5 inhibitors are contraindicated in men taking nitrates and should be used cautiously in men receiving an alpha-adrenergic blocker, due to an increased risk of hypotension.

- **Men with hypogonadism** – Treating men with ED and unequivocally low serum testosterone levels (ie, hypogonadism) with testosterone replacement, unless there are contraindications. According to the AUA ED Guidelines, testosterone should be evaluated in all men presenting with ED. However, testosterone therapy is currently not recommended as monotherapy for ED. Testosterone is prescribed to hypogonadal men with ED to enhance the efficacy of the PDE5 inhibitors, particularly if they are not effective. (See "Testosterone treatment of male hypogonadism".)

- **Treatment if PDE5 inhibitors are ineffective** – If PDE5 inhibitors are ineffective, we suggest vacuum devices, penile self-injectable drugs, and intraurethral alprostadil as second-line therapy ( figure 2). We often suggest trying a vacuum device first because it is noninvasive and less expensive than the other options. (See 'Penile self-injection' below and 'Vacuum-assisted erection devices' below.)

- **Surgery** – Surgical implantation of a penile prosthesis for men who cannot use or who have not responded to other therapies ( figure 2). (See 'Penile prostheses' below and "Surgical treatment of erectile dysfunction".)

  Penile revascularization is rarely required but can be beneficial in men with poor arterial inflow to the corpora cavernosa. According to the 2018 AUA ED guidelines, penile venous surgery is not recommended. (See "Surgical treatment of erectile dysfunction".)

- **Men with depression or anxiety** – Psychotherapy alone or in combination with psychoactive drugs in men with ED caused by depression or anxiety. (See 'Therapies for psychogenic ED' below.)

- **Men with cardiovascular disease or risks** – Therapy of ED in men with known cardiovascular disease or cardiovascular risk factors is reviewed separately [16,17]. (See "Sexual activity in patients with cardiovascular disease".)

**Lifestyle changes** — Both lifestyle modification (weight loss, physical activity) [18] and medical management of cardiovascular risk factors are effective for improving sexual function in some men with ED [19]. A study conducted in military veterans found that exercise for ≥18 metabolic equivalent (MET) hours/week is associated with better sexual function in both African Americans and White Americans [20]. In addition, gastric bypass surgery, which is usually associated with significant weight loss, may improve testosterone levels and erectile function [21]. In men with ED and sleep apnea, treatment with continuous positive airway pressure (CPAP) improved erectile function in some [22,23] and did not worsen obstructive sleep apnea [24], but not all [25,26], studies.

There is evidence that smoking increases the risk of ED and that stopping smoking can be beneficial [27,28].

The association of cardiovascular disease and the risk for later ED is discussed in detail separately. (See "Epidemiology and etiologies of male sexual dysfunction", section on 'Cardiovascular disease'.)

**Phosphodiesterase-5 inhibitors** — For men with ED, we recommend PDE5 inhibitors as initial therapy because of their efficacy, ease of use, and favorable side-effect profile. Sildenafil, vardenafil, tadalafil, and avanafil may have similar efficacy, but the certainty of evidence is very low for most studies comparing PDE5 inhibitor formulations and doses [29]. Of note, tadalafil has a longer duration of action and avanafil has a more rapid onset than other PDE5 inhibitors ( table 2A) [14,15,29]. (See 'Choice of drug' below.)

The rationale for the use of PDE5 inhibitors is based upon the role of nitric oxide-induced vasodilation, which is mediated by cyclic guanosine monophosphate (GMP) in initiating and maintaining an erection; detumescence is associated with catabolism of cyclic GMP by the PDE5 enzyme. PDE5 inhibitors act by increasing intracavernosal cyclic GMP levels by competitively inhibiting the PDE5 enzyme and, as a result, increase both the number and duration of erections in men with ED [30].

PDE5 inhibitors will not work without sufficient environmental and psychological cues that result in sufficient sexual arousal and stimulation to initiate the physiological changes in the penis.

An evaluation for the underlying cause of the sexual dysfunction should be done prior to initiating therapy with PDE5 inhibitors ( figure 2) (see "Evaluation of male sexual dysfunction"). PDE inhibitors are contraindicated in men taking nitrates and should be used cautiously in men receiving an alpha-adrenergic blocker.

Erectile function can be objectively measured using the International Index of Erectile Function (IIEF), the commonly used validated instrument to assess male sexual function in clinical ED studies ( table 5). A subset of the 15 IIEF questions (questions 1 through 5 and question 15) are termed the erectile function domain of the IIEF. Survey scores of men with ED are significantly lower than men without ED. IIEF scores remain low in placebo-treated men but may be comparable, in some treated men, with normal, healthy controls [31]. This is true even for men who have multiple factors contributing to their ED. A short form of the IIEF (the IIEF-5 or Sexual Health Inventory for Men [SHIM]) is a brief, more easily administered, and practical diagnostic tool in a clinical practice setting ( table 6).

In the clinical trial setting, an increase of ≥4 on the erectile function domain of the IIEF is considered a minimally clinically important difference (MCID) [32].

An important factor in the success of PDE5 inhibitor therapy is instruction and counseling on proper use, including onset of action of the drug and taking medications on an empty stomach ( table 2A). Repeat challenge with proper instruction and counseling of patients labeled as PDE5 inhibitor failures has been demonstrated to salvage approximately 25 to 30 percent of patients who were apparent initial nonresponders to PDE5 inhibitor therapy [33,34].

**Sildenafil** — Many clinical trials have demonstrated efficacy of sildenafil. In a quantitative meta-analysis of 27 trials in 6659 men with ED, a higher percentage of successful sexual intercourse was achieved with sildenafil compared with placebo (57 versus 21 percent, respectively) [35]. Similar results are seen in men with diabetes [36] and men with prostate cancer who have undergone prostatectomy or radiation therapy [37] (although most effective in

those who have undergone nerve-sparing prostatectomy [38]). PDE5 inhibitors also may be effective in treating ED caused by spinal cord injury [39]. (See "Radical prostatectomy for localized prostate cancer", section on 'Impotence'.)

Men with mild ED and men who do not complain of ED but who have risk factors for ED and IIEF scores <25 may benefit from treatment with sildenafil [40,41]. Sildenafil also can provide emotional benefits in men with ED [42].

For maximum effectiveness, sildenafil should be taken orally on an empty stomach approximately one hour before a planned sexual encounter. The initial dose should be 50 mg, and it should be reduced to 25 mg if side effects occur. If, on the other hand, it is well tolerated but the erectile response is not fully satisfactory, the dose can be increased to 100 mg. The duration of action is approximately four hours ( table 2A).

**Vardenafil** — Vardenafil shares a similar structure, onset, and duration of action and side-effect profile with sildenafil [43]. Although there are no direct comparison studies, the efficacy of vardenafil appears to be similar to that of sildenafil, with rates of successful penetration in the 65 to 80 percent range compared with 30 percent for placebo [44-46]. It is also effective for men with ED due to diabetes mellitus [47] or nerve-sparing radical prostatectomy [48]. (See "Radical prostatectomy for localized prostate cancer", section on 'Impotence'.)

Its duration of action, like sildenafil, is approximately four hours ( table 2A). Vardenafil is available as a 10 and 20 mg dose, but it has also been released in a new formulation, an ODT (ie, orally disintegrating) tablet, with a potentially more rapid onset than the standard oral formulation. It may be preferable for some patients in that it appears to have a more rapid onset of action and is effective when taken in the fed state [49,50]. High-fat, but not moderate-fat, meals may lower vardenafil's peak serum concentration by approximately 18 percent and delay its absorption by one hour [51].

**Tadalafil** — Tadalafil has a different chemical structure than sildenafil and vardenafil [52]. Although there are no direct comparison studies, tadalafil appears to be as effective as sildenafil and vardenafil, but it has a longer duration of action [53,54]. Tadalafil has been effective in some men with psychogenic ED [55]. The recommended starting dose for as-needed use is 10 mg, decreasing to 5 mg or increasing to 20 mg if necessary [56].

Lower doses of tadalafil (2.5, 5 mg) are available for once-daily administration [57,58]; this approach appears to be as effective as taking higher doses on an as-needed basis [59]. In one trial of 268 men randomly assigned to tadalafil 5 or 10 mg/day or placebo for 12 weeks, those receiving either dose of tadalafil experienced significantly greater improvement in erectile function than those receiving placebo (successful penetration in 36 to 39 versus 11 percent;

successful completion of intercourse in 45 to 50 versus 13 percent; and "no erectile dysfunction" in 50 versus 8 percent) [59].

Men can continue daily administration of tadalafil indefinitely. Some data suggest that daily tadalafil is more effective than on-demand tadalafil in improving endothelial function and long-term erectile function [60].

Daily tadalafil may be particularly effective in men with "complete" ED, defined as having a persistent failure to achieve an erection satisfactory for intercourse. These individuals often do not respond well to intermittent (as-needed) PDE5 inhibitor dosing. In one study, 595 men (mean age 58 years) with "complete" ED, approximately half of whom had hypertension and/or type 2 diabetes, received daily tadalafil (2.5 or 5 mg) or placebo for 12 weeks [61]. At the end of the treatment period, intercourse success rates were 12.5, 32, and 46 percent for placebo, tadalafil 2.5 and 5 mg groups, respectively.

Daily tadalafil has also been approved for treatment of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH). Significant improvement in symptoms, but not urodynamic parameters, has been demonstrated in individual trials and a meta-analysis of five randomized trials. Newer trials have found improvements in maximum urine flow rates in addition to symptom scores.

Daily dosing of tadalafil should not be prescribed in men with a creatinine clearance <30 mL/min. Men presenting with both ED and LUTS may benefit from the convenience of taking one medication to treat both conditions.

**Avanafil** — Avanafil is a newer PDE5 inhibitor that has been approved in the United States and Europe. It has enhanced PDE5 selectivity compared with the other PDE5 inhibitors, a more rapid onset of action, a plasma half-life that is similar to sildenafil and vardenafil, and it appears to be effective and well tolerated [62-64]. It is taken on an as-needed basis at a starting dose of 50 mg, increasing to 100 and 200 mg as needed. The 50 mg dose should be taken 30 minutes before sexual activity, while the 100 to 200 mg doses can be taken just 15 minutes in advance [65]. Avanafil is the only PDE5 inhibitor approved by the US Food and Drug Administration (FDA) for as early as 15 minute onset of action.

Avanafil is rapidly absorbed after oral administration (within 30 to 45 minutes), and absorption is not significantly impacted by food. Avanafil, like all other PDE5 inhibitors, is contraindicated with any form of nitrates. Its side-effect profile is similar to other PDE5 inhibitors.

