



First-Line Therapy for Erectile Dysfunction: The PDE-5 Inhibitors

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More than 150 million men worldwide experience some form of erectile dysfunction (ED), a condition that severely diminishes quality of life and may signal the presence of such life-threatening disorders as coronary artery disease (CAD) or type 2 diabetes mellitus (DM).^{1,2} Unfortunately, between 70% and 90% of these men do not receive treatment¹—and the reasons have nothing to do with the efficacy or safety of available therapies. Many men simply fail to discuss the subject of ED with a physician because they misunderstand its causes, feel that it signifies an inadequacy on their part, or are embarrassed to admit that they have a problem with sexual function.

When ED is addressed within the context of health care, the results are encouraging. Over the past decade, ED treatment has evolved at an extraordinary pace, due in large part to a greater understanding of male sexual health.³ Today's medical practitioners have at their disposal a vast armamentarium of new drugs, delivery methods, and combination therapies with which to help male patients achieve and maintain satisfying erections. Within this arena, no treatment has met with greater clinical success than the phosphodiesterase type-5 (PDE-5) inhibitors.¹ Practitioners who are able to broach the subject of ED with male patients, discuss such treatment options as the PDE-5 inhibitors, and explain how these drugs work can do much to enhance their patients' health and well-being.

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This article describes the mechanism of action and pharmacology of the three PDE-5 inhibitors in clinical use today: sildenafil, tadalafil, and vardenafil. It discusses their efficacy and safety and suggests ways to optimize therapeutic response and patient adherence. Finally, it briefly considers specific patient populations in whom ED is often refractory to treatment, outlining combination therapies and future trends.

The Science Behind the Drugs

An erection results from a complex series of neurovascular events. With sexual stimulation, nitric oxide (NO) is released from the nerve endings and vascular endothelial cells of the penis and diffuses into the corpora cavernosa. Through several downstream mediators, cyclic guanosine monophosphate (cGMP), a second messenger for the vasorelaxant effects of NO, triggers a cascade of events that reduces intracellular calcium availability and relaxes smooth muscle tissue of the arterioles supplying the corpora cavernosa, resulting in enhanced penile perfusion, engorgement of the corporal sinusoids, and erection.¹

By impeding the effects of PDE-5, which metabolizes cGMP, PDE-5 inhibitors potentiate the erectile response to NO. Since the effect of the PDE-5 inhibitors depends on the release of NO in response to sexual stimulation, patients should be counseled that these drugs simply amplify the natural erectile response to sexual stimulation. The PDE-5 inhibitors will produce no erectile response in the absence of sexual stimulation.^{1,3}

PDE-5 Pharmacology

The US Food and Drug Administration (FDA) has approved three oral PDE-5 inhibitors for use in the treatment of ED: sildenafil, which was approved in 1998, and tadalafil and vardenafil, which were approved

in 2003. All three drugs are distributed widely throughout the body, metabolized primarily through the hepatic cytochrome P450 system, and excreted predominantly as fecal metabolites.

Sildenafil and vardenafil have similar molecular structures. Both bind to cGMP, blocking the catalytic mechanism mediated by PDE-5 that dephosphorylates and breaks down cGMP. Tadalafil differs structurally from the other two.⁴ The three drugs differ in selectivity and inhibit PDE-5 at different concentrations. Time to onset of action and window of therapeutic opportunity based on half-life also vary (Table 1).⁴

In terms of patient acceptance or direct extrapolation to onset or duration of action, the implications of such subtle pharmacokinetic differences are unclear.⁴ For example, both sildenafil and vardenafil have half-life values of four to five hours, whereas the half-life of tadalafil is 17.5 hours.^{1,3,4} As would be expected, longer half-life of tadalafil offers a wider window of sexual opportunity, with some responders reporting successful coitus as many as 24 to 36 hours after administration. Yet, despite their shorter half-lives, sildenafil and vardenafil reportedly have improved “morning after” erections for many patients.

