Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient enough to permit satisfactory sexual performance. The term impotent is used mainly when describing men who experience erectile failure during attempted intercourse more than 75% of the time.

Pharmacologic treatment of ED has come a long way in recent years. With the introduction of sildenafil in 1998, new doors were opened in treatment. The first-line treatment options include the phosphodiesterase type 5 (PDE5) inhibitors, according to guidelines put forth by the American Urological Association, the American Association of Clinical Endocrinologists, and the European Association of Urology. The FDA has approved the use of both intracavernosal alprostadil therapy (direct delivery of the drug to the erectile chambers) and transurethral alprostadil therapy (direct delivery to the urethra) as second-line treatment alternatives.

In this article, I’ll take a look at PDE5 inhibitors and alprostadil. But first, let’s review the pathophysiology of and risk factors for ED.

A normal penile erection is caused by one of two main mechanisms: reflex erection or psychogenic erection. Reflex erections occur with tactile stimulus to the penis or genital area. Psychogenic erections occur when neural impulses are triggered that originate in response to erotic visual or auditory stimuli or those generated by fantasy. The erection is a hemodynamic event that’s caused by relaxation of both the arterial and corporal smooth muscle.

Relaxation of the corporal smooth muscle is caused by the release of acetylcholine by the parasympathetic nervous system. Acetylcholine causes the release of nitric oxide, which is needed to stimulate guanylate cyclase to produce cyclic guanosine monophosphate (cGMP). This causes the trabecular smooth muscle to relax. Thus, penile erection is caused by the combination of increased arterial inflow into the corporal bodies and an increase in the amount of oxygen that stimulates the synthesis of nitric oxide by the cavernosal nerves and endothelium, along with a decrease in venous outflow.

Increasing age is the main risk associated with developing ED. Other related risks include:

### Causes of ED

<table>
<thead>
<tr>
<th>Type of disorder</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Atherosclerosis, penile Raynaud’s phenomenon, cardiovascular disease, diabetes</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Spinal cord injury, cerebrovascular accident, peripheral neuropathy, diabetic neuropathy</td>
</tr>
<tr>
<td>Hormone/endocrine</td>
<td>Hypogonadism, hyperthyroidism, hyperglycemia, uncontrolled diabetes</td>
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<tr>
<td>Psychogenic</td>
<td>Performance anxiety, depression</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Pelvic radiation, lumbar sympathectomy, prostatectomy, renal transplant, spinal cord resection</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Anti-infectives, central nervous system depressants, diuretics, sympatholytics, nonselective beta-blockers, alpha-blockers, direct vasodilators, calcium channel blockers, antidepressants, antipsychotics, opioids, anxiolytics, cimetidine, steroids, statins</td>
</tr>
</tbody>
</table>
Contraindications and precautions for PDE5 inhibitor use

Contraindications
- Nitrates (Don’t give sildenafil within 4 hours of alpha-blocker administration; tamsulosin can be used with tadalafil.)
- Alpha-blockers
- Hypersensitivity

Precautions
- Cardiovascular disorders
- Left ventricular outflow obstruction
- BP changes
- Strong CYP3A4 inhibitors
- Priapism
- Hepatic impairment (vardenafil and tadalafil)
- QT prolongation (vardenafil and tadalafil)
- Renal impairment (vardenafil and tadalafil)
- Bleeding disorders
- Active peptic ulcer
- Anatomical deformities of the penis
- Conditions that predispose priapism (sickle cell anemia, multiple myeloma, leukemia)
- Class IA and III antiarrhythmics (Avoid concomitant use with vardenafil.)

• cardiovascular disease, including hypertension, atherosclerosis, and hyperlipidemia
• diabetes
• depression
• prostate disease
• alcoholism
• smoking
• obesity
• physical inactivity
• psychosexual relationship problems
• performance anxiety
• premature ejaculation
• increases in latency time associated with age.

Other causes may include pelvic, perineal, or penile trauma or surgery, postorgan transplant, androgen deficiency, neurologic disease, vascular insufficiency, endocrinopathy, and prescription or recreational drug use (see Causes of ED).