**Choice of drug** — All four PDE5 inhibitors (avanafil, sildenafil, vardenafil, and tadalafil) work to sustain levels of cyclic GMP within the penile corpora cavernosa to allow men with ED to achieve

erections in response to appropriate sexual stimuli. Sildenafil, vardenafil, tadalafil, and avanafil result in similarly high rates of successful sexual intercourse (68 to 69 percent compared with 33 to 35 percent for placebo) and similar side-effect profiles [14]. Therefore, a Clinical Practice Guideline from the American College of Physicians (ACP) recommends that the choice of PDE5 inhibitor be based upon on the patient's preferences, including cost, ease of use, desired duration of action, and adverse effects ( table 2A) [6].

- Sildenafil has the longest safety record of the four drugs.
- Nitrates are contraindicated with all available PDE5 inhibitors.
- Onset and duration of action separates one PDE5 inhibitor from another. Sildenafil, vardenafil, and tadalafil should be taken 60 minutes before sexual activity, although the onset of action may sometimes be more rapid than 60 minutes. Avanafil and the ODT vardenafil tablet are more rapid acting and can be taken 30 minutes before sexual activity. The duration of action for sildenafil, vardenafil, and avanafil is up to four to five hours (although some effect may persist for 8 to 12 hours for men with mild to moderate ED) [66]. In contrast, tadalafil is effective for up to 36 hours after dosing ( table 2A) [53].
- Daily, low-dose tadalafil administration eliminates the concern about onset and duration of action ( table 2A).
- Sildenafil and vardenafil must be taken on an empty stomach (high-fat meals and alcohol delay absorption). Food does not interfere with the absorption of tadalafil [67], avanafil, or ODT vardenafil ( table 2A).
- In one crossover comparison trial of sildenafil and tadalafil, 66.3 percent of men expressed a preference for tadalafil and 33.7 percent for sildenafil as a treatment for their ED [68]. The interval between dosing and sexual intercourse differed. On average, sildenafil-treated men had intercourse 2.2 hours after dosing, well within the four-hour window of opportunity stipulated on the label, whereas tadalafil-treated men were able to maintain efficacy but were able to delay sexual intercourse for 5.5 hours after dosing.

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Sildenafil, vardenafil, tadalafil, and avanafil appear to be equally effective, but tadalafil has a longer duration of action. Avanafil and ODT vardenafil have a more rapid onset [14,15].

### Adverse effects and precautions

**Cardiovascular** — PDE5 inhibitors are associated with a variety of cardiovascular effects. Sildenafil has two important cardiovascular actions in patients with heart disease: It is a vasodilator that can lower the blood pressure, and it can interact with nitrates. The most data are available for sildenafil. Sexual activity in patients with heart disease, including the management of ED, is reviewed in detail separately. (See "Sexual activity in patients with cardiovascular disease", section on 'Treatment of sexual dysfunction'.)

Key points include:

- PDE5 inhibitors are **contraindicated** in patients taking nitrates of any form, regularly or intermittently, as the combination can lead to severe hypotension. (See "Sexual activity in patients with cardiovascular disease", section on 'Adverse interaction with nitrates'.)

- Nitrate treatment should be delayed if a man who has taken a PDE5 inhibitor develops chest pain. The delay should be at least 12 hours if he has taken avanafil, 24 hours if he has taken sildenafil or vardenafil and 48 hours if tadalafil; the delay should be longer for each if he has renal or hepatic dysfunction. (See "Sexual activity in patients with cardiovascular disease", section on 'Adverse interaction with nitrates'.)

- Myocardial infarction and sudden death have been described with and after intercourse, both in men who have and have not taken a PDE5 inhibitor. Thus, the relation to the drug is uncertain. (See "Sexual activity in patients with cardiovascular disease", section on 'Does sildenafil promote MI?'.)

- Higher doses of PDE5 inhibitors are used for patients with pulmonary hypertension as monotherapy or in combination with other agents, such as guanylate cyclase stimulants (eg, riociguat). However, the FDA has issued a warning against this combination because of an excess risk of hypotension.

**Common side effects** — Side effects associated with sildenafil are related to its vasodilatory properties and are similar to those induced by nitrates. In a meta-analysis of 14 trials, adverse events with sildenafil included flushing, headaches, and dyspepsia in 12, 11, and 5 percent, respectively [35]. Nasal congestion has been described in other reports [69]. Side-effect profiles with vardenafil [46,47], avanafil, and tadalafil [53,70] are similar to sildenafil.

**Visual effects**

- **Blue vision** – Sildenafil occasionally causes "blue vision" in men. The PDE5 inhibitor in sildenafil cross-reacts with the PDE6 inhibitor, which is present in the retina and plays a

role in color vision [71]. It lasts two to three hours, and disappears spontaneously. Blue vision has not been reported with vardenafil, tadalafil, or avanafil ( table 2A).

- **More serious eye effects** – Rare cases of nonarteritic anterior ischemic optic neuropathy (NAION) have been reported in men taking PDE5 inhibitors [72-74]. NAION shares a number of risk factors with ED: age over 50 years, hypertension, dyslipidemia, and diabetes. However, the risk of NAION appears to be increased even after adjustment for these comorbidities [74]. The FDA added a warning label to reflect this risk. (See "Nonarteritic anterior ischemic optic neuropathy: Epidemiology, pathogenesis, and etiologies", section on 'Phosphodiesterase-5 inhibitors'.)

  Risks of other ocular adverse effects, including serious retinal detachment (SRD) and retinal vein occlusion (RVO) may also be increased. The absolute risk of developing any of these complications (SRD, RVO or ION) is very low (2 to 4 cases per 10,000 person-years) [74].

- **Men with retinitis pigmentosa** – Although there are no clinical data on the safety and efficacy of sildenafil in men with retinitis pigmentosa (a minority of whom have genetic disorders of retinal PDE), the manufacturer recommends caution in these patients.

  Men who develop visual symptoms on PDE5 inhibitors should be evaluated promptly. However, routine monitoring of visual function in asymptomatic men without known retinal disease is not currently recommended [75].

**Hearing loss** — Sildenafil, vardenafil, and tadalafil use have been associated with rare reports of sudden hearing loss [76-78]. Although no causal relationship has been demonstrated, the FDA requires that labeling of all PDE5 inhibitors include this potential risk [79]. The hearing loss is usually unilateral, occurs with the first 24 hours of drug administration, and is temporary in approximately one-third of patients [77,78].

**Potential risks** — PDE5 inhibitors can promote melanin synthesis in vitro [80], and some studies have reported an association between PDE5 use and a small increased risk of malignant melanoma [81,82]. However, a third study concluded that the association was unlikely to be causal, as greater exposure to PDE5 inhibitors was not associated with higher melanoma risk, the association was observed for other sun exposure-related conditions, and patients taking PDE5 inhibitors were more likely to have greater sun exposure [83].

**Drug interactions** — All PDE5 inhibitors are contraindicated in men taking concurrent nitrates ( table 2A). In spite of tadalafil's longer half-life, the duration of its interaction with nitrates does not appear to be prolonged [84]. However, it has been suggested that nitrates should be

avoided for at least 48 hours after the last tadalafil dose [85]. Other issues related to sexual activity in men with coronary heart disease are similar to those with sildenafil. (See "Sexual activity in patients with cardiovascular disease".)

Alpha-adrenergic antagonists, which are commonly used for the treatment of BPH, may cause symptomatic hypotension when taken in combination with PDE5 inhibitors ( table 2A) [86]. These drugs include terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin [87]. Tamsulosin and silodosin are better choices (ie, less or no hypotension) than doxazosin or terazosin [88,89].

Current labeling for all four PDE5 inhibitors recommends that a patient who is taking an alpha-blocker should be on a stable dose prior to initiating the PDE5 inhibitor (which should then be started at the lowest recommended dose). Conversely, in patients already taking a PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose ( table 2A). The use of PDE5 inhibitors for BPH is discussed separately. (See "Medical treatment of benign prostatic hyperplasia", section on 'Phosphodiesterase type 5 inhibitors'.)

PDE5 inhibitors should also be avoided in patients taking drugs that can prolong the half-life of sildenafil by blocking CYP3A4 ( table 7) (if used, the potential adverse effects should be stressed with the patient and the PDE5 starting dose should be decreased).

**Role of testosterone** — Testosterone is an important regulator of sexual desire and sexual function in men. ED and low testosterone levels often coexist in middle-aged and older men. Measurement of serum testosterone is recommended for men with ED [3,8], and testosterone replacement has been shown to improve libido, sexual activity, and erectile function in hypogonadal men [90-92]. As a result, combination therapy with a PDE5 inhibitor and testosterone has become increasingly common [3]. Data on the impact of testosterone on ED, either alone or combined with PDE5 inhibitors, have been conflicting [6,8,14,93-96], but there is emerging evidence that combination therapy may be useful for hypogonadal men who do not initially respond to PDE5 therapy alone [93,94].

A 2017 meta-analysis of 14 trials in 2298 patients assessed the effects of testosterone replacement therapy on sexual function [97]. Testosterone therapy was associated with an improvement in erectile function (as measured by IIEF) when compared with placebo. Men with more severe hypogonadism (serum testosterone level less than 8 nmol/L [231 ng/dL]) experienced the greatest improvement in erectile function.

Previous data on the impact of adding testosterone therapy to PDE5 inhibitors have been conflicting [8]. In a trial of 140 men with both ED and low serum testosterone levels (<330 ng/dL [11.45 nmol/L]) or free testosterone <50 pg/mL, sildenafil dose was first optimized, and then subjects (sildenafil responders only) were randomized to receive additional therapy with either

testosterone gel or placebo [96]. At the end of 14 weeks, erectile dysfunction domain (EFD) scores were no better in the testosterone group than the placebo group, in spite of significantly higher serum testosterone concentrations in the intervention group (mean 649 ng/dL [22.5 nmol/L]) than placebo (347 ng/dL [12 nmol/L]). One possible explanation for the lack of effect is that sildenafil use alone increased serum testosterone by approximately 100 ng/dL (from approximately 250 ng/dL at baseline to 350 ng/dL in both groups [8.7 to 12.1 nmol/L]), and perhaps higher serum testosterone concentrations do not provide additional benefit.

Of note, this study did not evaluate nonresponders to PDE5 inhibitors. The TADTEST study, published after the meta-analysis described above, did evaluate subjects (n = 173) who had not responded to tadalafil (10 mg/day for four weeks) and who had serum testosterone <400 ng/dL (13.9 nmol/L) who were then randomized to testosterone or placebo therapy for 12 weeks [93]. Erectile function improved in both the placebo and testosterone groups, but in a subgroup analysis, there was greater improvement with the addition of testosterone to tadalafil in men with baseline testosterone ≤300 ng/dL (10.4 nmol/L) versus no added benefit in men with baseline testosterone level >300 ng/dL (10.4 nmol/L). These findings suggest that maximal benefit of tadalafil may require longer than four weeks of treatment, and the addition of testosterone may only be beneficial in hypogonadal men (serum testosterone <300 ng/dL [10.4 nmol/L]) ng/mL. Similar results were reported in a second trial, where hypogonadal men who previously did not respond to PDE5 inhibitors had an improvement in erectile function with combined testosterone and tadalafil therapy [94].

