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Sexual Dysfunction Male sexual dysfunction affects up to 31% of middle-aged and elderly men, whereas female sexual dysfunction, although studied less intensely, has a higher prevalence (43%) than male sexual dysfunction. Demographic changes, the popularity of newer treatments, and greater awareness of sexual dysfunction by patients and society have led to increased diagnosis and associated health care expenditures for the management of this common disorder. Sexual health and satisfaction with sex life are important aspects of quality of life for many, includ ing those in poor health. Because many patients are reluctant to initi ate discussion of their sex lives, physicians should address this topic directly to elicit a history of sexual dysfunction. Specifically addressing sexual health should be a routine part of the clinical encounter, particu larly in those with cardiovascular risk factors. MALE SEXUAL DYSFUNCTION ■ ■PHYSIOLOGY OF MALE SEXUAL RESPONSE An erection is a neurovascular event, and the cardiovascular system needs to be intact for sexual stimulation to successfully result in an erection. Normal male sexual function includes (1) sufficient libido, (2) the ability to achieve and maintain penile erection, (3) ejaculation, and (4) detumescence. Libido refers to sexual desire and is influenced by a variety of visual, olfactory, tactile, auditory, imaginative, and hormonal stimuli. Sex steroids, particularly testosterone, act to increase libido. Libido can be diminished by emotional context, systemic illness, hor monal disturbances, psychiatric disorders, and medications. Penile tumescence leading to erection depends on an increased flow of blood into the lacunar network accompanied by complete relaxation of the arteries and corporal smooth muscle. The microarchitecture of the corpora is composed of a mass of smooth muscle (trabecula) that contains a network of endothelial-lined vessels (lacunar spaces). Subse quent compression of the trabecular smooth muscle against the fibro elastic tunica albuginea causes a passive closure of the emissary veins and accumulation of blood in the corpora. In the presence of a full erection and a competent valve mechanism, the corpora become non compressible cylinders from which blood does not escape. This cas cade of relaxation and venous occlusion culminates in a rigid erection. The central nervous system (CNS) exerts an important influence by either stimulating or antagonizing spinal pathways that mediate erectile function and ejaculation. The erectile response is mediated by a combination of central (psychogenic) innervation and peripheral (reflexogenic) innervation. Sensory nerves that originate from recep tors in the penile skin and glans converge to form the dorsal nerve of the penis, which travels to the S2-S4 dorsal root ganglia via the puden dal nerve. Parasympathetic nerve fibers to the penis arise from neurons in the intermediolateral columns of the S2-S4 sacral spinal segments. Sympathetic innervation originates from the T-11 to the L-2 spinal seg ments and descends through the hypogastric plexus. Neural input to smooth-muscle tone is crucial to the initiation and maintenance of an erection. There is also an intricate interaction between the corporal smooth-

muscle cell and its overlying endothelial cell lining (Fig. 409-1). Nitric oxide, which induces vascular relaxation, promotes erection and is opposed by endothelin 1 (ET-1) and Rho kinase, which mediate vascular contraction. Nitric oxide is synthesized from L-arginine by nitric oxide synthase (NOS) and is released from the nonadrenergic, noncholinergic (NANC) autonomic nerve supply to act postjunctionally on smooth-muscle cells. Nitric oxide increases the production of cyclic 3′,5′-guanosine monophosphate (cyclic GMP), which induces relaxation of smooth muscle (Fig. 409-2). Cyclic GMP is metabolized by phosphodiesterase type 5 (PDE-5). Inhibitors of PDE-5 such as the oral medications sildenafil, tadalafil, vardenafil, and avanafil maintain erections by reducing the breakdown of cyclic GMP. However, if nitric oxide is not produced at some level, PDE-5

inhibitors are ineffective, as these drugs facilitate, but do not initiate, the initial enzyme cascade. In addition to nitric oxide, vasoactive pros taglandins (PGE1, PGF2α) are synthesized within the cavernosal tissue and increase cyclic AMP levels, also leading to relaxation of cavernosal smooth-muscle cells.

