

Hot topics in erectile dysfunction

The answer to some simple questions asked in a 10-minute sexual history-taking session can help determine if ED is primarily a sexual dysfunction or the symptom of another problem.

ABSTRACT: Erectile dysfunction knowledge and management have improved vastly over the last 15 years. We now see erectile dysfunction as an indicator of vascular health and a sentinel marker for cardiovascular risk stratification. As a presenting symptom, erectile dysfunction should trigger a cardiovascular assessment. Erectile dysfunction and lower urinary tract symptoms may share similar pathophysiology, and both may be managed with phosphodiesterase type 5 inhibitors. Current postprostatectomy penile rehabilitation options include these agents as well as intracavernosal injections and vacuum erection device therapy. A simplified assessment approach that relies on questions about sexual history and a physical exam can help with diagnosis and treatment of erectile dysfunction.

A cross-sectional study of 3921 Canadian men, age 40 to 88, found the overall prevalence of erectile dysfunction (ED) was 49.4%,¹ and therefore ED affects an estimated 3 million Canadian men over the age of 40. Epidemiological studies of ED suggest approximately 5% to 20% of men have moderate to severe ED.² ED is a significant clinical problem largely undertreated in the community and has significant impact on the quality of life of sufferers and their partners and families.³ Physicians can help their patients by being aware of the link between ED and cardiovascular disease, the therapeutic options available for ED, and how to take a sexual history.

What is ED and who is at risk?

Erectile dysfunction is the “persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance.”⁴ “Sexual performance,” however, is not defined as sexual intercourse, and can mean other sexual activities such as solo practice (masturbation), partner activity with either gender, or other stimulatory methods. Since erection, ejaculation, and orgasm are all neuro-

logically separate, many men have discovered that orgasm is still possible despite significant erectile problems (e.g., those caused by diabetes) or ejaculatory alterations (e.g., no ejaculation after radical prostatectomy).

Functional erectile difficulties are the result of inadequate blood inflow, disrupted neurological signals, or venous leak. This pathophysiology stems from either poor sexual interest or central arousal to trigger the spinal cord erectile reflexes, medication affecting sexual abilities, or from a generalized medical condition. Endothelial and metabolic risk factors seen in cardiovascular disease, including lack of exercise, obesity, smoking, hypercholesterolemia, diabetes, and the metabolic syndrome, can also contribute to ED.⁵ The risk of ED, partic-

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ularly in a younger man, may be reduced by modifying these risk factors (e.g., increasing exercise and losing weight).⁶

The erectile process depends on the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway. There are two main sources of nitric oxide: from penile nerve endings (nNO) and from healthy endothelial lining (eNO). Hypertension, hyperlipidemia, smoking, and other factors can damage the source of eNO, and men with these conditions are therefore at higher risk for ED. These patients will also require higher doses of the phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil (Viagra), vardenafil (Levitra, Staxyn), and tadalafil (Cialis), since PDE5 inhibitors are reliant on the NO-cGMP pathway triggered by sexual arousal. Men at high risk for neurological ED include those with neurological conditions such as MS, Parkinson disease, and traumatic brain injury, or those who have undergone pelvic, prostate, bladder, or abdominal surgery that interferes with peripheral nerve innervation, reducing nNO. Radical prostatectomy in any form (open, laparoscopic, or robotic) often results in ED despite good nerve-sparing operative technique, because of both nerve and hemodynamic damage. Poor erectile function can also be caused by incompetence of the veno-occlusive mechanism through aging, Peyronies disease,⁷ low testosterone, and by surgical or congenital issues causing a deeper venous leak. Lower urinary tract symptoms (LUTS) are an independent risk factor for ED and may share similar pathophysiological mechanisms.⁸ Men with diabetes have ED secondary to neuropathy, vascular factors (both large vessel and small vessel disease), and functional and structural abnormalities within the corpus cavernosum itself.⁹ Further-

more, the quality of their erections is affected by glycemic control.¹⁰ Hypothyroidism and hypogonadism also affect erections.