### Other issues

**Men with diabetes** — Men with diabetes are at very high risk for developing ED. Intensive glycemic control may reduce the development of ED [98,99]. However, there are no data to suggest intensive therapy can reverse or improve ED once it has developed. The management of ED in men with diabetes is essentially the same as that for men without diabetes [100]. (See "Glycemic control and vascular complications in type 1 diabetes mellitus" and "Glycemic control and vascular complications in type 2 diabetes mellitus".)

**Recreational use** — Because sildenafil treatment is associated with a marked reduction in the postejaculatory refractory time [101], men are capable of having a second erection in a shorter time frame than was possible without this therapy. As a result, recreational use of sildenafil is common. However, although not a well-established risk, there are case reports of stroke in men taking high-dose sildenafil [102,103]. In a systematic review of published studies, sildenafil use among gay men was associated with sexual risk behavior and risk of sexually transmitted diseases, including human immunodeficiency virus (HIV) infection [104].

**Dietary supplements and counterfeit medications** — The FDA has issued a warning to consumers not to purchase or consume dietary supplements that claim to increase sexual stamina, confidence, and performance and/or claim to contain prescription-strength doses of sildenafil or tadalafil [105,106]. Current studies suggest that one-third to one-half of supplements claiming to be "natural" products for sexual enhancement contain synthetic chemicals, most commonly, PDE5 inhibitors or analogs of PDE5 inhibitors [107-110]. The concern is that patients who take nitrates for cardiovascular disease may experience a drastic lowering of blood pressure if these supplements are consumed.

For the past decade, international regulatory agencies have taken yearly action against websites that illegally sell potentially dangerous, unapproved prescription drugs. In 2016, 1283 packages were seized in Canada that contained counterfeit or unlicensed health products; 98 percent of these were sexual enhancement products that were either fake or unauthorized [111]. The ingredients in the health products were not reported.

The World Health Organization (WHO) reported in 2008 that 37 percent of the counterfeit medication involved the genitourinary therapeutic area [112]. Over the past decade, the number of drug fraud cases investigated by the FDA for has increased 10-fold in the United States [113]. In 2006, it was estimated that between 0.6 and 2.5 million European men were possibly exposed to illicit sildenafil compared with 2.5 million men using legal sildenafil [114].

**Additional options** — If PDE5 inhibitors are ineffective, we use vacuum erection devices, penile injections with vasodilating agents, or intraurethral alprostadil as other options. We often suggest trying a vacuum device first because it is noninvasive and less expensive than the other options.

**Vacuum-assisted erection devices** — Several mechanical devices have been developed that utilize vacuum pressure to encourage increases in arterial inflow and occlusive rings to limit venous egress from the penile corpora cavernosa ( figure 3 and table 2B). A certain amount of mechanical dexterity is required to use these devices effectively, but once men become comfortable with using the vacuum and restraining rings many men can create an erection sufficient for vaginal penetration and sexual intercourse. The men may have difficulty ejaculating externally, however, because the occlusive rings that prevent venous drainage also compress the penile urethra sufficiently to prevent seminal fluid from reaching and traversing the urethral meatus. A number of devices are available for purchase over the counter. Although the initial dropout rate may be as high as 50 percent, long-term satisfaction of patients and partners has been reported by several groups [115]. This is especially true in patients who do not respond to penile injections.

The vacuum erection device may be used with oral PDE5 inhibitors to augment an insufficiently rigid erection post-ingestion of the PDE5 inhibitor [116]. Vacuum erection devices should only be applied for a maximum of 30 minutes. These devices can also be used in patients taking blood thinners, albeit with caution. Clinical experience has suggested that these devices are most often used by couples in stable relationships.

Vacuum devices successfully create erections in as many as 60 to 70 percent of patients [117]. Satisfaction with vacuum-assisted erections has varied between 25 and 49 percent. As an example, one prospective study evaluated 18 men by questionnaire at six months: 16 (89 percent) were able to attain satisfactory erections, and the overall satisfaction rate was 83 percent [118]. Sixteen of the 18 men found the device easy to use.

**Penile self-injection** — Intracavernosal injection therapy with alprostadil (prostaglandin E1) and papaverine have been used for purposes of inducing erection ( figure 4 and table 2B). In the United States, prostaglandin E1 is the only FDA-approved drug for penile self-injection. The drug has vasodilatory properties and is also used in infants to maintain the patency of the ductus arteriosus before definitive cardiac surgery can be performed.

In other countries, a combination of vasointestinal peptide (VIP) and phentolamine are marketed as Invicorp ( table 2B). Some clinicians prefer compounded mixtures of phentolamine and papaverine (Bimix); prostaglandin E1 is sometimes added as a third component (Trimix). Compounded penile injections of Trimix are commonly utilized penile injections mainly due to excellent efficacy, cost, and finer ability to titrate the dose. It should be noted that compounded penile injections are considered off-label use. All penile injections, whether compounded or commercially available, increase the risk for penile plaque development, and patients should be counseled about this potential risk.

The sympathetic nervous system normally maintains the penis in a flaccid or non-erect state. Vasodilator drugs, when injected into the corpora cavernosa, inhibit or override sympathetic vasoconstriction and act as direct smooth muscle vasodilators. The relaxation of the smooth muscle trabeculae within the penile erectile bodies leads to an increase in blood flow to the penis. The increased inflow of blood engorges the penile corpora cavernosa sinusoidal spaces with sufficient pressure to compress the emissary veins that normally drain blood from the penis. The combination of accelerated arterial inflow and impeded venous outflow from the corpora cavernosa creates an erection ( figure 5).

Considerable education is required for men to become facile with penile self-injection. Men are trained in sterile methods and the proper technique for inserting an insulin syringe with a 26- to 30-gauge one-half-inch needle through the shaft of the penis and injecting the vasoactive agent

into one corporeal body ( figure 4). The cross circulation of the penile corpora allows medication injected into one penile corporeal body to diffuse over to the contralateral side, so that a full, firm erection can be expected within a few minutes after intrapenile installation of the drug [119,120].

In a study of 683 men using alprostadil penile self-injections over a six-month period, 87 percent of subjects of the 471 who completed the study were satisfied with results (as were 86 percent of their partners) [121]. Penile pain, which occurred in 50 percent of subjects, was the side effect most often cited by men who discontinued therapy.

**Priapism** — Priapism, or a prolonged erection lasting more than four to six hours, is a medical emergency often requiring immediate urologic attention to evacuate blood clogged within the corpora cavernosa [122]. Prolonged erections occur in 6 percent of men who use intracavernosal alprostadil and approximately 11 percent of those who use intracavernosal papaverine. Priapism should be reversed as quickly as possible; long durations of priapism may result in permanent corporal fibrosis and ED. The management of priapism is reviewed separately. (See "Priapism", section on 'Ischemic priapism'.)

Lower doses of intracavernosal injections should be used in men with neuropathic ED (due to spinal cord injury or multiple sclerosis), due to their risk of priapism.

One study evaluated the effects of prolonged priapism [123]:

- Most priapism that lasted 36 hours could be treated successfully by puncture and alpha-adrenergic drugs.
- After 48 hours, glandulocavernosal shunts were required to achieve detumescence. All the men developed fibrosis of the corpora cavernosa, and all but one were unable to continue with the injections of vasoactive drugs [5].

  The 2021 AUA Guidelines on Acute Ischemic Priapism recommend that clinicians consider placement of a penile prosthesis in a patient with untreated acute ischemic priapism greater than 36 hours or in those who are refractory to shunting.

**Intraurethral alprostadil** — Intraurethral administration of alprostadil (prostaglandin E1) provides a less invasive alternative to intrapenile injection ( table 2B).

After insertion of the alprostadil into the urethra, the penis is massaged for up to one minute to ensure equal distribution in the corpora cavernosa. Doses include 125, 250, 500, and 1000 mcg. Although this option is less invasive than penile injections, it appears to be less effective than penile injections; it also causes penile pain and bleeding in many men. The main limiting factor

to the use of intraurethral alprostadil is cost, with most insurance plans not offering coverage for this medication.

The efficacy of intraurethral alprostadil was evaluated in a double-blind, placebo-controlled trial in 1511 men with chronic ED from a variety of organic causes [124]. Two-thirds of these men responded to intraurethral alprostadil with an erection sufficient for intercourse; these men were then randomly assigned to therapy with either alprostadil or placebo. Successful intercourse on at least one occasion was much more likely with alprostadil (65 versus 19 percent with placebo). Among the men who responded to alprostadil, 7 of 10 applications were followed by successful intercourse.

Systemic effects were uncommon, but some men experienced penile pain. No subject experienced priapism or penile fibrosis (unlike what is seen when alprostadil is given by penile injection) (see 'Penile self-injection' above). The 19 percent response rate in the placebo group suggests that psychogenic factors were responsible for the sexual dysfunction in some men, since placebo injections do not induce erections in solely organic causes of impotence. A systematic review of three studies of intraurethral alprostadil reported similar efficacy [125].

Intraurethral administration of alprostadil should not be used in sickle cell anemia or sickle cell trait, leukemia, bone marrow problems (eg, multiple myeloma), or other conditions that may increase risk for a prolonged, painful erection (priapism). It also should not be used in men who have a deformed penis or certain other penile problems (eg, Peyronie's disease, fibrosis of the penis). The AUA ED Guidelines recommend that men with ED considering the use of intraurethral alprostadil should first undergo an in-office test due to the risk of hypotension.

### Surgical options

**Penile prostheses** — Surgical management of ED should be reserved for men who cannot use, or who have not responded to, first- and second-line therapies [126]. (See 'General principles' above and "Surgical treatment of erectile dysfunction", section on 'Penile prostheses'.)

Patients with curvature abnormalities (ie, Peyronie's disease) with ED or significant risk factors for future ED are candidates for the placement of a penile prosthesis at the time of their reconstructive surgery. (See "Surgical management of Peyronie's disease".)

**Penile revascularization** — For most men with vascular ED, we do not suggest arterial revascularization, as success rates are low. However, reasonable success rates may be achieved in young, nonsmoking, otherwise healthy men with recently acquired ED due to a focal arterial occlusion. Only 6 to 7 percent of men with vascular ED are candidates for penile revascularization using these restricted criteria; long-term success rates are in the 50 to 65

percent range. The Clinical Guidelines Panel of the AUA suggested that venous and arterial surgery was no longer justified for routine use, especially in patients with arteriosclerosis. This topic is reviewed in detail separately. (See "Surgical treatment of erectile dysfunction", section on 'Penile revascularization'.)

**Therapies for psychogenic ED**

- **Psychotherapy** – Psychological factors can play a role in the etiology of ED, alone or in combination with organic causes. ED is a common symptom of depression, and erectile function may be restored as psychotherapy or antidepressant drugs alleviate the depression.