Ejaculation is stimulated by the sympathetic nervous system; this results in contraction of the epididymis, vas deferens, seminal vesicles, and prostate, causing seminal fluid to enter the urethra. Seminal fluid emission is followed by rhythmic contractions of the bulbocavernosus and ischiocavernosus muscles, leading to ejaculation. This is followed by expulsion, characterized by stereotypic rhythmic contractions of the striated perineal muscles, leading to forceful expulsion of semen with the bladder neck closed. This emission and expulsion are controlled by the autonomic (parasympathetic and sympathetic) and somatic spinal centers, respectively. The synchronization between autonomic and somatic spinal centers is orchestrated by interneurons that form a spinal ejaculation generator that is present in mammals including man. Sexual Dysfunction CHAPTER 409 Premature ejaculation usually is related to anxiety or a learned behavior and is amenable to behavioral therapy or treatment with med ications such as selective serotonin reuptake inhibitors (SSRIs). Retro grade ejaculation (RE) results when the internal urethral sphincter does not close; it may occur in men with diabetes or after surgery involving the bladder neck. Anejaculation, the failure of a portion or the whole of the emission process often confused with RE, is commonly the result of selective alpha blockers used in male voiding dysfunction (e.g., tam sulosin, silodosin). Detumescence is mediated by norepinephrine from the sympathetic nerves, endothelin from the vascular surface, and smooth-muscle con traction induced by postsynaptic α-adrenergic receptors and activation of Rho kinase. These events increase venous outflow and restore the flaccid state. Venous leak can cause premature detumescence and is caused by insufficient relaxation of the corporal smooth muscle rather than a specific anatomic defect. Priapism refers to a persistent and painful erection and may be associated with sickle cell anemia, hyper coagulable states, spinal cord injury, or injection of vasodilator agents into the penis. ■ ■ERECTILE DYSFUNCTION Epidemiology Erectile dysfunction (ED) is not considered a normal part of the aging process. Nonetheless, it is associated with certain physiologic and psychological changes related to age. In the Massachusetts Male Aging Study (MMAS), a community-based survey of men aged 40–70, 52% of responders reported some degree of ED. Complete ED occurred in 10% of respondents, moderate ED in 25%, and minimal ED in 17%. The incidence of moderate or severe ED more than doubled between the ages of 40 and 70. In the National Health and Social Life Survey (NHSLS), which included a sample of men and women aged 18–59, 10% of men also reported being unable to main tain an erection. Incidence was highest among men in the age group 50–59 (21%) and men who were poor (14%), divorced (14%), and less educated (13%). The incidence of ED is also higher

among men with certain medical disorders, such as diabetes mellitus, obesity, lower urinary tract symp toms secondary to benign prostatic hyperplasia (LUTS/BPH), heart disease, hypertension, decreased high-density lipoprotein (HDL) lev els, and diseases associated with general systemic inflammation (e.g., rheumatoid arthritis). Cardiovascular disease and ED share etiologies as well as pathophysiology (e.g., endothelial dysfunction), and the degree of ED appears to correlate with the severity of cardiovascular disease. Consequently, ED represents a “sentinel symptom” in patients with occult cardiovascular and peripheral vascular disease. Smoking is also a significant risk factor in the development of ED. Medications used in treating diabetes or cardiovascular disease are additional risk factors (see below). There is a higher incidence of ED among men who have undergone radiation or surgery for prostate can cer and in those with a lower spinal cord injury. Psychological causes of ED include depression, anger, stress from employment or relationships, anxiety, and other stress-related causes.

