26 - 29.26 Phosphodiesterase 5 Inhibitors

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provided important information about the physiology of erection. Sexual stimulation causes the release of the neurotransmitter nitric oxide (NO), which increases the synthesis of cyclic guanosine monophosphate (cGMP), causing smooth muscle relaxation in the corpus cavernosum that allows blood to flow into the penis and results in turgidity and tumescence. The concentration of cGMP is regulated by the enzyme PDE-5, which, when inhibited, allows cGMP to increase and enhance erectile function. Because sexual stimulation is required to cause the release of NO, PDE5 inhibitors have no effect in the absence of such stimulation, an important point to understand when providing information to patients about their use. The congeners vardenafil and tadalafil work in the same way, by inhibiting PDE-5, thus allowing an increase in cGMP and enhancing the vasodilatory effects of NO. For this reason, these drugs are sometimes referred to as NO enhancers.

PHARMACOLOGICAL ACTIONS All three substances are fairly rapidly absorbed from the gastrointestinal tract, with maximum plasma concentrations reached in 30 to 120 minutes (median, 60 minutes) in the fasting state. Because it is lipophilic, concomitant ingestion of a high-fat meal delays the rate of absorption by up to 60 minutes and reduces the peak concentration by one quarter. These drugs are principally metabolized by the CYP3A4 system, which may lead to clinically significant drug–drug interactions, not all of which have been documented. Excretion of 80 percent of the dose is via feces, and another 13 percent is eliminated in the urine. Elimination is reduced in persons older than age 65 years, which results in plasma concentrations 40 percent higher than in persons age 18 to 45 years. Elimination is also reduced in the presence of severe renal or hepatic insufficiency. The mean half-lives of sildenafil and vardenafil are 3 to 4 hours, and that of tadalafil is about 18 hours. Tadalafil can be detected in the bloodstream 5 days after ingestion, and because of its long half-life, it has been marketed as effective for up to 36 hours—the so-called weekend pill. The onset of sildenafil occurs about 30 minutes after ingestion on an empty stomach; tadalafil and vardenafil act somewhat more quickly. Clinicians need to be aware of the important clinical observation that these drugs do not by themselves create an erection. Rather, the mental state of sexual arousal brought on by erotic stimulation must first lead to activity in the penile nerves, which then release NO into the cavernosum, triggering the erectile cascade, the resulting erection being prolonged by the NO enhancers. Thus, full advantage may be taken of a sexually exciting stimulus, but the drug is not a substitute for foreplay and emotional arousal. THERAPEUTIC INDICATIONS Erectile dysfunctions have traditionally been classified as organic, psychogenic, or mixed. Over the past 20 years, the prevailing view of the cause of erectile dysfunction has shifted away from psychological causes toward organic causes. The latter include diabetes mellitus, hypertension, hypercholesterolemia, cigarette smoking, peripheral vascular disease, pelvic or spinal cord injury, pelvic or abdominal surgery (especially prostate surgery), multiple sclerosis, peripheral neuropathy, and Parkinson’s disease. Erectile dysfunction is often induced by alcohol, nicotine, and other substances of abuse and by prescription drugs. These drugs are effective regardless of the baseline severity of erectile dysfunction, race, or age. Among those responding to sildenafil are men with coronary artery disease, hypertension, other cardiac disease, peripheral vascular disease, diabetes mellitus, depression, coronary artery bypass graft surgery, radical prostatectomy, transurethral resection of the prostate, spina bifida, and spinal cord injury, as well as persons taking antidepressants, antipsychotics, antihypertensives, and diuretics. However, the response rate is variable. Sildenafil has been reported to reverse selective serotonin reuptake inhibitor–induced anorgasmia in men. There are anecdotal reports of sildenafil having a therapeutic effect