ED as an indicator of vascular health

Multiple studies confirm that ED can be an indicator of cardiovascular disease. As a presenting symptom, ED provides an opportunity for physicians to improve men's health before they experience their first cardiovascular event, which could be sudden cardiac death.¹¹ Since penile arteries are typically 1 to 2 mm in diameter—notably smaller than coronary arteries (3 to 4 mm), carotid arteries (5 to 7 mm), and femoral arteries (6 to 8 mm)—the same level of plaque buildup has a greater effect on blood flow through the penile arteries.¹¹ ED can thus present before myocardial infarction (MI) or stroke. A 2006 study found that ED symptoms present 3 years earlier, on average, than the symptoms of coronary artery disease (CAD).¹² Interestingly, in this same study, all patients with type 1 diabetes and ED actually developed sexual dysfunction before CAD onset. The Prostate Cancer Prevention Trial (PCPT) results provided evidence of the association between new-onset ED and subsequent occurrence of cardiovascular events.¹³ In the placebo group (those without ED or cardiovascular disease) of the PCPT trial, 2% of the men experienced a first cardiovascular event 1 year after initial report of erectile dysfunction, while 11% experienced cardiovascular events by 5 years after onset of ED. The authors showed that incident erectile dysfunction had an equal or greater effect on subsequent cardiovascular events (angina, MI, stroke, transient ischemic attack, congestive heart failure, or cardiac arrhythmia) of the same magnitude as a family history of MI, ciga-

rette smoking, or measures of hyperlipidemia. In another study, moderate to severe ED was associated with a considerably increased risk for coronary heart disease (65% relative risk increase) or stroke (43% relative risk increase) within 10 years.¹⁴ A study of men with asymptomatic coronary artery atherosclerosis with and without ED found significantly higher high-sensitivity C-reactive protein levels, more impaired flow-mediated dilation of the brachial artery, and more frequent coronary artery calcification in the men with ED than without ED.¹⁵ These findings are particularly relevant to the younger man who may be asymptomatic before an acute coronary syndrome. Overall, ED may serve as a sentinel marker for cardiovascular risk stratification and prompt lifestyle modification and preventive therapeutic intervention. It has also more recently been suggested that measuring PSA levels and screening for ED and hypogonadism at age 40 can provide gender-specific determinants to assess general metabolic and cardiovascular health risks in men.¹⁶

Penile rehabilitation

Penile rehabilitation is the use of a drug, device, or both to maximize erectile ability by focusing on protection or preservation of penile tissues and their function. After radical prostatectomy (RP), bladder, or abdominal surgery, autonomic nerves responsible for erectile function are often compromised, resulting in erectile loss.

After prostatectomy, loss of oxygenation induces pro-apoptotic factors (i.e., loss of smooth muscle) and pro-fibrotic factors (i.e., an increase in collagen) within the corpora cavernosa. Damage to blood vessels and lack of erections lead to hemodynamic changes and poor oxygenation, which also contribute to cavernosal architecture changes and venous leak.¹⁷

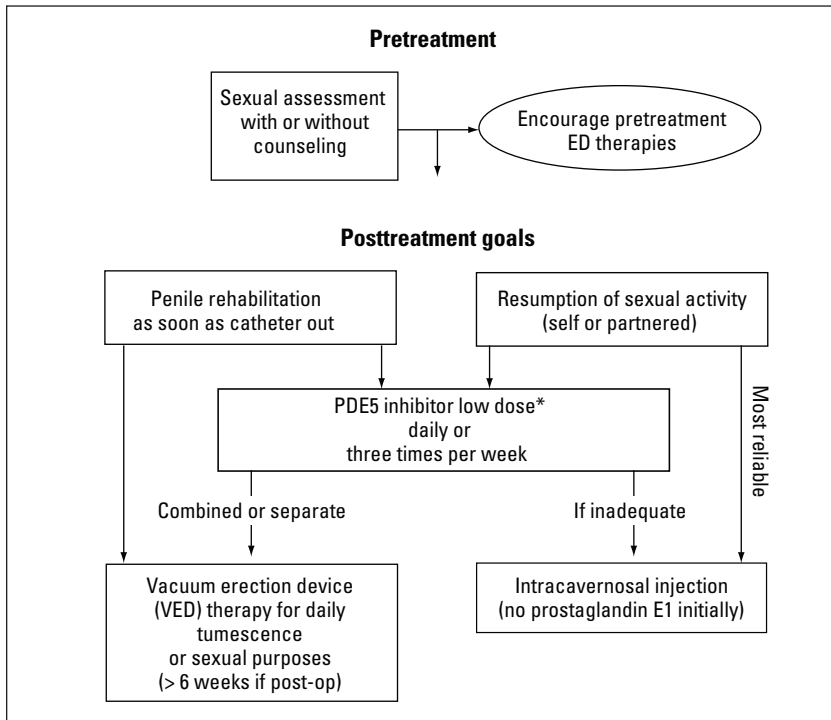


Figure. Penile rehabilitation.