Endothelial cell Parasympathetic nervous system Angiotensin II PGF2α Endothelin-1 PART 12 Endocrinology and Metabolism Tonic inhibition Rho kinase inhibitors NANC NO NO Smooth-muscle cell Adenylyl cyclase cAMP kinase cGMP kinase Guanylyl cyclase cGMP GTP Guanylyl cyclase agonists Decreased Ca2+ Decreased Ca2+ PDE5 inhibitors PDE5 5′ AMP FIGURE 409-1 Pathways that control erection and detumescence. Outflow from the parasympathetic nervous system leads to relaxation of the cavernous sinusoids in two ways, both of which increase the concentration of nitric oxide (NO) in smooth-muscle cells. First, NO is the neurotransmitter in nonadrenergic, noncholinergic (NANC) fibers; second, stimulation of endothelial nitric oxide synthase (eNOS) through cholinergic output causes increased production of NO. The NO produced in the endothelium then diffuses into the smooth-muscle cells and decreases its intracellular calcium concentration through a pathway mediated by cyclic guanosine monophosphate (cGMP), leading to relaxation. A separate mechanism that decreases the intracellular calcium level is mediated by cyclic adenosine monophosphate (cAMP). With increased cavernosal blood flow, as well as increased levels of vascular endothelial growth factor (VEGF), the endothelial release of NO is further sustained through the phosphatidylinositol 3 (PI3) kinase pathway. Active treatments (red boxes) include drugs that affect the cGMP pathway (phosphodiesterase type 5 [PDE-5] inhibitors and guanylyl cyclase agonists), the cAMP pathway (alprostadil), or both pathways (papaverine), along with neural-tone mediators (phentolamine and Rho kinase inhibitors). Agents that are being developed include guanylyl cyclase agonists (to bypass the need for endogenous NO) and Rho kinase inhibitors (to inhibit tonic contraction of smooth-muscle cells mediated through endothelin). α1, α-adrenergic receptor; GPCR, G protein–coupled receptor; GTP, guanosine triphosphate; iCa2+, intracellular calcium; NOS, nitric oxide synthase; PGE, prostaglandin E; PGF, prostaglandin F. (Reproduced with permission from KT McVary: Clinical practice. Erectile dysfunction. N Engl J Med 357:2472, 2007.) Sildenafil Vardenafil Tadalafil Avanafil L-Arginine NOS – NO PDE-5 Cyclic GMP 5’-GMP iCa2+ Smooth-muscle relaxation Erection FIGURE 409-2 Biochemical pathways modified by phosphodiesterase type 5 (PDE-5) inhibitors. Sildenafil, vardenafil, tadalafil, and avanafil enhance erectile function by inhibiting PDE-5, thereby maintaining high levels of cyclic 3′,5′-guanosine monophosphate (cyclic GMP). iCa2+, intracellular calcium; NO, nitric oxide; NOS, nitric oxide synthase.

Increased blood flow Increases sheer stress Pl3-kinase L-Arginine eNOS NO Alprostadil Sympathetic nervous system PGE Detumescence GPCR Phentolamine α1 cAMP ATP Papaverine PDE2, 3, 4 5′ AMP Relaxation Pathophysiology ED may result from three basic mechanisms: (1) failure to initiate

(psychogenic, endocrinologic, or neurogenic), (2) failure to fill (arteriogenic), and (3) failure to store adequate blood vol ume within the lacunar network (veno-occlusive dysfunction). These categories are not mutually exclusive, and multiple factors contribute to ED. Psychogenic factors frequently coexist with other etiologic fac tors and should be considered in all cases. Diabetic, atherosclerotic, and drug-related causes account for >80% of cases of ED in older men. Vasculogenic The most common organic cause of ED is a distur bance of blood flow to and from the penis. Atherosclerotic or traumatic arterial disease can decrease flow to the lacunar spaces, resulting in decreased rigidity and an increased time to full erection. Excessive out flow through the veins despite adequate inflow also may contribute to ED. Structural alterations to the fibroelastic components of the corpora may cause a loss of compliance and inability to compress the tunical veins. This condition may result from aging, increased cross-linking of collagen fibers induced by nonenzymatic glycosylation, hypoxemia, or altered synthesis of collagen associated with hypercholesterolemia. Neurogenic Disorders that affect the sacral spinal cord or the autonomic fibers to the penis preclude nervous system relaxation of penile smooth muscle, thus leading to ED. In patients with spinal cord injury, the degree of ED depends on the completeness and level of the lesion. Patients with incomplete lesions or injuries to the upper part of the spinal cord are more likely to retain erectile capabilities than

are those with complete lesions or injuries to the lower part. Although 75% of patients with spinal cord injuries have some erectile capability, only 25% have erections sufficient for penetration. Other neurologic disorders commonly associated with ED include multiple sclerosis and peripheral neuropathy. The latter is often due to either diabetes or alcoholism. Pelvic surgery may cause ED through disruption of the autonomic nerve supply. Endocrinologic Androgens increase libido, but their exact role in erectile function is unclear. Individuals with castrate levels of testos terone can achieve erections from visual or sexual stimuli. Nonethe less, normal levels of testosterone appear to be important for erectile function, in which the upregulation of nitric oxide synthase and the nitric oxide cascade is optimized (Fig. 409-1A). Androgen replacement therapy can improve depressed erectile function when it is secondary to hypogonadism; however, it is not useful for ED when endogenous testosterone levels are normal and should be avoided. Increased pro lactin may decrease libido by suppressing gonadotropin-releasing hormone (GnRH) resulting in decreased testosterone levels. Treatment of hyperprolactinemia with dopamine agonists can restore libido and eugonadism. Diabetic ED occurs in 35–75% of men with diabetes mellitus. Pathologic mechanisms are related primarily to diabetes-associated vascular and neurologic complications. Diabetic macrovascular com plications are related mainly to age, whereas microvascular complica tions correlate with the duration of diabetes and the degree of glycemic control (Chap. 415). Individuals with diabetes also have reduced amounts of nitric oxide synthase in both endothelial and neural tissues. Psychogenic Two mechanisms contribute to the inhibition of erections in psychogenic ED. First, psychogenic stimuli to the sacral cord may inhibit reflexogenic responses, thereby blocking activation of vasodilator outflow to the penis. Second, excess sympathetic stimula tion in an anxious man may increase penile smooth-muscle tone. The most common causes of psychogenic ED are performance anxiety, depression, relationship conflict, loss of attraction, sexual inhibition, conflicts over sexual preference, sexual abuse in childhood, and fear of pregnancy or sexually transmitted disease. Almost all patients with ED, even when it has a defined organic basis, develop a psychogenic component as a reaction to ED. Medication-Related Medication-induced ED (Table 409-1) is estimated to occur in 25% of men seen in general medical clinics. The adverse effects related to drug therapy are additive, especially in older men. In addition

