Taking the stress out of treating erectile dysfunction

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Case description

Mr E.P., aged 51 years, comes to your office complaining that he "can't get it up anymore!" He has noticed over the past year that it takes him longer to achieve an erection and that it is not as firm as it used to be. His erection allows penetration of his partner and lasts long enough to reach ejaculation about 80% of the time. He denies any problems with his libido.

His medical history is positive for hypertension, for which he takes 25 mg of hydrochlorothiazide and 100 mg of sustained-release metoprolol daily. He also takes multivitamins and occasional acetaminophen for headaches. He smokes on average 10 cigarettes a day and has done so for the past 30 years. Alcohol consumption consists of 3 to 4 glasses of red wine a week. He used to play recreational hockey but he hardly gets any exercise now. He denies chest pain and has shortness of breath only on extreme exertion. He was adopted and does not have any information about his family history.

On examination, his blood pressure is 145/88 mm Hg and his pulse is 75 beats per minute. He is 194 cm tall and weighs 105 kg, so his body mass index is 28 kg/m^2. Heart sounds are normal and no cardiomegaly is found on clinical examination. He has normal hair distribution, and genital examination reveals a normal, uncircumcised penis, a normal scrotum, and testicles measuring around 20 cm^3 with no nodules. Digital rectal examination revealed a 40-cm^3 size prostate with no nodules.

Mr E.P. is interested in knowing what is causing his erectile dysfunction (ED) and if the drugs for ED that are advertised on television will work for him.

Bringing evidence to practice

The Second International Consultation on Sexual Dysfunction defined ED as a "consistent or recurrent inability of a man to attain and/or maintain penile erection sufficient for sexual activity."[1] The pathophysiology of ED is an inability of the smooth muscle in the corpus cavernosum to relax enough for blood to fill it to a pressure that is almost equal to the systolic blood pressure. Normally, sexual stimulation will lead to stimulation of the cavernosal nerves, resulting in the release of nitric oxide from the endothelial cells. This in turn will increase the production of cyclic guanosine monophosphate, which will relax the smooth muscle by acting on the calcium channels.[2]

Many diseases, including diabetes, atherosclerosis, hypertension, multiple sclerosis, and dyslipidemia, affect endothelial cells and nerve endings, potentially leading to ED. Trauma to the nerves (eg, prostate surgery, bicycling injuries) will also lead to ED through similar mechanisms.[3]

Because of the pathology in the endothelial cells, ED has recently been used as a marker of endothelial dysfunction and cardiovascular disease (CVD).[3-5] Symptoms of ED tend to precede CVD by 3 or more years.[6,7] Erectile dysfunction can be treated in most patients with stable coronary artery disease as long as precautions are taken to avoid interaction between phosphodiesterase 5 (PDE5) inhibitors and nitrates. However, patients at high risk of CVD (those with unstable angina, myocardial infarction in the past 2 weeks, uncontrolled hypertension, or moderate to severe valve disease) might be advised to avoid sexual activity.[5]

There are several medications that can cause or contribute to ED, including several antihypertensive medications such as the thiazide and β-blocker that Mr E.P. is taking.[4,8] **Table 1**[9-12] lists some of the drugs associated with ED. Smoking also causes ED through various mechanisms; apart from endothelial damage, there is also a degradation of nitrous oxide by superoxide anions that are released by smoking. Smoking cessation might lead to reversal of ED.[13]

Table 1. Drugs associated with erectile dysfunction

TYPE OF DRUG	EXAMPLES
Acid suppression	ranitidine, cimetidine
Anticonvulsants	carbamazepine, gabapentin, phenytoin, phenobarbital, pregabalin,[11] topiramate
Antidepressants	SSRIs, TCAs, lithium, MAOIs
Antipsychotics	haloperidol, phenothiazines
Antihypertensives	BBs, methyldopa, clonidine; CCBs (less likely)
Cardiac-related	digoxin, fibrates, statins
Diuretics	spironolactone, thiazides (especially higher doses than are now used for hypertension, eg, hydrochlorothiazide ≥ 50 mg)
Hormonal	progesterone, estrogen, corticosteroids, 5α-reductase inhibitors, cyproterone acetate
Immunomodulators	interferon α
NSAIDs	indomethacin[12]