*Suggested doses for phosphodiesterase type 5 inhibitor therapy: daily tadalafil (Cialis) 5 mg, sildenafil (Viagra) 25 mg, or vardenafil (Levitra) 5 mg; or three times per week tadalafil 20 mg, sildenafil 50 mg, or vardenafil 10–20 mg.

There is also a higher percentage of Peyronies disease following radical prostatectomy.¹⁸

The theory behind better spontaneous recovery of post-RP erectile function relates not only to young age, presurgical potency, and small tumor size (where removal is less likely to affect the neurovascular bundles), but also to factors mitigating early post-surgical erectile loss through improved oxygenation with the use of vacuum erection device (VED) therapy, intracavernosal injections (ICI), and the use of PDE5 inhibitors.

PDE5 inhibitors

While early postprostatectomy PDE5 inhibitor use may not create an erection (the chance of a PDE5 inhibitor working will increase as nerve regrowth takes place, even up to 4 years

post-RP), experimental data suggest a penile protective role for daily or three times a week doses of a PDE5 inhibitor. It also appears that on-demand use of a PDE5 inhibitor may be at least as efficacious as daily use and is safe in properly selected patients.¹⁹ Cost is the main reason patients do not continue with PDE5 therapy.

The adage of “erections maintain erections” is the basis for mechanical or pharmacological assistance with oxygenation and preservation of penile architecture post-RP. The **Figure** demonstrates that pretreatment counseling (including the use of erectogenic agents prior to treatment) is important, and that the two goals of treatment—penile rehabilitation and resumption of sexual activity—are not mutually exclusive, and at least one goal should be pursued.

Intracavernosal injections

The use of intracavernosal injections to instigate erections by bypassing the NO-cGMP pathway, and directly relaxing the penile smooth muscle through the cyclic adenosine monophosphate (cAMP) pathway, is the gold standard for attaining erections. Prostaglandin E1 (alprostadil) 20 µg/mL is the mainstay of ICI treatment, but some men experience penile aching, especially within the first year post-RP. In these cases the use of papaverine plus phentolamine (bimix) or the diluted form of prostaglandin E1 (10 µg/mL), or more commonly a trimix solution (containing prostaglandin, papaverine, and phentolamine) is more acceptable. MUSE (medicated urethral system for erection) is an intraurethral pellet of prostaglandin E1, which has limited effectiveness in many men post-RP. However, in studies initiating its use shortly after RP, MUSE has been found to be safe and tolerable, and, like ICI, appears to shorten the recovery time to regain erectile function, although some men experience mild penile aching or urethral burning, resulting in discontinuation due to dissatisfaction at a rate of about one-third.²⁰ An erectile ring used with the administration of MUSE may help prevent systemic loss of the drug.

Vacuum erection device therapy

Vacuum erection device therapy is rapidly gaining popularity following surgical or radiation treatment for prostate cancer, as it is not dependent on nerve status, or, to some extent, on vascular status. While further prospective studies are required, VED therapy can, theoretically, play a role in corporeal rehabilitation and prevention of veno-occlusive dysfunction post-RP by facilitating tissue oxygenation and reducing cavernosal fibrosis in

the absence of nocturnal erections.²¹ There is also some evidence of preservation of penile length and girth when used early following prostate brachytherapy and external beam radiation for prostate cancer,²² and some propose VED as the most reliable first-line therapy for RP patients.

Combination therapy

Combination therapy is another option in the hard-to-treat ED patient. The use of VED with either oral or injectable erectogenic agents is acceptable, as is the use of the latter two together in hard-to-treat ED patients. The risk of prolonged erection is tied more to the use of ICI than to PDE5 inhibitors, since the latter would require continuous sexual arousal, and therefore rarely causes priapism. In some cases, using both the cAMP and the cGMP pathways will maximize smooth muscle relaxation more than either alone. Combination therapy, however, should only be undertaken by physicians who feel they have adequate experience in dealing with ED; otherwise, a referral to a sexual medicine specialist or urologist is in order.

In British Columbia, ICI medications can be obtained through Special Authority following prostate cancer treatments, whereas PDE5 inhibitors, VED, and MUSE cannot. If all reversible methods for ED fail, a referral to a urologist or the Men's Health Initiative regarding eligibility for penile prosthesis should be made.