to the drug itself, the underlying disease being treated is likely to contribute to sexual dysfunction (e.g., hypertension). Among the antihypertensive agents, the thiazide diuretics and beta blockers have been implicated most frequently. Calcium channel blockers and angiotensin-converting enzyme inhibitors are cited less frequently. These drugs may act directly at the corporal level (e.g., calcium chan nel blockers) or indirectly by reducing pelvic blood pressure, which is important in the development of penile rigidity. α-Adrenergic blockers are less likely to cause ED. Estrogens, GnRH agonists, H2 antagonists, and spironolactone cause ED by suppressing gonadotropin production or by blocking androgen action. Antidepressant and antipsychotic agents—particularly neuroleptics, tricyclics, and SSRIs—are associ ated with erectile, ejaculatory, orgasmic, and sexual desire difficulties. Among the SSRIs, paroxetine and escitalopram have been associated with the highest risk of sexual dysfunction. Bupropion, nefazodone, and mirtazapine appear less likely to cause sexual dysfunction. A number of molecular pathways have been implicated in antidepressantinduced sexual adverse events. Serotonin has been hypothesized to inhibit normal sexual response by decreasing dopamine-enhanced libido, arousal, and erection and by increasing prolactin release. SSRIs have also been shown to be potent inhibitors of nitric oxide synthase. If there is a strong association between the institution of a drug and the onset of ED, alternative medications should be considered. Other wise, it is often practical to treat the ED without attempting multiple changes in medications as it may be difficult to establish a causal role for a drug.

TABLE 409-1 Drugs Associated with Erectile Dysfunction CLASSIFICATION DRUGS POSSIBLE SUBSTITUTES Diuretics Thiazides Spironolactone Antihypertensives Calcium channel blockers α-Adrenergic blockers Prazosin Terazosin Doxazosin ACE inhibitors Sexual Dysfunction CHAPTER 409 Methyldopa Clonidine Reserpine Beta blockers Guanethidine Cardiac/ antihyperlipidemics Digoxin Gemfibrozil Clofibrate Antidepressants Selective serotonin reuptake inhibitors Bupropion Nefazodone Mirtazapine Tricyclic antidepressants Lithium Monoamine oxidase inhibitors Tranquilizers Butyrophenones Phenothiazines H2 antagonists Ranitidine Proton pump inhibitors (PPI) Omeprazole Esomeprazole Pantoprazole Rabeprazole Cimetidine Hormones Progesterone Estrogens Corticosteroids GnRH agonists 5α-Reductase inhibitors Cyproterone acetate Cytotoxic agents Cyclophosphamide Methotrexate Roferon-A Anticholinergics Disopyramide Anticonvulsants Recreational Ethanol Cocaine Marijuana Abbreviations: ACE, angiotensin-converting enzyme; GnRH, gonadotropin-releasing hormone. APPROACH TO THE PATIENT Erectile Dysfunction A good physician–patient relationship helps unravel the possible causes of ED, many of which require discussion of personal and sensitive topics. For this reason, a primary care provider is often ideally suited to initiate the evaluation. However, a significant percentage of men experience ED and remain undiagnosed unless specifically questioned about this issue. By far the two most com mon reasons for underreporting of ED are patient embarrassment and perceptions of physicians' inattention to the disorder. Once