All three PDE-5 inhibitors are rapidly absorbed after ingestion, with median time to maximum concentration being one hour for sildenafil and vardenafil and two hours for tadalafil.⁵⁻⁷ Patients who do not experience a rapid beneficial effect should delay sexual intercourse for one to two hours after taking the drug, at which point serum concentrations will have peaked.³ High-fat meals slow the absorption of sildenafil and vardenafil; tadalafil is unaffected by dietary intake.⁵⁻⁷

Efficacy and Safety

All three PDE-5 inhibitors have proven effective in improving erectile function across a broad range of etiologies.¹ In fact, sildenafil, the PDE-5 inhibitor that has been available the longest, has confirmed efficacy in the following organic causes of ED: cardiovascular disease (CVD), spinal cord injury, end-stage renal disease, multiple sclerosis, Parkinson disease, spina bifida, and iatrogenic ED (for example, that induced by surgery, radiation, or antiandrogen therapy for prostate cancer or selective serotonin reuptake inhibitor therapy for major depressive disorder).¹ Furthermore, the PDE-5 inhibitors have been evaluated in numerous placebo-controlled, double-blind trials and open-label studies, using a variety of outcome measures, patient subgroups, and regional populations. Although differences in trial designs and outcome measures make it impossible to compare the three drugs in a parallel manner, most studies suggest that the PDE-5 inhibitors have similar efficacy and toxicity profiles.^{1,3}

In the 1998 dose-response study of 861 men conducted by Goldstein et al⁸, 56% to 84% of patients taking 25 to 100 mg sildenafil experienced subjective improvement in erectile function. At doses higher than 100 mg, little benefit and considerably more adverse effects were noted.⁸

The efficacy of vardenafil was found to be similar in a 2002 study of 805 men conducted by Hellstrom et al.⁹ Of the patients randomly assigned to receive vardenafil 10 mg and 20 mg, 73% and 81%, respectively, reported improvement in erections.⁹

Phase III studies of tadalafil involving 1,112 patients were reported by Brock et al¹⁰ in 2002. They showed tadalafil 20 mg improved erections in 81% of those receiving treatment.¹⁰

Table 1. Pharmacologic Properties of PDE-5* Inhibitors^{†,4}

	50% inhibitory concentration (nM)	Median time to maximal concentration (h)	Half-life (h)
Sildenafil	3.90	1	4.00
Tadalafil	1.05	2	17.50
Vardenafil	0.70	1	4.50–4.80

The PDE-5 inhibitors sildenafil, tadalafil, and vardenafil differ in selectivity, as documented by their 50% inhibitory concentrations; times to onset of action; and different windows of opportunity, based on their half-lives. For example, the long half-life of tadalafil may allow a longer window of opportunity, but also may complicate dosing instructions. However, it is important to recognize that differences in these pharmacological properties may not translate into differences in efficacy, patient acceptance, or direct extrapolation to time of onset or duration of action.

*PDE-5 = phosphodiesterase type 5. [†]Unpublished, personal data.
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Table 2. Most Common* Adverse Effects of PDE-5[†] Inhibitors⁵⁻⁷

	Frequency reported vs placebo (%)		
	Sildenafil	Vardenafil	Tadalafil
Headache	16 vs 4	15 vs 4	11–15 vs 5
Flushing	10 vs 1	11 vs 1	2–3 vs 1
Dyspepsia	7 vs 2	4 vs 1	4–10 vs 1
Rhinitis	4 vs 2	9 vs 3	–
Urinary tract infection	3 vs 2	–	–
Abnormal vision [‡]	3 vs 0	–	–
Diarrhea	3 vs 1	–	–
Dizziness	–	–	–
Sinusitis	–	3 vs 1	2–3 vs 1
Flu syndrome	–	3 vs 2	–
Rash	–	–	–
Back pain	–	–	3–6 vs 3
Myalgia	–	–	1–4 vs 1
Limb pain	–	–	1–3 vs 1

*Occurring in 3% or more patients. [†]PDE-5 = phosphodiesterase type 5. [‡]Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision.

Adverse Effects

The adverse effects most commonly associated with PDE-5 inhibitor therapy include headache, flushing, dyspepsia, rhinitis, back pain, and myalgia (Table 2).⁵⁻⁷ Generally, these effects result from the inhibition of PDE-5 and other PDEs in nonpenile tissue—most likely, vascular or gastrointestinal smooth muscle.