  However, some of the most effective antidepressant drugs of the SSRI class (eg, fluoxetine, sertraline, paroxetine) decrease both libido and erectile function [127]. However, SSRIs can cause delayed ejaculation, an effect that is beneficial for men with premature ejaculation (PE). (See "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management" and 'Premature ejaculation' below.)

  Psychological counseling, including the use of sensate focus exercises by both partners, can be helpful for men with performance anxiety. This is usually best accomplished by referral to a certified sexual therapy counselor. A meta-analysis of psychotherapy interventions suggests that psychotherapy, in particular group psychotherapy, is beneficial [128]. In a systematic review of 13 studies in 597 men, the combination of psychological intervention and a PDE5 inhibitor were more effective than either psychological intervention or PDE5 inhibitor alone on erectile function and long-term sexual satisfaction in men with psychogenic ED [129].

  Finally, a position statement by the European Society of Sexual Medicine recommends including the partner in the assessment and treatment of ED and to actively work on interpartner agreement and shared decision-making regarding possible treatment options [130].

- **Yohimbine** – Yohimbine, a drug that blocks presynaptic alpha-2-adrenergic receptors, resulting in increased cholinergic and decreased adrenergic tone, has also been used for the management of psychogenic ED. It may be more effective than placebo in men with psychogenic ED, but data are limited [131-133]. We suggest not using yohimbine, given the limited data for efficacy and the availability of effective alternatives (PDE5 inhibitors).

**Regenerative and restorative therapies** — Experimental therapies for ED are currently in development [3]. These treatment options are known as regenerative or restorative therapies

and include:

- **Stem cell therapy** – The use of stem cells to treat erectile dysfunction is being investigated [134]. The majority of studies have used adipose-derived stem cells (ADSCs) with transplantation performed via intracavernous injection. Others use alternative strategies such as periprostatic application (linked or not linked to a scaffold) and intravenous injection. This technology has not yet undergone clinical trials and remains investigational [135,136].

- Another emerging technology to treat ED is **low-intensity shock therapy (LIST)**, the delivery of several thousand low-intensity shocks to the penis over several weeks [137]. LIST has been reported to induce angiogenesis, stimulate neovascularization in the penile tissue, improve penile blood flow and endothelial function, and convert PDE5 inhibitor nonresponders to responders. However, clinical trial efficacy data have been inconsistent [138]. LIST is still considered still considered investigational by major societies such as the AUA and the Sexual Medicine Society of North America [139,140].

- **Hyperbaric oxygen therapy** has also been investigated as a potential therapy for ED. While some data suggest potential improvement in erectile function [1], no benefit was observed in men with ED post-radical prostatectomy [141].

- **Platelet-rich plasma (PRP)** – Although there are little data to support its efficacy [142], some centers are offering PRP injections to men with ED as a form of autologous cell therapy. Further studies are needed before suggesting this approach.

  PRP has the least amount of supporting data in terms of efficacy. Only one trial suggested benefit in improving erectile function. The AUA has downgraded their recommendation for PRP from "investigational" to "experimental" due to lack of data to support its use in men with ED [140,143].

**Ineffective or no longer used** — Other therapies that are ineffective or have been tried in the past include:

- **Melanocortin receptor agonists** – Preliminary data suggest that melanocortin receptor agonists, which act on the central nervous system rather than the vascular system, may be effective for ED [144]. However, there are currently no approved or commercially available compounds.

- Apomorphine – Apomorphine has been shown to be inferior to sildenafil in treating men with ED [145]. The drug was approved for ED in some countries, but commercially available

products were discontinued because of its poor efficacy [146].

## EJACULATORY DISORDERS

**Premature ejaculation** — Premature ejaculation (PE) is also referred to as rapid or early ejaculation and is defined according to three essential criteria: (1) brief ejaculatory latency; (2) loss of control; and (3) psychological distress in the patient and/or partner.

PE can be divided into lifelong or acquired premature ejaculation. According to the 2020 American Urological Association (AUA) Disorders of Ejaculation Guidelines [147], lifelong premature ejaculation is defined as consistently poor ejaculatory control, associated bother, and ejaculation within approximately two minutes of initiation of penetrative sex that has been present since sexual debut. Acquired premature ejaculation is defined as consistently poor ejaculatory control, associated bother, and ejaculation latency that is markedly reduced from prior sexual experience during penetrative sex.

Other subtypes of PE include global versus situational PE, and the co-occurrence of other sexual problems, particularly erectile dysfunction (ED). (See "Epidemiology and etiologies of male sexual dysfunction", section on 'Premature ejaculation'.)

Management depends upon the etiology, but the mainstays of therapy [148] include selective serotonin reuptake inhibitors (SSRIs) [149], topical anesthetics [150], and psychotherapy when psychogenic and/or relationship factors are present [151].

- We consider SSRIs to be first-line treatment. Available agents and dosages include paroxetine (10 to 40 mg/day), sertraline (50 to 200 mg/day), fluoxetine (20 to 40 mg/day), citalopram (20 to 40 mg/day), and escitalopram (10 to 20 mg/day) [152,153]. SSRIs should be started at the lowest dose and titrated up as needed at three- to four-week intervals.

  A meta-analysis of available trials suggests that paroxetine may be the most effective (nine-minute ejaculation delay over baseline) [154]. The full therapeutic effect of SSRIs is typically not seen until after two to three weeks of therapy, and symptoms return if treatment is stopped.

  If SSRIs are ineffective or not tolerated, we consider the serotonergic tricyclic clomipramine (12.5 to 50 mg/day) to be second-line therapy [152].

  An additional SSRI, dapoxetine, also appears to be effective, based upon five trials of over 6000 men with PE who were randomly assigned to receive placebo or dapoxetine (30 mg or 60 mg/day) [155]. Unlike other SSRIs, which are most effective when taken daily,

dapoxetine is taken on-demand one to three hours before intercourse. Dapoxetine is not commercially available in all countries, including the United States.

- Phosphodiesterase (PDE) inhibitors may also be effective for the treatment of PE, but mainly in men with PE and coexisting ED [152,156]. Two meta-analyses have assessed the efficacy of PDE5 inhibitors for PE [157,158]. The main findings were: Both SSRIs and PDE5 inhibitors are more effective than placebo, PDE5 inhibitors are either as effective as SSRIs [157] or slightly more effective [158], and combined therapy is more effective than either therapy alone.

  For men with both ED and PE, we suggest starting a PDE5 inhibitor first to treat the ED. If the patient still has PE, we then add an SSRI.

- Tramadol, an analgesic that has some activity at opioid receptors but also inhibits reuptake of serotonin and norepinephrine, may also be effective [159,160]. Tramadol is recommended by the AUA PE Guidelines as a second-line agent if SSRIs and clomipramine are ineffective or not tolerated. However, it should be used with extreme caution, given the potential risk of addiction and side effects associated with opioids. (See "Pharmacologic management of chronic non-cancer pain in adults", section on 'Opioids'.)

- Topical anesthetics are also more effective than placebo. Multicenter trials with an aerosolized, lidocaine-prilocaine spray have been reported to improve ejaculatory latency, ejaculatory control, and sexual satisfaction when applied topically to the glans penis five minutes before intercourse [161,162]. In a meta-analysis of eight trials, topical anesthetic agents were more effective than placebo and were well tolerated by patients and their partners. [150].

- Behavioral and psychological therapies are effective in some men [152]. These interventions are designed to achieve a number of goals: improve self-confidence and communication in the relationship and, ultimately, increase the ejaculation latency.

- Combined pharmacologic and behavioral treatment appears to be more effective than pharmacotherapy alone [152]. We suggest this approach in men with PE who have a clear psychosocial precipitant or in those with individual or couple issues that could impact the success of pharmacotherapy alone.

**Other** — Ejaculatory dysfunction includes a spectrum of disorders in men ranging from delayed ejaculation to a complete inability to ejaculate, anejaculation, and retrograde ejaculation. Men with delayed ejaculation, anejaculation, and anorgasmia may have an organic and/or psychogenic etiology. This topic and the management of ejaculatory disorders due to

antidepressant drugs are discussed in detail separately. (See "Epidemiology and etiologies of male sexual dysfunction", section on 'Other ejaculatory disorders' and "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management".)

Lack of ejaculation is common in men with mild, moderate, or severe lower urinary tract symptoms (LUTS) and in men who are treated for these symptoms with tamsulosin [163]. Treatment of LUTS with alfuzosin has been shown to reduce ejaculatory dysfunction [164]. As previously noted, forward ejaculation is not possible in men whose ED is treated with a vacuum constrictor device. (See 'Vacuum-assisted erection devices' above.)

Low serum testosterone concentrations have also been associated with ejaculatory dysfunction (see "Epidemiology and etiologies of male sexual dysfunction", section on 'Other ejaculatory disorders'). However, testosterone therapy is not effective for ejaculatory disorders, suggesting that the relationship is not causal. This was illustrated in a trial of 76 men with one or more ejaculatory symptoms (delayed ejaculation, anejaculation, low ejaculate volume, and/or decreased force of ejaculation) and low serum testosterone concentrations (<300 ng/dL [<10.41 nmol/L] on two occasions), randomly assigned to testosterone solution (2%, 60 mg) or placebo for 16 weeks [165]. Although testosterone therapy increased mean serum testosterone concentrations to the normal male range (214 to 488 ng/dL [7.4 to 16.9 nmol/L]), there were no improvements in parameters of ejaculatory function.

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Male sexual dysfunction".)

## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5$^{th}$ to 6$^{th}$ grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10$^{th}$ to 12$^{th}$ grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Sex problems in men (The Basics)")
- Beyond the Basics topics (see "Patient education: Sexual problems in men (Beyond the Basics)")

## SUMMARY AND RECOMMENDATIONS

- **Goals of therapy** – Therapy of men with sexual dysfunction is aimed at improving libido and addressing the two vital sexual functions: the capacity to acquire and sustain penile erections and treating premature ejaculation (PE). Optimal treatment varies, depending upon the factor(s) that have reduced libido or caused erectile or ejaculatory dysfunction.
- **Erectile dysfunction** – For men with erectile dysfunction (ED), initial steps include ( figure 2) (see 'Overview of management approach' above):
  - **Identify etiology** – (See "Epidemiology and etiologies of male sexual dysfunction".)
  - **Identify cardiovascular risk factors** – Identifying and treating cardiovascular risk factors, such as smoking, obesity, hypertension, and dyslipidemia, as both lifestyle measures and pharmacotherapy for risk factor reduction may be effective for prevention and treatment of ED ( table 1 and table 4 and algorithm 1).
  - **Use of PDE5 inhibitors** – We recommend phosphodiesterase-5 (PDE5) inhibitors as initial therapy (**Grade 1B**). This is based upon their established efficacy, ease of use, and favorable side-effect profile. Sildenafil, vardenafil, tadalafil, and avanafil appear to have similar efficacy, but tadalafil has a longer duration of action ( table 2A). (See 'Phosphodiesterase-5 inhibitors' above.)