History: Medical, sexual, and psychosocial Physical examination Serum: Testosterone and prolactin levels Lifestyle risk management Medication review Problem resolved Problem persists Patient/partner education Goal-directed therapy planning Sex therapy Special testing PART 12 Endocrinology and Metabolism Treatment success Oral PDE-5 inhibitors Intraurethral or injection therapy Treatment success Vacuum device Implantation/ vascular surgery FIGURE 409-3 Algorithm for the evaluation and management of patients with erectile dysfunction. PDE, phosphodiesterase. the topic is initiated by the physician, patients are more willing to discuss their potency issues. A

complete medical and sexual history should be taken in an effort to assess whether the cause of ED is organic, psychogenic, or multifactorial (Fig. 409-3). Both the patient and his sexual partner should be interviewed regarding sexual history. ED should be distinguished from other sexual problems, such as premature ejaculation. Lifestyle factors such as sexual orientation, the patient's distress from ED, perfor mance anxiety, and details of sexual techniques should be addressed. Validated questionnaires are available to assess ED, including the International Index of Erectile Function (IIEF) and the more easily administered Sexual Health Inventory for Men (SHIM), a validated abridged version of the IIEF. These can assess the severity of ED, measure treatment effectiveness, and guide future management. The initial evaluation of ED begins with a review of the patient's medical, surgical, sexual, and psychosocial histories. The history should note whether the patient has experienced pelvic trauma, surgery, or radiation. In light of the increasing recognition of the relationship between lower urinary tract symptoms (LUTS/BPH) and ED, it is advisable to evaluate for the presence of associated uri nary symptoms. Questions should focus on the onset of symptoms, the presence and duration of partial erections, and the progression of ED. A history of nocturnal or early morning erections may be useful for distinguishing physiologic ED from psychogenic ED. Nocturnal erections occur during rapid eye movement (REM) sleep and require intact neurologic and circulatory systems. Organic causes of ED generally are characterized by a gradual and persistent change in rigidity or the inability to sustain nocturnal, coital, or self-stimulated erections. It is also important to address libido, as decreased sexual drive and ED are sometimes the earliest signs of decreased testosterone levels. It is useful to ask whether the prob lem is confined to coitus with one partner or also involves other partners; ED not uncommonly arises with new or extramarital sexual relationships. Situational ED, as opposed to consistent ED, suggests psychogenic causes. For men with recalcitrant ED, referral to a mental health professional may promote treatment adherence, reduce performance anxiety, and integrate treatments into a sexual relationship. Ejaculation is much less commonly affected than erec tion, but questions should be asked about whether ejaculation is normal, premature, delayed, or absent. Relevant risk factors should be identified, such as diabetes mellitus, cardiovascular disease, and neurologic disorders. The patient's surgical history should be explored with an emphasis on bowel, bladder, prostate, and vascular procedures. A complete drug history, including tobacco, alcohol, marijuana, and illicit drug inquiries, is also important. Social

changes that may precipitate ED are also crucial to the evaluation, including health worries, spousal death, divorce, relationship dif ficulties, and financial concerns. Because ED commonly involves a host of endothelial cell risk factors, men with ED report higher rates of overt and silent myocar dial infarction. Therefore, ED in an otherwise asymptomatic male warrants consideration of other vascular disorders, including coro nary disease. It is now widely recognized that ED often precedes the development of symptomatic coronary disease by several years. In addition, several studies now suggest that ED itself is an indepen dent risk factor for the development of CVD even after correcting for other cardiovascular risk factors. Men who suffer from ED are at high risk for concomitant LUTS from BPH and vice versa. Given that some treatments of one dis order will impact the other, the clinician should consider an assess ment of LUTS in any man with ED. The physical examination is an essential element in the assess ment of ED. Signs of hypertension as well as evidence of thyroid, hepatic, hematologic, cardiovascular, or renal diseases should be sought. An assessment should be made of the endocrine and vascu lar systems, the external genitalia, and the prostate gland. The penis should be palpated carefully along the corpora to detect fibrotic plaques. Reduced testicular size and loss of secondary sexual char acteristics are