PDE5 inhibitors and lower urinary tract symptoms

Current data show that PDE5 inhibitors prescribed for lower urinary tract symptoms (LUTS) reduce obstructive and irritative voiding symptoms but have no effect on uroflowmetry parameters of postvoid residual volume.²³ It appears PDE5 inhibitors may have the same efficacy as alpha-adrenergic

antagonists for the treatment of LUTS, or combination therapy of the two could be another option. However, while further research is needed to establish the efficacy and safety of these agents in the treatment of LUTS, a recent study has shown the daily use of tadalafil is helpful in urinary symptoms secondary to benign prostatic hypertrophy, and has been shown to be well tolerated and efficacious throughout 1 year of treatment.²⁴

What's new in ED therapy?

PDE5 inhibitors for ED therapy have been on the market for over 10 years and are still considered effective first-line agents. Testosterone replacement therapy (TRT) should be considered in those eligible hypogonadal patients who do not respond to PDE5 inhibitor therapy alone, as TRT may result in successful PDE5 inhibitor use. The use of oral ED medication is also associated with increased female partner satisfaction, particularly with the female partner's perception of the quality of the relationship.²⁵ PDE5 inhibitors are extremely safe and are proving useful in other disorders; they have already been approved for use in pulmonary hypertension. Their therapeutic potential extends to the cardiovascular, gastrointestinal, cutaneous, and nervous systems to such a degree that these agents may be beneficial in a multitude of conditions, including Raynaud syndrome, heart failure, essential hypertension and stroke, Peyronies disease, stuttering priapism, and altitude sickness.²⁶ Several new PDE5 inhibitors are expected to enter the market in future: avanafil, udenafil, SLx-2101, and mirodenafil (SK 3530).²⁷ Avanafil, one of the new PDE5 inhibitors currently undergoing clinical trials, appears to have enhanced selectivity, faster onset of action, and a favorable side effect profile relative to the currently available

agents.²⁸ Other molecules being considered for treating ED include selective dopamine, glutamate, serotonin, and melanocortin receptor agonists, guanylate cyclase activators, rho-kinase inhibitors, and hexarelin analogues, while the first trials of gene therapy and tissue engineering for reconstruction of corporal tissue are underway.

Simplified ED assessment

Many physicians in a busy practice shy away from sexual issues such as ED because they feel assessment will either take too long or they won't know what to offer beyond PDE5 inhibitors. Although the prospect of uncovering complex psychosocial issues, relationship distress, psychiatric illness, and addictions causing or contributing to ED concerns some physicians, a simplified ED assessment approach can make diagnosis and treatment quite manageable.

After a brief 10-minute sexual history taking (see questions below), a physical examination should assess basic secondary sex characteristics, evidence of endocrine or cardiovascular abnormalities, and anatomical changes to the penis (e.g., tight foreskin, obvious Peyronies disease plaques). A digital rectal exam should also be performed. Blood work should only be reserved for assessment of medical factors that may be contributing to ED. Serum testosterone levels should be obtained if the patient is at risk for hypogonadism, especially if there is a sexual history of reduced libido, delayed orgasm, or other typical hypogonadal symptoms (fatigue, lack of energy, mood changes, etc.).

Questions for sexual history taking

A direct approach based on leading questions is best for sexual history taking. If the medical, psychiatric, and

surgical history are not already known, or there is too little time for a physical exam, another visit should be scheduled.

1. Clarify the nature of the sexual problem. What is the problem exactly? For example, “I can’t perform,” could mean erectile dysfunction, premature ejaculation (and normal loss

ability to sustain), and erections with self-stimulation. It is helpful to normalize masturbation in a permissive way. For instance, “Many men with erection difficulties with their partner will self-stimulate to see if the erections are any better. What is your experience?” Men with difficulties only

be used to describe the erection quality if the partner is male.

5. Ask about the rest of the man’s sexual response. What is the level of sexual desire, ability to ejaculate or reach orgasm, and orgasmic quality?

6. Ask if there are any sexual concerns with the partner. Is there ED or lack of orgasm for the partner that needs to be addressed? If the partner is a menopausal woman, is there dyspareunia secondary to dryness that needs to be addressed?

7. Ask how each partner has reacted to the problem. Has there been distancing, hesitancy, guilt, or blame? What is the man’s perception of his partner’s support, or conversely, intolerance or pressure?

8. Ask if the man has tried any medical or psychologically based therapies. Which treatments have been tried? Were the trials adequate? Were they successful or not?

9. Ask about the sexual context of the couple. Is there still affectionate or even sexual activity without penetration or has the couple stopped having sex? If so, for how long?