on sexual inhibition in women as well. PRECAUTIONS AND ADVERSE REACTIONS A major potential adverse effect associated with use of these drugs is myocardial infarction (MI). The U.S. Food and Drug Administration (FDA) distinguished the risk of MI caused directly by these drugs from that caused by underlying conditions such as hypertension, atherosclerotic heart disease, diabetes mellitus, and other atherogenic conditions. The FDA concluded that when used according to the approved labeling, the drugs do not by themselves confer an increased risk of death. However, there is increased oxygen demand and stress placed on the cardiac muscle by sexual intercourse. Thus, coronary perfusion may be severely compromised, and cardiac failure may occur as a result. For that reason, any person with a history of MI, stroke, renal failure, hypertension, or diabetes mellitus and any person older than the age of 70 years should discuss plans to use these drugs with an internist or a cardiologist. The cardiac evaluation should specifically address exercise tolerance and the use of nitrates. Use of PDE-5 inhibitors is contraindicated in persons who are taking organic nitrates in any form. Also, amyl nitrate (poppers), a popular substance of abuse used by homosexual men to enhance the intensity of orgasm, should not be used with any of the erection-enhancing drugs. The combination of organic nitrates and PDE inhibitors can cause a precipitous lowering of blood pressure and can reduce coronary perfusion to the point of causing MI and death. Adverse effects are dose dependent, occurring at higher rates with higher dosages. The most common adverse effects are headache, flushing, and stomach pain. Other less common adverse effects include nasal congestion, urinary tract infection, abnormal vision (colored tinge [usually blue], increased sensitivity to light, or blurred vision), diarrhea, dizziness, and rash. No cases of priapism were reported in premarketing trials. Supportive management is indicated in cases of overdosage. Tadalafil has been associated with back and muscle pain in about 10 percent of patients. Recently, there have been 50 reports and 14 verified cases of a serious condition in men taking sildenafil called nonarteritic anterior ischemic optic neuropathy. This is an eye ailment that causes restriction of blood flow to the optic nerve and can result in permanent vision loss. The first symptoms appear within 24 hours after use of sildenafil and include blurred vision and some degree of vision loss. The incidence of this effect is very rare—1 in 1 million. In the reported cases, many patients had preexisting eye problems that may have increased their risk, and many had a history of heart disease and diabetes, which may indicate vulnerability in these men to endothelial damage. In addition to vision problems, in 2010, a warning of possible hearing loss was reported based on 29 incidents of the problem since introduction of these drugs. Hearing loss usually occurs within hours or days of using the drug and in some cases is both unilateral and temporary. No data are available on the effects on human fetal growth and development or testicular morphologic or functional changes. However, because these drugs are not

considered an essential treatment, they should not be used during pregnancy. TREATMENT OF PRIAPISM Phenylephrine (Neo-Synephrine) is the drug of choice and first-line treatment of priapism because the drug has almost pure α-agonist effects and minimal β activity. In short-term priapism (less than 6 hours), especially for drug-induced priapism, intracavernosal injection of phenylephrine can be used to cause detumescence. A mixture of 1 ampule of phenylephrine (1 mL/1,000 µg) should be diluted with an additional 9 mL of normal saline. Using a 29-gauge needle, 0.3 to 0.5 mL should be injected into the corpora cavernosa, with 10 to 15 minutes between injections. Vital signs should be monitored, and compression should be applied to the area of injection to help prevent hematoma formation. Phenylephrine can also be used orally, 10 to 20 mg every 4 hours as needed, but it may not be as effective or act as rapidly as the injectable route. DRUG INTERACTIONS The major route of PDE-5 metabolism is through CYP3A4, and the minor route is through CYP2C9.