    Current practice guidelines suggest that the choice of PDE5 inhibitor should be based upon on the patient's preferences, including cost, ease of use, and adverse effects. (See 'Choice of drug' above.)

    - **Use with nitrates** – PDE5 inhibitors are **contraindicated** in men taking nitrates and should be used cautiously in men receiving an alpha-adrenergic blocker, due to an increased risk of hypotension. (See 'Adverse effects and precautions' above and 'Drug interactions' above.)

- **Other treatment options** – Other therapies that have been shown to be effective: vacuum devices ( figure 2 and figure 3 and table 2B), penile self-injectable drugs ( figure 4), and intraurethral alprostadil.
  - **Vacuum device** – We often suggest that men start with vacuum devices. (See 'Penile self-injection' above and 'Vacuum-assisted erection devices' above.)
  - **Penile prosthesis** – We suggest that surgical implantation of a penile prosthesis be reserved for men who cannot use or who have not responded to less invasive therapies ( figure 2) (**Grade 2B**). (See 'Penile prostheses' above.)
  - **Testosterone therapy** – Testosterone replacement therapy should only be used in men with documented hypogonadism. (See 'Role of testosterone' above.)

- **Men with psychogenic ED** – For men with psychogenic ED, we refer to a certified sexual therapy counselor or a psychologist.
- **Men with PE** – For men with PE, we suggest selective serotonin reuptake inhibitors (SSRIs) as initial therapy (**Grade 2C**). (See 'Premature ejaculation' above.)

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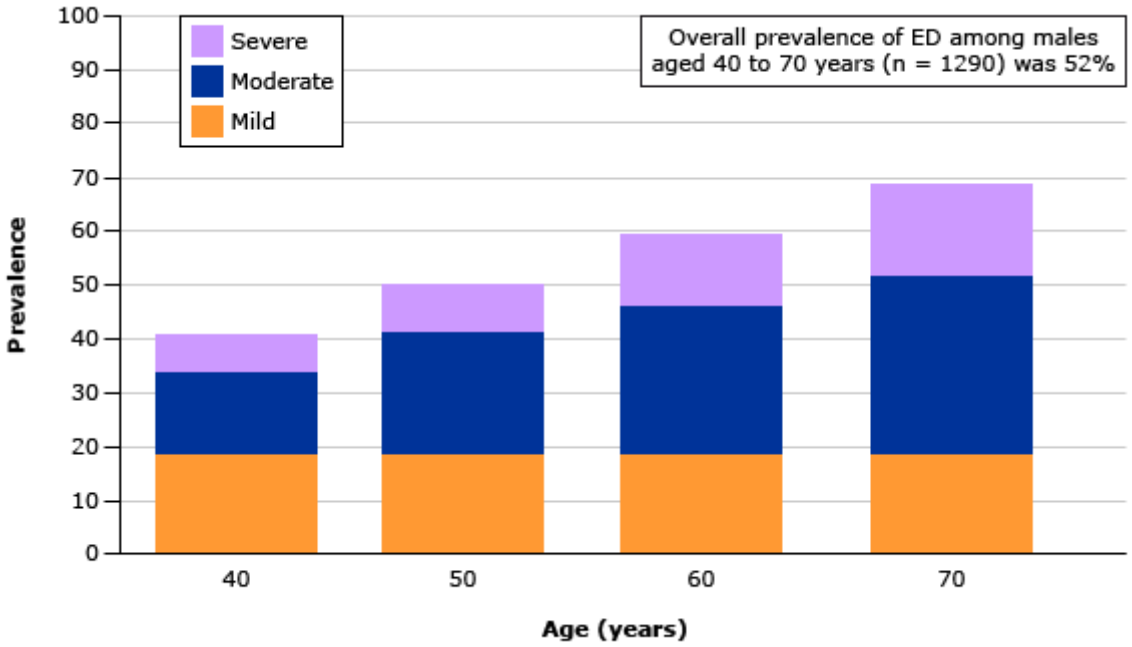
Topic 7469 Version 39.0

## GRAPHICS

### Prevalence and severity of ED in the Massachusetts Male Aging Study (MMAS)




The overall prevalence of mild, moderate, and severe ED was 17.2, 25.2, and 9.6%, respectively.

ED: erectile dysfunction.

*Original figure modified for this publication. 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; 151:54. Illustration used with the permission of Elsevier Inc. All rights reserved.*

Graphic 107343 Version 2.0

## Etiologies of erectile dysfunction[1-3]

| | |
|---|---|
| **Vascular** | Cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, smoking, major surgery (radical prostatectomy) or radiotherapy (pelvis or retroperitoneum) |
| **Neurologic** | Spinal cord and brain injuries, Parkinson disease, Alzheimer disease, multiple sclerosis, stroke, major surgery (radical prostatectomy) or radiotherapy of the prostate |
| **Local penile (cavernous) factors** | Peyronie's disease, cavernous fibrosis, penile fracture |
| **Hormonal** | Hypogonadism, hyperprolactinemia, hyper- and hypothyroidism, hyper- and hypocortisolism |
| **Drug induced** | Antihypertensives, antidepressants, antipsychotics, antiandrogens, recreational drugs, alcohol |
| **Psychogenic** | Performance-related anxiety, traumatic past experiences, relationship problems, anxiety, depression, stress |

ED is classified as organic (ie, vasculogenic, neurogenic, local penile [cavernous] factors, hormonal, drug-induced), psychogenic, or mixed psychogenic and organic. ED usually develops from a mix of psychogenic and organic factors[1,2]. Psychological factors are involved in the development of ED and include performance-related issues (eg, performance anxiety), traumatic past experiences, relationship problems, anxiety, depression, and stress[1-3]. Taking a comprehensive medical history may reveal one of the many common disorders associated with ED[1].

ED: erectile dysfunction.

*References:*

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3. *Grant P, Jackson G, Baig I, Quin J. Erectile dysfunction in general medicine. Clin Med 2013; 13:136.*

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## Oral treatments for male sexual dysfunction

| Medication | Mechanism and clinical use | Adverse effects and precautions | Drug interactions* | Usual dosing¶ |
|---|---|---|---|---|
| **Phosphodiesterase type 5 (PDE5) inhibitors** | | | | |
| Sildenafil | Inhibits enzyme phosphodiesterase 5, allowing cyclic GMP to accumulate within penis.<br><br>Effective for as-needed treatment of organic, psychogenic, or mixed type ED. | Applies to **all** PDE5 inhibitors:<br>▪ Headaches, dyspepsia, vasodilation, diarrhea, rhinitis, epistaxis, blue tinge to vision, other visual disturbances.<br>▪ **Contraindicated if using nitrates or riociguat**Δ due to risk of severe hypotension and syncope.<br>▪ Co-administration with alpha-1 blockers may cause symptomatic hypotension. If co-administered, we suggest first stabilizing patient on alpha-1 blocker dose prior to starting PDE5 inhibitor at a reduced dose. Tamsulosin and silodosin may be better tolerated than other alpha-1 blockers. | Sildenafil is metabolized by CYP3A4.<br><br>Strong inhibitors of CYP3A4 (eg, protease inhibitors§, systemic-azole antifungals, certain macrolide antibiotics) elevate sildenafil concentrations.<br><br>Inducers of CYP3A4 may reduce sildenafil concentrations.<br><br>A list of CYP3A4 inhibitors and inducers is provided in a separate table*.<br><br>We suggest avoidance of large amounts of grapefruit and its juice (a CYP3A4 inhibitor) and alcohol which may enhance hypotensive effect.<br><br>Use with nitrates or guanylate cyclase stimulators (eg, riociguat) is contraindicated (refer to adverse | Taken one hour before sex and effective up to four hours.<br><br>Dose: 50 to 100 mg on empty stomach.<br><br>Administration with a high-fat meal may delay absorption.<br><br>A reduced dose of 25 mg is recommended if coadministered with a strong inhibitor of CYP3A4 or an alpha-1 blocker and in patients with renal impairment (Crcl <30 mL/minute) or moderate hepatic impairment¶.<br><br>Applies to **all** PDE5 inhibitors: Stimulation needed for erection. |

| | | | | |
|---|---|---|---|---|
| | | ▪ Safety is uncertain in patients with severe renal or hepatic impairment, coagulopathy, hypotension, unstable or advanced cardiovascular disease, or retinal disorders◇. | effects/precautions in this table and accompanying text) | |
| Vardenafil | Same as sildenafil. | Similar efficacy, adverse effects, and precautions to sildenafil, EXCEPT visual color distortions reported much less frequently◇.<br><br>Use not recommended in hemodialysis or severe hepatic impairment. | Same as sildenafil. | Similar onset and duration of action as sildenafil.<br><br>Dose: 10 to 20 mg on empty stomach about 60 minutes before sexual activity.<br><br>Patients ≥65 years old: 5 mg initially.<br><br>Orally disintegrating tablet (ODT): 10 mg on empty stomach (no titration).<br><br>Administration with a high-fat meal may delay absorption.<br><br>A reduced dose of 2.5 or 5 mg is recommended if coadministered with a strong |

| | | | | |
|---|---|---|---|---|
| | | | | inhibitor of CYP3A4 or an alpha-1 blocker, respectively*.<br><br>Dose adjustment for moderate hepatic impairment needed¶. |
| Tadalafil | Similar onset of action as sildenafil.<br><br>Duration of action up to 36 hours.<br><br>Effective for as-needed **or** daily treatment of organic, psychogenic, or mixed type ED. | Similar efficacy, side effects, and precautions to sildenafil, EXCEPT visual color distortions reported much less frequently◇.<br><br>Daily use not recommended in severe renal or hepatic impairment. | Same as sildenafil. | Tadalafil has a much longer duration of action than sildenafil.<br><br>Dose for as-needed treatment: 10 to 20 mg about 60 minutes before sexual activity.<br><br>10 mg not more than once every 72 hours is recommended if coadministered with a strong inhibitor of CYP3A4.<br><br>Dose adjustment for renal or hepatic impairment is necessary when used as-needed¶.<br><br>**or** |

| | | | | |
|---|---|---|---|---|
| | | | | Daily treatment: 2.5 to 5 mg once daily (assumes normal renal and hepatic function).<br>2.5 mg once daily is recommended if coadministered with a strong inhibitor of CYP3A4 or alpha-1 blocker*.<br>Administration with a high-fat meal does not alter absorption. |
| Avanafil | Onset of action of 15 to 30 minutes is more rapid than sildenafil. | Similar efficacy, adverse effects, and precautions to sildenafil, EXCEPT visual color distortions reported much less frequently◇.<br>Use not recommended in severe renal or hepatic impairment. | Same as sildenafil, EXCEPT use of avanafil with medications that are strong inhibitors of CYP3A4 is not recommended.<br>A list of strong inhibitors of CYP3A4 (to be **avoided** with avanafil) is provided separately*.<br>Grapefruit and grapefruit juice should be avoided within 24 hours of use. | 100 to 200 mg as early as 15 minutes before sexual activity.<br>Administration with a high-fat meal may delay absorption.<br>A reduced dose of 50 mg is recommended if coadministered with an alpha-1 blocker or moderate inhibitor of CYP3A4*.<br>50 mg dose should be taken about 30 |