Getting to the bottom of the problem
The initial management of ED should begin with identification of any underlying comorbidities or psychosexual dysfunctions. It’s important to keep the previously mentioned risk factors in mind when diagnosing a man who presents with signs and symptoms consistent with ED. If the patient presents with underlying conditions, these diseases or medications must be addressed as part of treatment. A medical and sexual history, physical exam, psychosocial evaluation, and related lab tests should be completed. Lab tests include a complete blood count, urinalysis, lipid profile, fasting blood glucose level, thyroid function test, hemoglobin A1c, luteinizing hormone, follicle-stimulating hormone, and serum testosterone level.

After all testing and medical history assessments are completed, any one of the approved treatments for ED may be considered. These include oral PDE5 inhibitors, intracavernous injection of alprostadil, and intraurethral alprostadil.

PDE5 inhibitors
The PDE5 inhibitors sildenafil, vardenafil, and tadalafil should be considered as a first-line therapy for the treatment of ED, unless otherwise contraindicated. These drugs work by competitively inhibiting the cGMP-specific PDE5 enzyme that results in the increase in the effect of nitric oxide secondary to an increase in intracavernosal cGMP levels. All three PDE5 inhibitors have specific dosing recommendations for normal individuals, as well as those with hepatic or renal impairment and elderly patients. Dose adjustments must be made when used concurrently with such agents as erythromycin, ketoconazole, indinavir, and ritonavir.

There’s no interaction between any of the PDE5 inhibitors and the use of alcohol; however, patients should be informed that consuming large quantities of alcohol can increase the risk of orthostatic hypotension. Signs and symptoms that you need to teach your patient about include increased heart rate, decreased standing BP, dizziness, and headache.

All three PDE5 inhibitors have common adverse reactions that have been reported throughout clinical trials. These include headache, dyspepsia, flushing, and nasal
congestion. Sildenafil and vardenafil users may experience changes in color vision, especially seeing objects and surroundings as being blue-green in color. The use of vardenafil has been shown to cause a mild prolongation of the QT interval. The package insert states that caution should be used in those patients who have a history of QT prolongation or those taking medications that may increase the QT interval. Patients taking tadalafil may develop back pain and myalgia.

The PDE5 inhibitors shouldn’t be used in combination with organic nitrates because the use of these two medications together can increase the risk of developing hypotension associated with the nitrate use. Also, the concomitant use of any of the PDE5 inhibitors along with alpha-blocker therapy should be avoided. All three medications interact to some degree with alpha-blockers. See Contraindications and precautions for PDE5 inhibitor use for more information.

Two types of alprostadil delivery
Alprostadil is a second-line treatment option in the management of ED. This medication, which is also considered prostaglandin E1, is a naturally occurring acidic lipid. Alprostadil causes penile erection by relaxing the trabecular smooth muscles of the corpus cavernosum and increasing the diameter of the cavernous arteries.

Alprostadil is available as both an intracavernous injection and a transurethral formulation. Intracavernosal alprostadil therapy is the direct delivery of the drug into the erectile chamber. The transurethral alprostadil delivery system uses direct delivery into the urethra. The onset of action is different depending on the formulation: for intracavernosal administration the onset is 2 to 5 minutes; for transurethral administration, 5 to 10 minutes.

The adverse reactions associated with the use of intracavernous alprostadil injection include local injection site reactions such as ecchymosis, hematoma, edema, and pain. The transurethral formulation can cause penile pain, bleeding, and urethral burning. Both types of alprostadil may also cause priapism (prolonged erection), headache, dizziness, hypotension, back pain, and upper respiratory tract infections.

The precautions, warnings, and contraindications are the same for both the intracavernosal and transurethral formulations of alprostadil. The only difference is that transurethral alprostadil shouldn’t be used for sexual intercourse with a woman who’s pregnant or who may become pregnant. See Contraindications and precautions for alprostadil use for more information.

Putting a spring in his step
Since the introduction of sildenafil to the market more than 10 years ago, men have been given a new lease on life when it comes to dealing with ED. The three PDE5 inhibitors, sildenafil, vardenafil, and tadalafil, are all considered first-line treatment options for patients with ED, unless contraindicated. Other options include intracavernosal alprostadil injections and transurethral alprostadil.

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