Inducers or inhibitors of these enzymes will therefore affect the plasma concentration and half-life of sildenafil. For example, 800 mg of cimetidine (Tagamet), a nonspecific CYP inhibitor, increases plasma sildenafil concentrations by 56 percent, and erythromycin (E-mycin) increases plasma sildenafil concentrations by 182 percent. Other, stronger inhibitors of CYP3A4 include ketoconazole (Nizoral), itraconazole (Sporanox), and mibefradil (Posicor). In contrast, rifampicin, a CYP3A4 inducer, decreases plasma concentrations of sildenafil. LABORATORY INTERFERENCES No laboratory interferences have been described. DOSAGE AND CLINICAL GUIDELINES Sildenafil is available as 25-, 50-, and 100-mg tablets. The recommended dose of sildenafil is 50 mg taken by mouth 1 hour before intercourse. However, sildenafil may take effect within 30 minutes. The duration of the effect is usually 4 hours, but in healthy young men, the effect may persist for 8 to 12 hours. Based on effectiveness and adverse effects, the dose should be titrated between 25 and 100 mg. Sildenafil is recommended for use no more than once a day. The dosing guidelines for use by women, an off-label use, are the same as those for men. Increased plasma concentrations of sildenafil may occur in persons older than 65 years of age and those with cirrhosis or severe renal impairment or using CYP3A4 inhibitors. A starting dose of 25 mg should be used in these circumstances. An investigational nasal spray formulation of sildenafil has been developed that acts within 5 to 15 minutes of administration. This formulation is highly water soluble, and it

is rapidly absorbed directly into the bloodstream. Such a formulation would permit more ease of use. Vardenafil is supplied in 2.5-, 5-, 10-, and 20-mg tablets. The initial dose is usually 10 mg taken with or without food about 1 hour before sexual activity. The dose can be increased to a maximum of 20 mg or decreased to 5 mg based on efficacy and side effects. The maximum dosing frequency is once per day. As with sildenafil, dosages may have to be adjusted in patients with hepatic impairment or in patients using certain CYP3A4 inhibitors. A 10 mg orally disintegrating form of vardenafil (Staxyn) is available. It is placed on the tongue approximately 60 minutes before sexual activity and should not be used more than once a day. Tadalafil is available in 2.5-, 5-, or 20-mg tablets for oral administration. The recommended dose of tadalafil is 10 mg before sexual activity, which may be increased to 20 mg or decreased to 5 mg depending on efficacy and side effects. Once-a-day use of the 2.5- or 5-mg pill is acceptable for most patients. Similar cautions apply as mentioned earlier in patients with hepatic impairment and in those taking concomitant potent inhibitors of CYP3A4. As with other PDE-5 inhibitors, concomitant use of nitrates in any form is contraindicated. REFERENCES Chivers ML, Rosen RC. Phosphodiesterase type 5 inhibitors and female sexual response: faulty protocols or paradigms? J Sex Med. 2010;7(2 Pt 2):858–872. Claes HI, Goldstein I, Althof SE, Berner MM, Cappelleri JC, Bushmakin AG, Symonds T, Schnetzler G. Understanding the effects of sildenafil treatment on erection maintenance and erection hardness. J Sex Med. 2010;7(6):2184–2191. Hatzimouratidis K, Burnett AL, Hatzichristou D, McCullough AR, Montorsi F, Mulhall JP. Phosphodiesterase type 5 inhibitors in postprostatectomy erectile dysfunction: A critical analysis of the basic science rationale and clinical application. Eur Urol. 2009;55(2):334–347. Hosain G, Latini DM, Kauth M, Goltz HH, Helmer DA. Sexual dysfunction among male veterans returning from Iraq and Afghanistan: Prevalence and correlates. J Sex Med. 2013;10(2):516–523. Khan AS, Sheikh Z, Khan S, Dwivedi R, Benjamin E. Viagra deafness—Sensorineural hearing loss and phosphodiesterase-5 inhibitors. Laryngoscope. 2011;121(5):1049–1054. Kotera J, Mochida H, Inoue H, Noto T, Fujishige K, Sasaki T, Kobayashi T, Kojima K, Yee S, Yamada Y, Kikkawa K, Omori K. Avanafil, a potent and highly selective phosphodiesterase-5 inhibitor for erectile dysfunction. J Urol. 2012;188(2):668–674. McCullough AR, Hellstrom WG, Wang R, Lepor H, Wagner KR, Engel JD. Recovery of erectile function after nerve sparing radical prostatectomy and penile rehabilitation with nightly intraurethral alprostadil versus

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