| | | | | |
|---|---|---|---|---|
| | | | | minutes before sexual activity. |
| **Other therapies** | | | | |
| Yohimbine<br>In United States yohimbine is available as an ingredient in some non-prescription dietary supplements (yohimbe)¥. | Blocks presynaptic alpha-2 receptors.<br>Stimulates mid-brain, increases libido.<br>Might increase local blood flow or decrease outflow.<br>Used for psychogenic ED.<br>May have placebo effect.<br>Alternative to testosterone for libido. | Dizziness, flushing, nausea, headache, anxiety, insomnia, elevated blood pressure, and increased heart rate; avoid with benign prostatic hyperplasia.<br>Potency and purity of dietary supplements may not be assured.<br>Long-term use is not recommended. | May interact with antihypertensives, antidepressants, or stimulant medications*. | 15 to 30 mg daily in two or three divided doses. |
| Trazodone | Serotonin modulation and alpha-1 antagonism.<br>Used for psychogenic ED.<br>May benefit males suffering from premature ejaculation.<br>Low dose for psychogenic ED may not be effective for treatment of depression. | Dizziness, lethargy, sedation.<br>Dose-related orthostatic hypotension, gastrointestinal toxicity, QTc prolongation, and weight gain.<br>May cause priapsim. | Trazodone is metabolized by CYP1A2, 2D6, and 3A4; it is an inducer of P-gp*. | 25 to 100 mg before sleep. |

CYP: cytochrome P450 drug metabolism; ED: erectile dysfunction; NAION: non-arteritic anterior ischemic optic neuropathy; P-gp: P-glycoprotein efflux transporters; SSRI: selective serotonin reuptake inhibitor; UDP-GT: glucuronyltransferase drug metabolism (glucuronidation).

* A list of strong inhibitors and inducers of CYP3A4 that can interact with PDE5 inhibitors is provided separately. This table does **not** provide a complete list of drug interactions. Specific drug interactions

and management suggestions may be determined by using Lexi-Interact, the drug interactions program included with UpToDate.

¶ One-half of the usual PDE5 dose shown above may have adequate effect and better tolerability in some patients. The co-administration of more than one PDE5 inhibitor or use more than once per day is not recommended. Dose recommendations are based upon product information approved in United States and assume normal renal and hepatic function. Specific recommendations for use in setting of renal or hepatic impairment may be found in the Lexicomp drug monographs. Dose recommendations approved in other countries may differ. Consult locally approved product information.

Δ Riociguat is used in treatment of pulmonary arterial hypertension.

◇ Rarely, vision loss and non-arteritic anterior ischemic optic neuropathy (NAION) described in temporal association with PDE5 inhibitor in post-marketing reports. Precise causality (ie, PDE5 and/or patient-specific risk factors) not determined.

§ Protease inhibitors include atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir and tipranavir. Interaction is of greater significance in ritonavir- or cobicistat-boosted regimens.

¥ Additional information on yohimbe-containing supplements is available from the US National Library of Medicine MedlinePlus database.

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*Data courtesy of authors with additional data from The Medical Letter; 56 (1442):34 May, 2014 and United States approved prescribing information available at National Library of Medicine DailyMed website.*

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Graphic 80719 Version 20.0

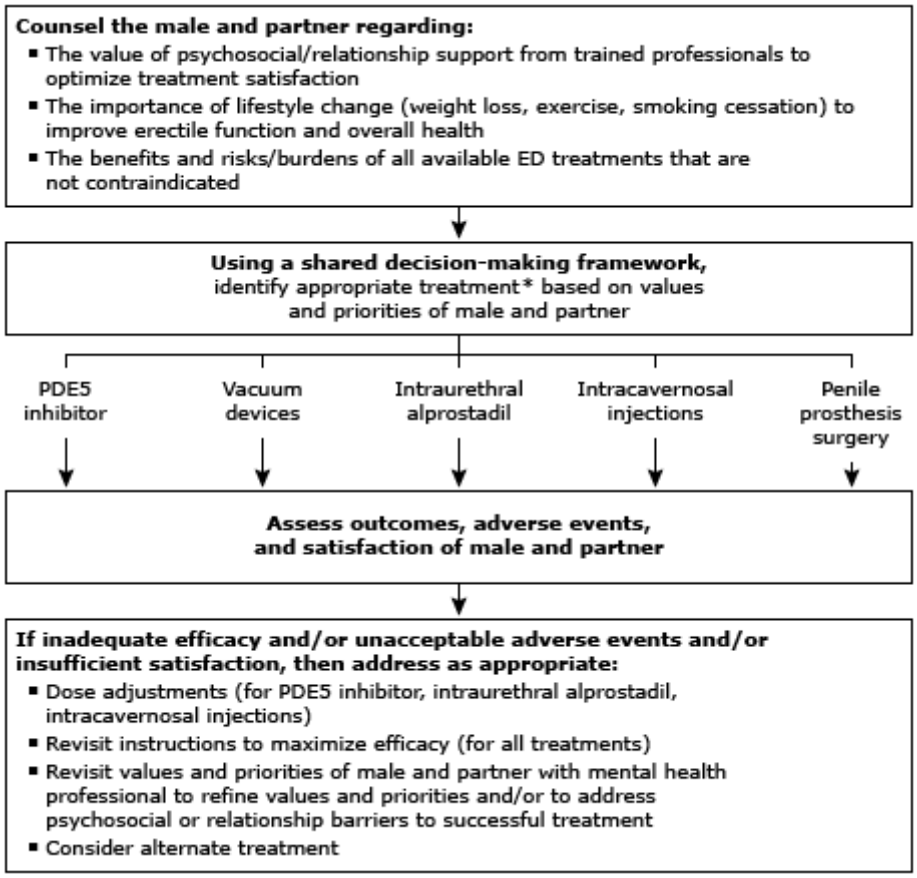
## Suppositories, injections, and devices for treatment of male sexual dysfunction

| Treatment | US trade name | Method of use and effect | Advantages and limitations | Usage pattern |
|---|---|---|---|---|
| **Suppository** | | | | |
| Alprostadil intraurethral pellet | Muse | Alprostadil (prostaglandin E1) in gel form delivered by applicator into meatus of penis.<br>Causes vasodilation by direct vascular smooth muscle relaxation allowing blood flow and entrapment in penis. | Less invasive than intracavernosal injections, but also less effective. Can be used twice daily.<br>Not recommended with pregnant partners. | Inserted 5 to 10 minutes before sex. Effects last up to 1 hour. |
| **Penile injection** | | | | |
| Alprostadil | Caverject<br>Edex | Prostaglandin E1 injected into base of penis. Causes smooth muscle relaxation in corpus cavernosae. | Effective in 50 to 85 percent of cases.<br>Disadvantages include dislike of penile self-injection, pain at injection site, requires reconstitution and sterile technique, not for use more than three times per week or more than once per 24 hours. Bleeding risk with anticoagulants. | Inject 10 to 20 minutes before sex. Erections may last over an hour. |

| | | | | |
|---|---|---|---|---|
| | | | Priapism occurs uncommonly. | |
| Vasoactive intestinal peptide (VIP, aviptadil) and phentolamine | Invicorp (not available in US) | Causes vasodilation by direct vascular smooth muscle relaxation allowing blood flow and entrapment in penis. | Possibly more effective than alprostadil. Causes less pain. Priapism rare. | Inject 10 to 20 minutes before sex. Requires stimulation to have erection. |
| **Device** | | | | |
| Vacuum pump | Various | Removes air from chamber over penis, creating a vacuum and drawing blood into penile cavernosae. Elastic tourniquet at base holds blood in penis. | One-time expense. Safe if erection not maintained more than one hour. May not be acceptable to partner. Penis is hinged at base. May interfere with ejaculation. Can cause bruising of penis. | Inflated just before sexual activity. Erection lasts until elastic ring removed. |

Graphic 53269 Version 4.0

## Approach to the management of the patient with erectile dysfunction




ED: erectile dysfunction; PDE5: phosphodiesterase type 5.

* For males with testosterone deficiency, defined as the presence of symptoms and signs and a total testosterone <300 ng/dL, counseling should emphasize that restoration of testosterone levels to therapeutic levels is likely to increase efficacy of ED treatments other than prosthesis surgery.

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Graphic 107342 Version 3.0

## Clinical clues to causes of erectile dysfunction

| Finding | Cause |
|---|---|
| Rapid onset | Psychogenic |
| | Genitourinary trauma (eg, radical prostatectomy) |
| Nonsustained erection | Anxiety |
| | Venous leak |
| Depression or use of certain drugs | Depression |
| | Drug induced |
| Complete loss of nocturnal erections | Vascular disease |
| | Neurologic disease |

Graphic 61756 Version 5.0

## Cardiovascular risk stratification in males with erectile dysfunction[1,2]

| Low-risk category | Intermediate-risk category | High-risk category |
|---|---|---|
| Asymptomatic, <3 risk factors for CAD (excluding sex) | ≥3 risk factors for CAD (excluding sex) | High-risk arrhythmias |
| | Mild or moderate, stable angina | Unstable or refractory angina |
| | Previous (>6 to 8 week) or recent (2 to 6 week) MI | Recent (<2 week) MI |
| LVD/CHF (NYHA class I or II) | LVD/CHF (NYHA class III) | LVD/CHF (NYHA class IV) |
| Post-successful coronary revascularization | Noncardiac sequelae of atherosclerotic disease (eg, stroke, peripheral vascular disease) | Hypertrophic obstructive and other cardiomyopathies |
| Controlled hypertension | | Uncontrolled hypertension |
| Mild valvular disease | | Moderate-to-severe valvular disease |

The Princeton Consensus (Expert Panel) Conference is dedicated to optimizing sexual function and preserving cardiovascular health[1]. Patients with ED can be stratified into three cardiovascular risk categories as summarized in this table, which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity[1,2].

CAD: coronary artery disease; MI: myocardial infarction; LVD: left ventricular dysfunction; CHF: congestive heart failure; NYHA: New York Heart Association; ED: erectile dysfunction.