For example, sildenafil and, to a lesser extent, vardenafil cross-react slightly with PDE-6, which may explain why some patients (3% or less) using these drugs at therapeutic doses have reported experiencing mild and transient abnormal vision, consisting primarily of color-tinged vision but also including increased sensitivity to light or blurred vision. Tadalafil, on the other hand, has been shown to cross-react with PDE-11 at therapeutic concentrations, though this has not demonstrated itself to be a clinical issue.^{1,3}

The FDA has received some reports (fewer than 50 to date) of nonarteritic anterior ischemic optic neuropathy (NAION) associated with PDE-5 inhibitor use. In most cases, affected patients had underlying anatomic or vas-

cular risk factors for developing NAION, including low cup-to-disc ratio (“crowded disc”), age over 50 years, diabetes, hypertension, CAD, hyperlipidemia, or cigarette smoking. Because the number of reported cases is so small and the majority of events occurred within populations that would have been considered at risk for NAION, the FDA has been unable to determine whether there is a direct relationship between these events and the use of PDE-5 inhibitors.¹¹

The FDA continues to evaluate the issue and, in the interim, has issued two recommendations for physicians prescribing PDE-5 inhibitors: (1) Advise patients who have already experienced NAION in one eye that vasodilators, such as PDE-5 inhibitors, increase the risk of subsequent NAION; (2) Advise patients that, in the event of a sudden loss of vision in one or both eyes, they should stop use of all PDE-5 inhibitors and seek immediate medical attention.¹¹

Use in Cardiac Disease

The association between ED and cardiac disease is covered extensively in another article in this supplement (see *Understanding the Link Between Erectile Dysfunction and Cardiovascular Disease* on page 4). For the purposes of this discussion, it would suffice to say that ED commonly occurs in men with CAD and that, in general, when PDE-5 inhibitors are used appropriately in such patients, these agents are safe and effective. Worldwide clinical trials data show no increased risk of cardiac events among users of PDE-5 inhibitors.^{1,3,12}

Patients who develop angina during sexual activity after taking a PDE-5 inhibitor should discontinue sexual activity, relax for 5 to 10 minutes, and seek emergency care if pain persists.¹³ They should inform emergency medical personnel that they have taken a PDE-5 inhibitor so that nitrates will not be administered.¹³ Patients who have an acute MI after taking a PDE-5 inhibitor may be given standard therapies, with the exception of organic nitrates.³

Nitrates should not be administered within 24 hours of sildenafil or vardenafil use, or within 48 hours of tadalafil use.^{12,13} Currently, there is no pharmacologic antidote to the interaction between PDE-5 inhibitors and nitrates.³ Patients who develop hypotension in response to this combination should be placed in the Trendelenburg position and given intravenous fluids, with alpha-agonists (such as phenylephrine) added as needed.¹³ Although exceedingly rare, treatment-resistant, refractory hypotension may require intra-aortic balloon counterpulsation, as recommended by the Second Princeton Consensus Conference.¹³

Morganroth et al¹⁴ observed that PDE-5 inhibitors have a minimal effect on the QTc interval on electro-

cardiography. Vardenafil, however, is not recommended for patients who have congenital prolonged QT syndrome or take either type-1A antiarrhythmics (such as quinidine or procainamide) or type-3 antiarrhythmics (such as amiodarone or sotalol).¹⁵

Use With Antihypertensive Agents

The American Urological Association's update on the management of ED warns that all three PDE-5 inhibitors interact to some degree with alpha-adrenergic blockers, a class of drugs used primarily to treat lower urinary tract symptoms in men and, less commonly, hypertension.¹⁶ Concurrent use of alpha blockers and PDE-5 inhibitors may cause some patients to develop orthostatic hypotension, though studies suggest that the interaction is unlikely in long-term alpha blocker therapy.¹² In patients who remain hemodynamically stable while using alpha blockers, PDE-5 inhibitors should be initiated at the lowest recommended starting dose and gradually titrated upward. Similarly, patients using PDE-5 inhibitors and requiring alpha blocker therapy should start at low doses and gradually titrate the alpha blocker upward to effect.⁵⁻⁷ Tamsulosin (0.4 mg daily) does not appear to affect blood pressure when given to men receiving tadalafil at stable doses.⁶ For patients taking both a PDE-5 inhibitor and an alpha blocker, prescribing physicians should consider volume status and any other antihypertensive medicines the patient may be taking. All of these factors affect the safety of combined therapy.¹⁷

Other antihypertensive agents, such as calcium channel blockers, are well tolerated by men concurrently taking any of the three PDE-5 inhibitors.¹⁵ Concomitant administration of these drugs appears to cause no or only small additive drops in blood pressure.¹⁵