BB—β-blocker, CCB—calcium channel blocker, MAOI—monoamine oxidase inhibitor, NSAID—nonsteroidal anti-inflammatory drug, SSRI—selective serotonin reuptake inhibitor, TCA—tricyclic antidepressant.
Data from Katz and Katz,[9] McVary,[10] Hitiris et al,[11] and Miller et al.[12]

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*The full version of the RxFiles erectile dysfunction treatment chart is available at **www.cfp.ca**. Go to the full text of the article online, then click on **CFPlus** in the menu at the top right of the page.

The evaluation of a patient with ED consists mainly of a comprehensive medical, sexual, and psychosocial history and a physical examination. The physical examination might not always identify the cause of the ED, but it might rule out other rare causes such as Peyronie disease, prostate cancer, hypogonadism, or decreased peripheral pulses. Specific laboratory tests will depend on the individual patient, but they might include measurement of fasting glucose levels, lipid profile, and in selected cases bioavailable testosterone levels.[14] Special investigations such as imaging and neurological testing are not in the scope of the family physician; they might be ordered by urologists in cases that are complex or refractory to treatment. Reversible causes of ED should be explored, including relationship or psychological factors, depression, obesity and fitness status, medications (see **Table 1**[9-12]), illicit drug use, and excessive alcohol consumption.[15] In cases where ED appears to have arisen suddenly, emotional issues such as performance anxiety might be predominant and benefit most from counseling. Whenever possible, interviewing and involving the partner will be useful.

Phosphodiesterase 5 inhibitors are effective first-line oral pharmacotherapy for ED. A systematic review found that they improved sexual intercourse success compared with placebo (69% vs 36%; number needed to treat=3).[16] The absolute contraindications for these drugs are allergy to the drug and concomitant use of nitroglycerin for angina. (Also beware of the use of recreational drugs such as inhalational "poppers" that contain nitroglycerin.)

There are 3 PDE5 inhibitors currently approved in Canada: sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis). They have similar efficacy but differ in terms of their pharmacokinetics. Key issues to consider for individualization of therapy are frequency of intercourse (daily vs as-needed dosing), need for spontaneity (long acting vs short acting),

Table 2. Comparison of PDE5 inhibitors

CHARACTERISTIC	SILDENAFIL (VIAGRA)	TADALAFIL (CIALIS)	VARDENAFIL (LEVITRA)
Onset	≤30-60 min	≥30-60 min	≤30-60 min
Peak effect	1 h	2 h	1 h
Duration	>4 h	36 h	>4 h
Available doses	25, 50, 100 mg	2.5, 5, 10, 20 mg	5, 10, 20 mg
Usual starting dose	50 mg	10 mg (see Comments regarding daily dosing)	10 mg
Maximum dose	100 mg	20 mg	20 mg
Cost per 8 doses (usual dose)	$105	$125	$110
Effect of fatty meal	Delay onset by 60 min; might decrease effect	Meal has no effect	Delay onset by 60 min; might decrease effect
Unique consideration	"Blue vision" effect more common	Very long acting	QT interval drug interactions (eg, TCAs)
Monitor (baseline)	Liver, renal	Liver, renal	Liver
Contraindications[5]	History of MI in past 90 d or stroke in past 6 mo; angina: unstable or occurring with sexual activity; nitrate use; hypotension (BP <90/50 mm Hg) or uncontrolled hypertension (BP >170/100 mm Hg); priapism, retinitis pigmentosa; history of NAION; previous PDE5 inhibitor allergy		
Common side effects	Headache, flushing (approximately 10%); dyspepsia, dizziness, rhinitis, altered, hazy, or blurred vision (<10%); myalgia (possibly more with tadalafil)		
Serious side effects	Rare: prolonged erection (<4 h), priapism Very rare or uncertain: NAION, MI, hearing loss[18]		
Drug interactions (common and important; not exhaustive)	Drugs that cause hypotension (α_1 blockers,[19] nitrates, vasodilators): increased hypotensive effect, heart rate, and MI risk Nitrate washout time required: 24 h for sildenafil and vardenafil; 48 h for tadalafil CYP 3A4 inhibitors (eg, azole antifungals, erythromycin, grapefruit juice, protease inhibitors, verapamil): increased levels of the PDE5		
Comments	PDE5 inhibitors might be effective in several ED-associated conditions such as diabetes,[20] spinal cord injury,[21] and follow-up to treatment for prostate cancer[22] Moderate to high doses are useful to ensure initial treatment success; however, consider lower dose if the patient is elderly, has hepatic or renal dysfunction (vardenafil does not require dose adjustment for renal function), or is taking concomitant CYP 3A4 inhibitors Because of tadalafil's long action, daily dosing of 2.5-5 mg (or 5-10 mg 3 times/wk) might be an option for some; use lowest effective dose[23,24]		