*References:*

1. *Wespes E, Eardley I, Guiliano F, et al. European Association of Urology Guidelines on Male Sexual Dysfunction: erectile dysfunction and premature ejaculation. 2013. Available at: www.uroweb.org/gls/pdf/14_Male%20Sexual%20Dysfunction_LR.pdf (Accessed on November 24, 2013).*
2. *Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc 2012; 87:766.*

Graphic 97651 Version 5.0

## International index of erectile dysfunction (IIEF)

**INSTRUCTIONS:** These questions ask about your sex life **over the past four weeks**. Please answer the following questions as honestly and clearly as possible. In answering these questions, the following definitions apply:

- **Sexual activity** includes intercourse, caressing, foreplay, and masturbation
- **Sexual intercourse** is defined as vaginal penetration of the partner (you entered your partner)
- **Sexual stimulation** includes situations like foreplay with a partner, looking at erotic pictures, etc
- **Ejaculate** is defined as the ejection of semen from the penis (or the feeling of this)

**Check ONLY one box per question.**

1. **Over the past four weeks**, how often were you able to get an erection during sexual activity?

- ☐ 0 = No sexual activity
- ☐ 1 = Almost never or never
- ☐ 2 = A few times (much less than half the time)
- ☐ 3 = Sometimes (about half the time)
- ☐ 4 = Most times (much more than half the time)
- ☐ 5 = Almost always or always

2. **Over the past four weeks**, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?

- ☐ 0 = No sexual activity
- ☐ 1 = Almost never or never
- ☐ 2 = A few times (much less than half the time)
- ☐ 3 = Sometimes (about half the time)
- ☐ 4 = Most times (much more than half the time)
- ☐ 5 = Almost always or always

**The next eight questions will ask about the erections you may have had during sexual intercourse.**

3. **Over the past four weeks**, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?

- ☐ 0 = Did not attempt intercourse
- ☐ 1 = Almost never or never
- ☐ 2 = A few times (much less than half the time)
- ☐ 3 = Sometimes (about half the time)

- [ ] 4 = Most times (much more than half the time)
- [ ] 5 = Almost always or always

4. **Over the past four weeks**, during sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner?

- [ ] 0 = Did not attempt intercourse
- [ ] 1 = Almost never or never
- [ ] 2 = A few times (much less than half the time)
- [ ] 3 = Sometimes (about half the time)
- [ ] 4 = Most times (much more than half the time)
- [ ] 5 = Almost always or always

5. **Over the past four weeks**, during sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?

- [ ] 0 = Did not attempt intercourse
- [ ] 1 = Extremely difficult
- [ ] 2 = Very difficult
- [ ] 3 = Difficult
- [ ] 4 = Slightly difficult
- [ ] 5 = Not difficult

6. **Over the past four weeks**, how many times have you attempted sexual intercourse?

- [ ] 0 = No attempts
- [ ] 1 = One to two attempts
- [ ] 2 = Three to four attempts
- [ ] 3 = Five to six attempts
- [ ] 4 = 7 to 10 attempts
- [ ] 5 = 11 or more attempts

7. **Over the past four weeks**, when you attempted sexual intercourse, how often was it satisfactory for you?

- [ ] 0 = Did not attempt intercourse
- [ ] 1 = Almost never or never
- [ ] 2 = A few times (much less than half the time)
- [ ] 3 = Sometimes (about half the time)
- [ ] 4 = Most times (much more than half the time)
- [ ] 5 = Almost always or always

8. **Over the past four weeks**, when you attempted sexual intercourse, how much have you enjoyed sexual intercourse?

- ☐ 0 = No intercourse
- ☐ 1 = No enjoyment
- ☐ 2 = Not very enjoyable
- ☐ 3 = Fairly enjoyable
- ☐ 4 = Highly enjoyable
- ☐ 5 = Very highly enjoyable

9. **Over the past four weeks**, when you had sexual stimulation or intercourse, how often did you ejaculate?

- ☐ 0 = No sexual stimulation/intercourse
- ☐ 1 = Almost never or never
- ☐ 2 = A few times (much less than half the time)
- ☐ 3 = Sometimes (about half the time)
- ☐ 4 = Most times (much more than half the time)
- ☐ 5 = Almost always or always

10. **Over the past four weeks**, when you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?

- ☐ 0 = No sexual stimulation/intercourse
- ☐ 1 = Almost never or never
- ☐ 2 = A few times (much less than half the time)
- ☐ 3 = Sometimes (about half the time)
- ☐ 4 = Most times (much more than half the time)
- ☐ 5 = Almost always or always

**The next five questions ask about sexual desire. Let's define sexual desire as a feeling that may include wanting to have a sexual experience (for example, masturbation or intercourse), thinking about having sex, or feeling frustrated due to lack of sex.**

11. **Over the past four weeks**, how often have you felt **sexual desire**?

- ☐ 1 = Almost never or never
- ☐ 2 = A few times (much less than half the time)
- ☐ 3 = Sometimes (about half the time)
- ☐ 4 = Most times (much more than half the time)
- ☐ 5 = Almost always or always

| |
|---|
| 12. **Over the past four weeks**, how would you rate your level of **sexual desire**? |
| ☐ 1 = Very low or not at all |
| ☐ 2 = Low |
| ☐ 3 = Moderate |
| ☐ 4 = High |
| ☐ 5 = Very high |
| 13. **Over the past four weeks**, how satisfied have you been with your overall **sex life**? |
| ☐ 1 = Very dissatisfied |
| ☐ 2 = Moderately dissatisfied |
| ☐ 3 = About equally satisfied and dissatisfied |
| ☐ 4 = Moderately satisfied |
| ☐ 5 = Very satisfied |
| 14. **Over the past four weeks**, how satisfied have you been with your **sexual relationship** with your partner? |
| ☐ 1 = Very dissatisfied |
| ☐ 2 = Moderately dissatisfied |
| ☐ 3 = About equally satisfied and dissatisfied |
| ☐ 4 = Moderately satisfied |
| ☐ 5 = Very satisfied |
| 15. **Over the past four weeks**, how do you rate your **confidence** that you can get and keep an erection? |
| ☐ 1 = Very low |
| ☐ 2 = Low |
| ☐ 3 = Moderate |
| ☐ 4 = High |
| ☐ 5 = Very high |

*Reproduced from: Rosen RC, Riley A, Wagner G, et al. The international index of erectile dysfunction (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; 49:822. Illustration used with the permission of Elsevier Inc. All rights reserved.*

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Graphic 98030 Version 2.0

## The IIEF-5 questionnaire

| **Over the past six months:** | | | | | |
|---|---|---|---|---|---|
| 1. How do you rate your confidence that you could get and keep an erection? | **Very low** | **Low** | **Moderate** | **High** | **Very high** |
| | 1 | 2 | 3 | 4 | 5 |
| 2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration? | **Almost never or never** | **A few times** (much less than half the time) | **Sometimes** (about half the time) | **Most times** (much more than half the time) | **Almost always or always** |
| | 1 | 2 | 3 | 4 | 5 |
| 3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner? | **Almost never or never** | **A few times** (much less than half the time) | **Sometimes** (about half the time) | **Most times** (much more than half the time) | **Almost always or always** |
| | 1 | 2 | 3 | 4 | 5 |
| 4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse? | **Extremely difficult** | **Very difficult** | **Difficult** | **Slightly difficult** | **Not difficult** |
| | 1 | 2 | 3 | 4 | 5 |
| 5. When you attempted sexual intercourse, how often was it satisfactory for you? | **Almost never or never** | **A few times** (much less than half the time) | **Sometimes** (about half the time) | **Most times** (much more than half the time) | **Almost always or always** |
| | 1 | 2 | 3 | 4 | 5 |
| | **Total score:** | | | | |
| | 1 to 7: Severe ED | 8 to 11: Moderate ED | 12 to 16: Mild-moderate ED | 17 to 21: Mild ED | 22 to 25: No ED |

IIEF: International index of erectile dysfunction; ED: erectile dysfunction.

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Graphic 97456 Version 3.0

## Cytochrome P450 3A (including 3A4) inhibitors and inducers

| Strong inhibitors | Moderate inhibitors | Strong inducers | Moderate inducers |
|---|---|---|---|
| ▪ Atazanavir<br>▪ Ceritinib<br>▪ Clarithromycin<br>▪ Cobicistat and cobicistat-containing coformulations<br>▪ Darunavir<br>▪ Idelalisib<br>▪ Indinavir<br>▪ Itraconazole<br>▪ Ketoconazole<br>▪ Levoketoconazole<br>▪ Lonafarnib<br>▪ Lopinavir<br>▪ Mifepristone<br>▪ Nefazodone<br>▪ Nelfinavir<br>▪ Ombitasvir-paritaprevir-ritonavir<br>▪ Ombitasvir-paritaprevir-ritonavir plus dasabuvir<br>▪ Posaconazole<br>▪ Ritonavir and ritonavir-containing coformulations<br>▪ Saquinavir<br>▪ Telithromycin<br>▪ Tucatinib<br>▪ Voriconazole | ▪ Amiodarone*<br>▪ Aprepitant<br>▪ Berotralstat<br>▪ Cimetidine*<br>▪ Conivaptan<br>▪ Crizotinib<br>▪ Cyclosporine*<br>▪ Diltiazem<br>▪ Duvelisib<br>▪ Dronedarone<br>▪ Erythromycin<br>▪ Fedratinib<br>▪ Fluconazole<br>▪ Fosamprenavir<br>▪ Fosaprepitant*<br>▪ Fosnetupitant-palonosetron<br>▪ Grapefruit juice<br>▪ Imatinib<br>▪ Isavuconazole (isavuconazonium sulfate)<br>▪ Lefamulin<br>▪ Letermovir<br>▪ Netupitant<br>▪ Nilotinib<br>▪ Ribociclib<br>▪ Schisandra<br>▪ Verapamil | ▪ Apalutamide<br>▪ Carbamazepine<br>▪ Enzalutamide<br>▪ Fosphenytoin<br>▪ Lumacaftor<br>▪ Lumacaftor-ivacaftor<br>▪ Mitotane<br>▪ Phenobarbital<br>▪ Phenytoin<br>▪ Primidone<br>▪ Rifampin (rifampicin) | ▪ Bexarotene<br>▪ Bosentan<br>▪ Cenobamate<br>▪ Dabrafenib<br>▪ Dexamethasone¶<br>▪ Dipyrone<br>▪ Efavirenz<br>▪ Elagolix, estradiol, and norethindrone therapy pack$^{\Delta}$<br>▪ Eslicarbazepine<br>▪ Etravirine<br>▪ Lorlatinib<br>▪ Mitapivat<br>▪ Modafinil<br>▪ Nafcillin<br>▪ Pexidartinib<br>▪ Rifabutin<br>▪ Rifapentine<br>▪ Sotorasib<br>▪ St. John's wort |

- For drug interaction purposes, the inhibitors and inducers of CYP3A metabolism listed above can alter serum concentrations of drugs that are dependent upon the CYP3A subfamily of liver enzymes, including CYP3A4, for elimination or activation.