Other Precautions and Potential Interactions

Prescribing information for all three PDE-5 inhibitors warns against use by patients with severe CVD, left ventricular outflow obstruction, or conditions not studied in clinical trials, such as degenerative retinal disorders and tendency to develop priapism (as in sickle cell anemia or leukemia).⁵⁻⁷ Generally, PDE-5 inhibitors are not recommended for use in patients with unstable angina, heart failure, recent MI, uncontrolled arrhythmia, or poorly controlled blood pressure (resting blood pressure below 90/50 mm Hg or above 170/100 mm Hg).⁵⁻⁷

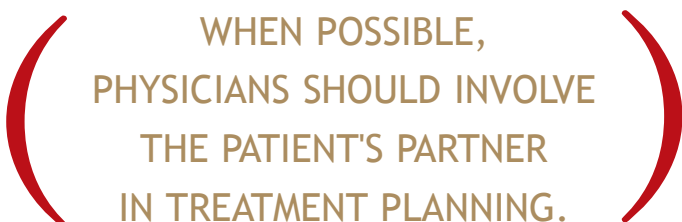
Drugs that inhibit cytochrome P3A4, such as protease inhibitors, azole antifungal agents, and erythromycin, can impair the metabolic breakdown of PDE-5 inhibitors and may require a dose reduction.¹³ Agents that induce cytochrome P3A4, such as rifampin, may boost metabolism of these drugs, necessitating higher doses.³ Advanced age (over 65 years), hepatic impairment, and

severe renal insufficiency are associated with elevated plasma levels of PDE-5 inhibitors. Affected patients, therefore, require lower starting doses.³

Optimizing Response and Adherence

When possible, physicians should involve the patient's partner in treatment planning.¹ Partner involvement increases the likelihood that the prescribed regimen accurately reflects the couple's treatment goals, expectations, and preferences and, thereby, promotes both patient adherence and therapeutic response.

Although PDE-5 inhibitors are effective across a wide range of ED etiologies and patient populations, at least 30% of men fail to respond to treatment, and there are any number of reasons patients may be dissatisfied with



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it. Routine follow-up is advised after patients using a PDE-5 inhibitor have made five to six sexual attempts.¹⁸

Subtherapeutic dosing and poor counseling are the leading causes of treatment failure. Salvage strategies include patient education and lifestyle modification, reduction of ED/cardiovascular risk factors, dose adjustment or change of PDE-5 inhibitor agents, androgen replacement for hypogonadal men, psychosexual or relationship counseling, or progression to second-line treatment options.¹⁸

Both patient and partner should be counseled on the need for adequate sexual stimulation to promote PDE-5 inhibitor efficacy. Patients should also be advised to use a PDE-5 inhibitor several times before deciding it is ineffective. The cumulative probability of success with sildenafil, for example, increases with each of the first six to eight attempts, after which it reaches a plateau of success.¹⁹

Counseling should take into account the couple's cultural and religious background, lifestyle, and any specific needs or concerns. Risk factor modification may be advised for patients who smoke, abuse alcohol, or lead sedentary lifestyles (see *Erectile Dysfunction: The Role of Lifestyle Modification* on page 12).¹

Special Considerations

Certain patient populations—men who have had radical prostatectomy and those with hypogonadism or DM—are at elevated risk for ED and, within these patient populations, ED may be more difficult to treat.

Nevertheless, all three PDE-5 inhibitors have proven beneficial in treating ED in men with one of these comorbid conditions.^{1,3}

Phosphodiesterase type-5 inhibitor therapy has improved return to sexual function for many men who have been treated for prostate cancer. Patients who have had external beam radiotherapy or brachytherapy with curative intent may experience delayed onset ED. These men are good candidates for PDE-5 inhibitors.²⁰⁻²²

Nerve-sparing radical prostatectomy typically delays return of erectile function from 12 to 18 months. For patients who have undergone this type of surgery, PDE-5 inhibitors may enhance both time to return of coitus and quality of erections. Following radical prostatectomy, penile rehabilitation with daily PDE-5 inhibitor therapy is an off-label treatment regimen.²⁰⁻²²

Men with hypogonadism who do not respond to PDE-5 inhibitor therapy may benefit from adjunctive testosterone replacement therapy.^{1,3} The management of ED in diabetes is discussed at length in another article in this supplement (see *Erectile Dysfunction in Men With Diabetes Mellitus* on page 8).