10. Determine if the man (and his partner, if there is one) is motivated to continue to seek help.

The answers to these questions will help determine a therapeutic direction: Is ED primarily a sexual dysfunction or the symptom of a much bigger problem (i.e., marital discord)? If you suspect the latter, ED therapies may not help unless they are used in a context of relationship therapy or treatment of the psychosocial issue (i.e., mindfulness for anxiety and arousal difficulties), which may or may not be the expertise of the treating physician. That said, ED issues stemming from more medically or surgically related causes will still have a psychological component that needs to be acknowledged for treatment to be successful. Most therapies tend to

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of tumescence interpreted as ED), or fears of infertility. Make sure the diagnosis is correct.

2. Classify the problem by duration. Was the onset of the problem gradual, acute, or has it been lifelong? For example, a young man who has never had a normal firm erection should be seen by urology to rule out a rare but possible congenital or vascular problem. More typically, a man with diabetes may experience variable quality and reliability of erections over the years as his blood sugars fluctuate and his diabetes progresses.

3. Classify the problem by situation. Is the difficulty always present (generalized erectile dysfunction) or does it occur only sometimes (situational erectile dysfunction)? Ask about three scenarios: the presence, frequency, and quality of REM sleep erections (on awakening or during the night), erections with partner (quality and

in partner situations (situational ED) are less likely to have a medical cause for their ED. Ask whether non-coital activities (such as hand or oral stimulation) affect the erection quality, and in cases where there are multiple partners, whether the ED remains regardless of partner.

4. Obtain a more detailed description of the quality and duration of the erection. Are the erections easily attained but lost quickly? To describe erections, we use a scale of 0 to 10, where 0 is no tumescence (fully flaccid) and 10 is rigid (as seen in young men). A rating of 5/10 is where the penis is tumescent, bendable (without pain) but not firm enough for vaginal penetration, 6/10 is adequate for penetrative activities with assistance (i.e., hand guidance), and 7/10 is adequate for penetration without assistance. A similar descriptive 1 to 10 scale or percentage rating system can

more successful if the partner is involved from the start.

Furthermore, constellations of symptoms can point to underlying causes. For example, men with hypogonadism who have undergone testosterone replacement therapy to physiological levels may or may not have improved erectile ability, but TRT will assist with the efficacy of PDE5 inhibitors, improve sexual drive, and usually help with delayed ejaculation. It is important to note that hypogonadism and depression often overlap. Men with type 1 diabetes are more likely to develop ED and retrograde ejaculation. Men with anxiety are more likely to lose their erection with performance pressure and ejaculate fast as a result of the noradrenergic stimulation. Further assistance with history taking around ED is available.²⁹

Other ED assessment tools

In clinical trials, the use of the International Index of Erectile Function (IIEF), a scale to assess male sexual function, is appropriate since it can measure the degree (mild, moderate, or severe) of erectile impairment, but the IIEF is limited in that it only measures heterosexual sexual activity that has occurred within the last 4 weeks.³⁰ A shortened version (sexual health inventory for men, or SHIM) is available³¹ and can be found on the Men's Health Initiative web site (www.aboutmen.ca).³² While the SHIM can help assess the severity of ED, clinically it is only useful for the regularly sexually active man who has a female partner. However, since it is important to stay neutral in terms of gender of sexual partner and the fact that erection difficulties may stem from masturbatory practices (as may be seen in the single younger, or older widowed or institutionalized man), the use of more descriptive scales noted above are

more helpful clinically, since the erectile difficulties are based on patient's (or partner's) subjective estimation, and as such, improvements (if they occur) on ED therapies can be noted regardless of type of sexual practice.

Summary

The link between ED and cardiovascular disease prediction is well established, and men presenting with ED should be assessed for risk factors and not just treated medically for their ED. Assertive medical management and lifestyle changes can potentially prevent a future high-risk cardiac event. Penile rehabilitation should be offered to those who wish it and may be provided in the form of PDE5 inhibitors, VED, ICI, or combination therapy, depending on patient motivation and cost. The benefits of PDE5 inhibitors are expanding beyond urological use. New drugs for ED will potentially allow for more personalized medicine

and may even have a role in preventing certain ED risk factors. Physicians need to know how to take a brief but informative sexual history in men presenting with ED and be aware of the current trends of practice in the ED world.

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Competing interests

Dr Elliott is on the advisory boards and CME curriculum panels and has given lectures for the PDE5 inhibitor companies (Bayer, Lilly, and Pfizer). She has received an educational grant to cover partial expenses at the American Urological Association meeting (not fees for speaking).

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