- These classifications are based upon US Food and Drug Administration (FDA) guidance.[1,2] Other sources may use a different classification system resulting in some agents being classified differently.
- Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration.
- Weak inhibitors and inducers are not listed in this table with exception of a few examples. Clinically significant interactions can occasionally occur due to weak inhibitors and inducers (eg, target drug is highly dependent on CYP3A4 metabolism and has a narrow therapeutic index). Accordingly, specific interactions should be checked using a drug interaction program such as the Lexicomp drug interactions program included within UpToDate.
- Refer to UpToDate topics on specific agents and indications for further details.

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* Classified as a weak inhibitor of CYP3A4 according to FDA system.[1]

¶ Classified as a weak inducer of CYP3A4 according to FDA system.[1]

Δ The fixed-dose combination therapy pack taken in the approved regimen has moderate CYP3A4 induction effects. When elagolix is used as a single agent, it is a weak CYP3A4 inducer. Norethindrone and estradiol are not CYP3A4 inducers.

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*References:*

1. *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry (January 2020) available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions.*
2. *US Food & Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: FDA.gov website.*

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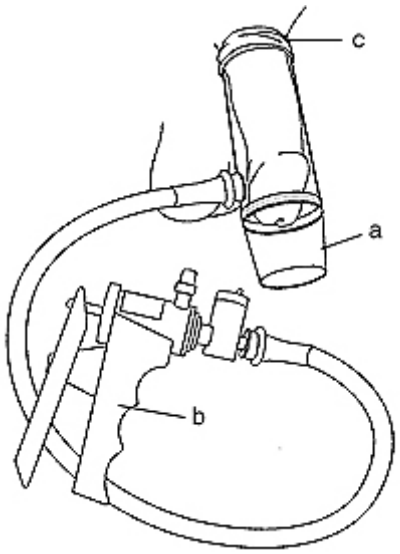
Graphic 76992 Version 86.0

## Vacuum constrictor device




A vacuum-constrictor device causes an erection by creating a partial vacuum around the penis, which draws blood into the corpora cavernosa. Pictured here are the necessary components: (a) a plastic cylinder, which covers the penis; (b) a pump, which draws air out of the cylinder; and (c) an elastic ring, which, when fitted over the base of the penis, traps the blood and sustains the erection after the cylinder is removed.

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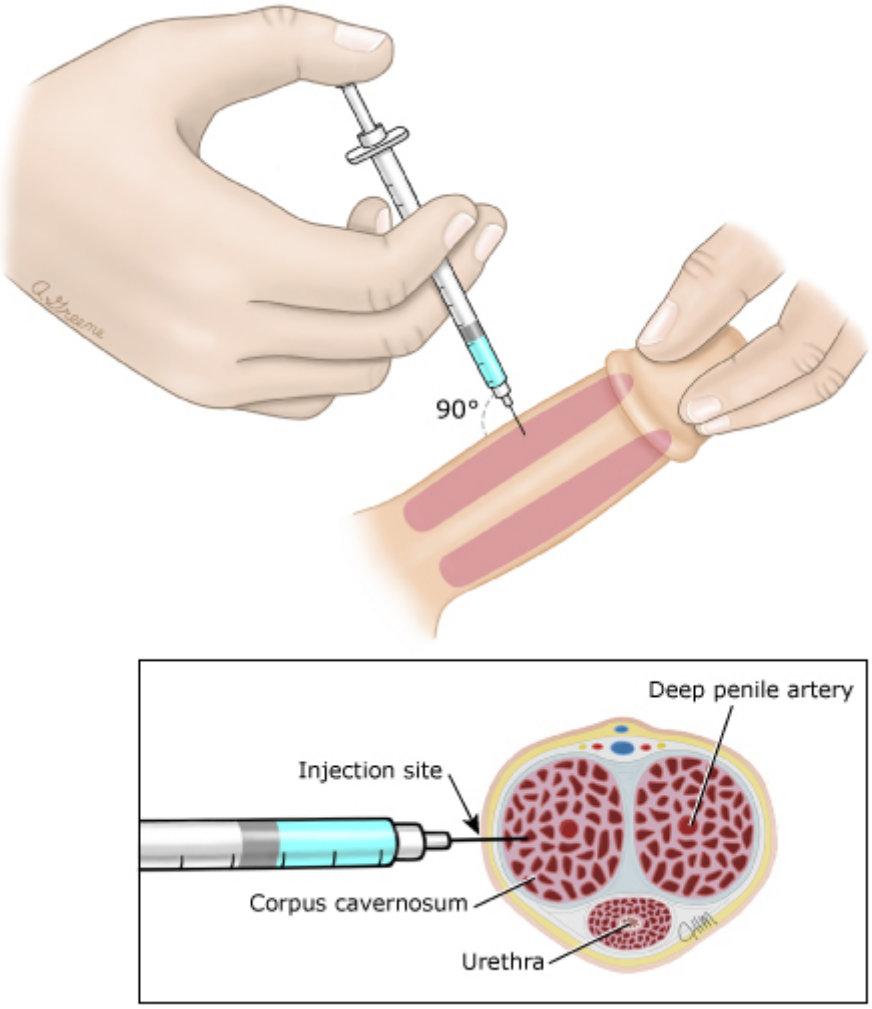
Graphic 54878 Version 1.0

## Method of administering intrapenile injection




To be fully effective, the medications must be injected directly into 1 of the penile erectile bodies, the corporus cavernosum. The medication will diffuse over to the other side of the penis so that symmetrical erection is achieved. A cross section of the penis shows the relationship of the site of injection to the corpora cavernosae. Most males use an insulin syringe with a 26- to 30-gauge 1/2-inch needle.

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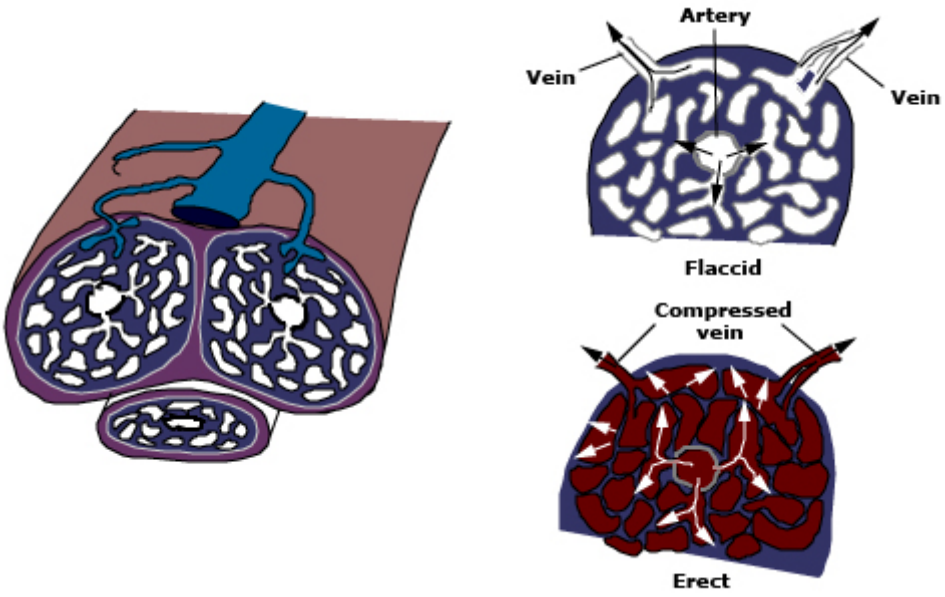
Graphic 60326 Version 3.0

## Penile blood flow in erection




Cross-section of corpora cavernosae illustrating penile blood flow in the flaccid and erect state. As intracavernosal pressure rises, emissary veins are occluded to maintain erectile function.

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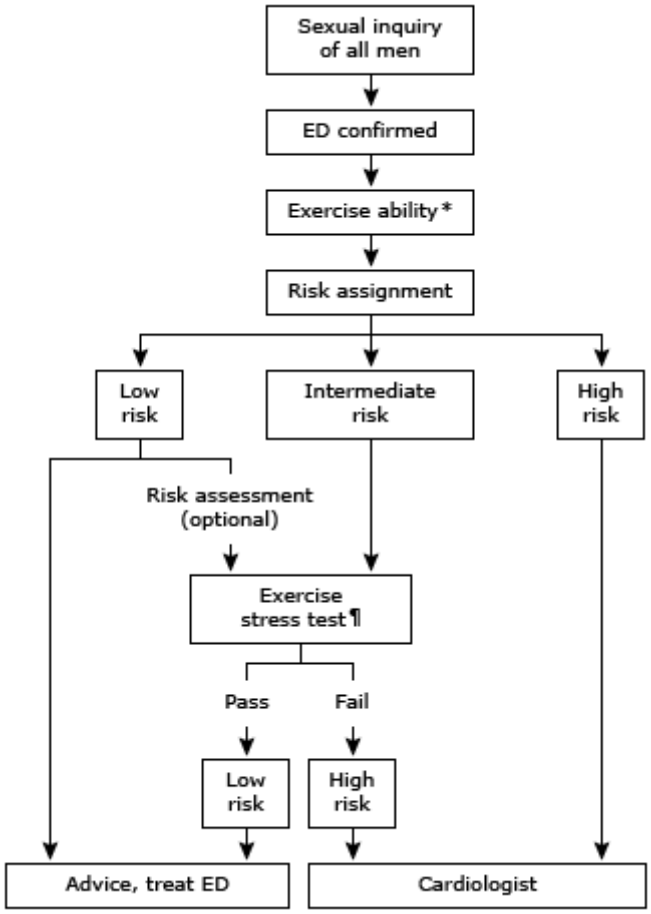
Graphic 60979 Version 1.0

## Estimate of CV risk with sexual activity: Princeton III Consensus recommendations




Algorithm from the Princeton III Consensus recommendations used to estimate the CV risk associated with sexual activity in patients with ED and known CVD.

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CV: cardiovascular; ED: erectile dysfunction; CVD: cardiovascular disease; CIMT: carotid intima media thickness; ABI: ankle-brachial index.

* Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing two flights of stairs in 10 seconds.

¶ Sexual activity is equivalent to four minutes of the Bruce treadmill protocol. The option of CIMT and ABI instead is also given.

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Graphic 97648 Version 2.0

## Contributor Disclosures

**Mohit Khera, MD, MBA, MPH** Consultant/Advisory Boards: AbbVie [Testosterone];Acerus Pharmaceuticals [Testosterone];Boston Scientific [Erectile dysfunction];Clarus [Testosterone];Endo International [Testosterone, Peyronie disease];Metuchen [Erectile dysfunction]. All of the relevant financial relationships listed have been mitigated. **Peter J Snyder, MD** Grant/Research/Clinical Trial Support: AbbVie [Hypogonadism]; Crinetics [Acromegaly]; Novartis [Cushing's]; Recordati [Cushing's]. Consultant/Advisory Boards: AbbVie [Hypogonadism]; Novartis [Cushing's]; Pfizer [Acromegaly]; Teva Pharmaceuticals [Cushing's]. All of the relevant financial relationships listed have been mitigated. **Michael P O'Leary, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose. **Kathryn A Martin, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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