Combination Therapies

Patients who are dissatisfied with the outcome of PDE-5 inhibitor therapy should be referred to a urologist. The first steps in managing their ED include taking an in-depth sexual history, assessing androgen status, providing counseling, and initiating a retrial of the same PDE-5 inhibitor or introducing another. The assessment of risk factors may suggest a need for specialized testing or triage for slightly more invasive therapy: intracavernous injections (ICIs), transurethral alprostadil, or the mechanical options of a vacuum tumescence device or a penile prosthesis. A brief description of these options follows, though an extensive discussion is beyond the scope of this article. It should be noted, however, that the FDA has not approved PDE-5 inhibitor therapy in combination with any other vasoactive pharmacotherapy for the treatment of ED. Any such combination treatment is “off label” and, therefore, should be undertaken with caution.³

Intracavernous Injections Options

A decade ago, ICI with alprostadil was approved for the management of ED. For patients who fail to respond to PDE-5 inhibitors following radical prostatectomy, combination therapy consisting of alprostadil by ICI and oral sildenafil has demonstrated a response rate of approximately 50% to 68%.²³ Regardless of the etiology of PDE-5 inhibitor failure, ICI therapy can salvage up to 90% of all cases, using such drug combinations as papaverine/phentolamine and alprostadil/papaverine/phentolamine in various concentrations.^{16,24}

Table 3. Reviewing Erectile Dysfunction Treatment

- Phosphodiesterase type 5 (PDE-5) inhibitors are the first-line treatment for most men with erectile dysfunction (ED).
- Sildenafil, tadalafil, and vardenafil are efficacious, safe, and easy to use across diverse patient populations and ED etiologies.
- Satisfaction with treatment approaches 80%.
- Patient re-education, lifestyle modification, dose adjustment or change of PDE-5 inhibitor agents, correction of ED/cardiovascular risk factors, sexual or relationship counseling, or androgen replacement for hypogonadal men can salvage up to 50% of PDE-5 inhibitor failures.
- Treatment is generally well tolerated and patient drop out due to adverse events is low.
- Various second-line ED treatment options are available, including intracavernous injections, transurethral alprostadil, vacuum tumescence devices, and combination therapy. Implantation of penile prosthesis remains a third-line option with high patient satisfaction rates.

To assure efficacy and minimize complications, expertise is required in the areas of dosing, ICI mixes, patient education, and patient follow-up. Priapism has been reported in 4% to 20% of clinical series using office penile injection testing or home ICI therapy.³

Transurethral Alprostadil

The only pharmacologic agent approved by the FDA for intraurethral administration is alprostadil, the synthetic form of prostaglandin E1. The 3 x 1 mm suppository pellet is administered through an applicator known as a medicated urethral system for erection, or MUSE (Vivus, Inc, Mountain View, CA). The medication is rapidly absorbed. Dosages of 500 mcg alprostadil delivered by MUSE have the vasodilatory effects of 10 mcg delivered by intracavernous injection, but the associated degree of veno-occlusion (and, thus, penile rigidity) is generally less.

Combination therapy with MUSE and sildenafil has been shown to salvage patients failing monotherapy with either drug.²⁵ Federal drug administration guidelines call for physicians to establish initial MUSE dosing in a clinical setting in which they can monitor the patient for potential adverse events, including hypotension (reported to occur in 3% of patients using MUSE for the first time) and priapism.¹⁶ About 10% of female partners of MUSE users report vaginal discomfort after ejaculation.³

Vacuum Tumescence Devices

Vacuum tumescence devices engorge the penis through negative pressure created within a plastic cylinder applied by means of a manual or battery-operated pump. A rubber ring is then applied to the penile base to maintain the erection. To avoid injury, the ring must be removed within 30 minutes. In many patients, this device can produce an erection that is near normal and sufficiently rigid for intercourse—though the portion of the penis proximal to the ring will not be rigid and this may cause the penis to pivot.³ The addition of a PDE-5 inhibitor may enhance the quality of erection obtained and contribute to glans engorgement. Patient acceptability and success rates vary. Efficacy may be limited in men with severe vascular insufficiency.¹⁶

Future Trends

Over the past decade, ED treatment has advanced at an extraordinary pace. Today, physicians can offer patients a number of potential treatments for ED, starting with the PDE-5 inhibitors (Table 3).

Novel PDE-5 inhibitors are under investigation. The next generation of such agents may offer a more rapid onset of action, prolonged period of efficacy, and even more PDE-5 selectivity (and, therefore, fewer adverse effects) than the agents in current use. Investigators are also hoping to develop ED regimens that use the three approved PDE-5 inhibitors and address such pathophysiologic processes as pulmonary hypertension, endothelial dysfunction, and lower urinary tract symptoms secondary to benign prostatic hyperplasia.¹

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