suggestive of hypogonadism. Neurologic examination should include assessment of anal sphincter tone, investigation of the bulbocavernosus reflex, and testing for peripheral neuropathy. Although hyperprolactinemia is uncommon, a serum prolactin level should be measured in hypogonadal men, as decreased libido and/or ED may be the presenting symptoms of a prolactinoma or another mass lesion of the sella (Chap. 392). The serum testosterone level should be measured, and if it is low, gonadotropins should be measured to determine whether hypogonadism is primary (testicu lar) or secondary (hypothalamic-pituitary) in origin (Chap. 403). If not performed recently, serum chemistries, hemoglobin A1c, and lipid profiles may be of value, as they can yield evidence of diabetes, hyperlipidemia, or other systemic diseases associated with ED. Additional diagnostic testing is rarely necessary in the evalua tion of ED. However, in selected patients, specialized testing may provide insight into pathologic mechanisms of ED and aid in the selection of treatment options. Optional specialized testing includes (1) studies of nocturnal penile tumescence and rigidity, (2) vascular testing (in-office injection of vasoactive substances, penile Dop pler ultrasound), (3) neurologic testing (biothesiometry-graded vibratory perception, somatosensory-evoked potentials), and (4) psychological diagnostic tests. The information potentially gained from these procedures must be balanced against their invasiveness, cost, and impact on ultimate treatment outcome. Clinicians should counsel men with ED who have comorbidities known to negatively affect erectile function that lifestyle modifica tions, including changes in diet and increased physical activity, improve overall health and can improve ED. TREATMENT Male Sexual Dysfunction PATIENT EDUCATION Patient and partner education is essential in the treatment of ED. In goal-directed therapy, education facilitates understanding of the disease, the results of the tests, and the selection of treatment. Discussion of treatment options helps clarify how treatment is best offered and stratify first- and second-line therapies. Patients with high-risk lifestyle issues such as obesity, smoking, alcohol abuse, and recreational drug use should be counseled on the role those factors play in the development of ED. Therapies currently employed for the treatment of ED include oral PDE-5 inhibitor (PDE-5i) therapy (most commonly used), injection therapies, testosterone therapy, penile devices, and

TABLE 409-2 PDE-5 Inhibitorsa DRUG ONSET OF ACTION T1/2 DOSE ADVERSE EFFECTS CONTRAINDICATIONS Sildenafil Tmax 30–120 min Duration 4 h High-fat meal decreases absorption Alcohol use may affect efficacy 2–5 h 25–100 mg Starting dose 50 mg Vardenafil Tmax 30–120 min Duration 4–5 h High-fat meal decreases absorption ETOH may affect efficacy 4.5 h 5–10 mg Headache, flushing, rhinitis, dyspepsia Tadalafil Tmax 30–60 min Duration 12–36 h Plasma concentration not affected by food or ETOH 17.5 h 10 or 20 mg; 2.5 or 5 mg for daily dose Avanafil Tmax 30 min Duration 2 h Plasma concentration not affected by food 3–5 h 50, 100, and 200 mg dose aSildenafil, vardenafil, tadalafil, and the newest option, avanafil, appear to be equally effective, but tadalafil has a longer duration of action and avanafil has a more rapid onset. Abbreviations: ETOH, ethanol; PDE-5, phosphodiesterase type 5. psychological therapy. In addition, limited data suggest that treat ments for underlying risk factors and comorbidities—for example, weight loss, exercise, stress reduction, and smoking cessation—may improve erectile function. ORAL AGENTS Sildenafil, tadalafil, vardenafil, and avanafil are the only approved and effective oral agents for the treatment of ED. These four medi cations have markedly improved the management of ED because they are effective for the treatment of a broad range of etiologies. They belong to a class of medications that are selective and potent inhibitors of PDE-5, the predominant phosphodiesterase isoform found in the penis. They are administered in graduated doses and enhance erections after sexual stimulation (Fig. 409-2). The onset of action is ~30–120 min,

depending on the medication used and other factors, such as recent food intake. Reduced initial doses should be considered for patients who are elderly, are taking concomitant alpha blockers, have renal insufficiency, or are taking medications that inhibit the CYP3A4 metabolic pathway in the liver (e.g., erythromycin, cimetidine, ketoconazole, clarithromycin, dil tiazem, itraconazole, ritonavir, verapamil, grapefruit, and possibly itraconazole and mibefradil), as they may increase the serum con centration of the PDE-5i or promote hypotension. Initially, there were concerns about the cardiovascular safety of these drugs. It is known that these agents can act as mild vasodilators. Earlier con cerns that the use of PDE-5is would increase cardiovascular events have been reversed as more studies support that a general popula tion of men with ED who take PDE-5is have lower rates of major adverse cardiovascular events and lower overall mortality rates than men not exposed to PDE-5is, even after correcting for baseline car diovascular risks and concomitant medicines. These studies suggest that PDE-5is may have a significant cardiovascular protective effect and may have potential as preventive cardiology agents. Several randomized trials have demonstrated the efficacy of this class of medications. There are no compelling data to support the superiority of one PDE-5i over another. Subtle differences between agents have variable clinical relevance (Table 409-2). Patients may fail to respond to a PDE-5i for several reasons (Table 409-3). Some patients may not tolerate PDE-5i secondary to adverse events from vasodilation in nonpenile tissues expressing PDE-5 or from the inhibition of homologous nonpenile isozymes (i.e., PDE-6 found in the retina). Abnormal vision attributed to the effects of PDE-5i on retinal PDE-6 is of short duration, reported only with sildenafil, and not clinically significant. A more serious