BP—blood pressure, CYP—cytochrome P450, ED—erectile dysfunction, MI—myocardial infarction, NAION—nonarteritic ischemic optic neuropathy, PDE5—phosphodiesterase 5, TCA—tricyclic antidepressant.
Data from Brien and Trussell,[5] Tsertsvadze et al,[16] Downey,[17] the FDA Drug Safety Newsletter,[18] Kloner,[19] Vardi and Nini,[20] Giuliano et al,[21] Miles et al,[22] Roehrborn et al,[23] and Kloner et al.[24]

rapidity of onset, and absorption of the drug (ie, whether the drug will be taken with meals or not). **Table 2**[5,16-24] provides a comparison of PDE5 inhibitors. A full version of the RxFiles erectile dysfunction treatment chart is available online at **CFPlus**.*

For those unable to take PDE5 inhibitors, other options such as intracavernosal prostaglandin injection, vacuum devices, and intraurethral prostaglandin can be considered. Penile implants are also available as a last resort.

Back to Mr E.P.

Mr E.P. has several modifiable factors that could be the cause of his ED. The first priority is smoking cessation counseling with or without pharmacologic assistance. The need for an exercise program and weight loss should also be explored. Mr E.P. could begin drug therapy for his ED right away, as the effects of smoking cessation might take a while to make a difference. Second, his medication for hypertension could be adjusted, providing he has no contraindications to the other drug classes. An angiotensin-converting enzyme inhibitor (or angiotensin

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receptor blocker) is unlikely to contribute to ED and would be an alternative to either or both of the β-blocker and thiazide.[8] Thiazides at high doses (eg, ≥50 mg hydrochlorothiazide) can contribute to ED. Lower thiazide doses, more common in the treatment of hypertension, are less likely to cause ED. However, reducing the hydrochlorothiazide dose to 12.5 mg daily, or withdrawing the drug completely, could be tried. Screening for type 2 diabetes and hyperlipidemia should be considered, with appropriate management and CVD risk factor modification.

The primary differences among the 3 PDE5 inhibitors should be explained to Mr E.P. to assist him in making an informed choice (**Table 2**[5,16-24]). If spontaneity is a priority, he might wish to opt for tadalafil. If cost is a factor, sildenafil or vardenafil might be preferred; however, cost differences are minimal. If rapid onset is important, vardenafil might have slightly faster onset, followed by sildenafil. Patients should be given a starting dose high enough to avoid the psychological effects of a poor response.[10] Mr E.P. should also be counseled about the need to wait long enough after taking the dose to allow for the onset of effect. For PDE5 inhibitors to work effectively, sexual arousal is a requirement. If he is not responding to one of the PDE5 inhibitors at the maximum dose, options include reassessing for and treating any other causes (eg, counseling for relationship or psychogenic issues), trying one of the other PDE5 inhibitors, or considering other treatment options such as prostaglandin injections or vacuum devices. In complex or resistant cases, referral to urology, endocrinology, cardiology, or psychology might be indicated.

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