Headache, flushing, dyspepsia, nasal congestion, altered vision Nitrates Hypotension Cardiovascular risk factors Retinitis pigmentosa Change dose with some antiretrovirals Should be on stable dose of alpha blockers Same as sildenafil May have minor prolongation of QT interval Concomitant use of class I antiarrhythmic Sexual Dysfunction CHAPTER 409 Headache, dyspepsia, backpain, nasal congestion, myalgia Same as sildenafil Headache, flushing, nasal congestion nasopharyngitis back pain Same as sildenafil concern is the possibility that PDE-5is may cause nonarteritic ante rior ischemic optic neuropathy (NAION); although data to support that association are limited, it is prudent to avoid the use of these agents in men with a prior history of NAION. Testosterone supplementation combined with a PDE-5i may be beneficial in improving erectile function in hypogonadal men with ED who are unresponsive to PDE-5i alone. Side effects associated with PDE-5is include headaches (19%), facial flushing (9%), dys pepsia (6%), and nasal congestion (4%). Approximately 7% of men using sildenafil may experience transient altered color vision (blue halo effect), and 6% of men taking tadalafil may experience loin pain. PDE-5i is contraindicated in men receiving nitrate therapy for cardiovascular disease, including agents delivered by the oral, sublingual, transnasal, and topical routes as they can potentiate its hypotensive effect. Likewise, amyl/butyl nitrate “poppers” may have a fatal synergistic effect on blood pressure. PDE-5is also should be avoided in patients with congestive heart failure and cardiomyopa thy because of the risk of vascular collapse. Because sexual activity leads to an increase in physiologic expenditure (5–6 metabolic equivalent tasks [METs]), physicians have been advised to exercise caution in prescribing any drug for sexual activity to those with active coronary disease, heart failure, borderline hypotension, or hypovolemia and to those on complex antihypertensive regimens. Although the various forms of PDE-5is have a common mecha nism of action, there are a few differences among the four agents (Table 409-2). Tadalafil is unique in its longer half-life, and avanafil appears to have the fastest onset of action. Although there are pharmacokinetic and pharmacodynamic differences among these agents, clinically relevant

differences are not clear. TABLE 409-3 Issues to Consider if Patients Report Failure of Phosphodiesterase Type 5 Inhibitor (PDE-5i) to Improve Erectile Dysfunction

1. A trial of medication on at least 6 different days at the maximal dose should be performed before declaring patient nonresponsive to PDE-5i use.
2. Confirm that the patient did not partake in a high-fat meal prior to taking medication; pertains to sildenafil.
3. Failure to include physical and psychic stimulation at the time of foreplay to induce endogenous NO.
4. Took medications at an appropriate time frame prior to step 3: half-hour prior for avanafil, 1 h for sildenafil/vardenafil, or 2.5 h for tadalafil.
5. Unrecognized hypogonadism. Abbreviation: NO, nitric oxide.

ANDROGEN THERAPY Testosterone replacement is used to treat both primary and second ary causes of hypogonadism (Chap. 403). Men with ED and testos terone deficiency (TD) who are considering ED treatment with a PDE-5i should be informed that PDE-5is may be more effective if combined with testosterone therapy. Androgen supplementation in the setting of normal testosterone is not efficacious in the treatment of ED and is discouraged secondary to additional risk for toxicity without benefit.

The increased scrutiny of testosterone caused the U.S. Food and Drug Administration (FDA) to issue a warning that there is a “weak signal” that testosterone replacement therapy increases the risk of thromboembolic events and may have addictive properties. Although testosterone therapy has known risks, such as water reten tion in heart failure patients and worsening sleep apnea, increasing evidence suggests that, when monitored appropriately, this therapy decreases the risk for metabolic syndrome, changes body composi tion by increasing lean muscle mass, and improves insulin sensi tivity and average hemoglobin A1c. This evidence, combined with the fact that hypogonadism is a known risk factor for metabolic syndrome and cardiovascular disease, has led to the conclusion that testosterone therapy for age-related hypogonadism in fact improves overall health and decreases the risk of cardiovascular events. It is important to note that men with secondary hypogonadism who desire fertility should not be treated directly with testosterone, but with an alternative such as the selective estrogen receptor modu lator (SERM) clomiphene citrate, which increases gonadotropin levels, stimulating testicular testosterone production. PART 12 Endocrinology and Metabolism Testosterone circulates in the body in two forms: free and unbound or that bound to proteins such as albumin or sex hor mone–binding globulin (SHBG). SHBG has a very high affinity for testosterone, and thus, testosterone bound to SHBG does not bind to the androgen receptor and is not bioavailable. Bioavailable testosterone is any testosterone that is not bound to SHBG. Unfor tunately, reliable assays to directly measure bioavailable testosterone or free testosterone are expensive, difficult to perform, and thus not offered by most laboratories. However, direct measurement of SHBG is inexpensive and reliable, allowing free and bioavailable testosterone to be calculated. Men who receive testosterone should be reevaluated after 3–6 months and at least annually thereafter for testosterone levels, erectile func tion, and adverse effects, which may include gynecomastia, sleep apnea, development or exacerbation of LUTS or BPH, prostate cancer, lowering of HDL, erythrocytosis, and elevations of liver function tests. Periodic reevaluation should include measurement of hemoglobin, liver function tests, prostate-specific antigen, and digital rectal examination. Therapy should be discontinued in patients who do

not respond within 6 months without an alternate explanation (e.g., elevated estradiol). VACUUM CONSTRICTION DEVICES Vacuum constriction devices (VCDs) are a well-established non invasive therapy. They are a reasonable treatment alternative for select patients who cannot take PDE-5is or do not desire other interventions. VCDs draw venous blood into the penis and use a constriction ring to restrict venous return and maintain tumes cence. Adverse events with VCD include pain, numbness, bruising, and altered ejaculation. Additionally, many patients complain that the devices are cumbersome and that the induced erections have a nonphysiologic appearance and feel. INTRAURETHRAL ALPROSTADIL If a patient fails to respond to oral agents, a reasonable next choice is intraurethral or self-injection of vasoactive substances. Intraure thral prostaglandin E1 (alprostadil), in the form of a semisolid pellet (doses of 125–1000 μg), is delivered with an applicator. Approxi mately 65% of men receiving intraurethral alprostadil respond with an erection when tested in the office, but <50% achieve successful coitus at home.

INTRACAVERNOSAL SELF-INJECTION Injection of synthetic formulations of alprostadil is effective in 70–80% of patients with ED, but discontinuation rates are high because of the invasive nature of administration. Doses range between 1 and 40 μg. Injection therapy is contraindicated in men with a history of hypersensitivity to the drug and men at risk for priapism (hypercoagulable states, sickle cell disease). Side effects include local adverse events, prolonged erections, pain, and fibrosis with chronic use. Various combinations of alprostadil, phentol amine, and/or papaverine sometimes are used. SURGERY An important but less frequently used form of therapy for ED involves the surgical implantation of a semirigid or inflatable penile prosthesis. Because of the permanence of prosthetic devices, patients should first consider less invasive options for treatment. These surgical treatments are associated with a low rate of compli cations and are used for those who do not want the less spontaneous medical treatments, in PDE-5i–refractory ED, or in men who can not tolerate such medications. Despite the requirement for surgery, penile prostheses are associated with very high rates of patient and partner satisfaction. SEX THERAPY A course of sex therapy may be useful for addressing specific interpersonal factors that may affect sexual functioning. These approaches may be useful in patients who have psychogenic or social components to their ED, although data from randomized trials are inconsistent. It is preferable to include both partners in therapy if the patient is involved in an ongoing relationship. FEMALE SEXUAL DYSFUNCTION Female sexual dysfunction (FSD) includes chronic sexual conditions in the domains of desire, arousal, pain, and muted orgasm. The associ ated risk factors for FSD are similar to those in males: cardiovascular disease, endocrine disorders, hypertension, neurologic disorders, and smoking (Table 409-4). Women with hypertension report significantly lower sexual satisfaction (especially younger women). ■ ■EPIDEMIOLOGY Epidemiologic data are limited, but the available estimates suggest that as many as 43% of women complain of at least one sexual problem. Despite their frequency and impact, FSDs are substantially undetected by clinicians and undertreated even when recognized. Despite the recent interest in organic causes of FSD, desire and arousal phase disor ders (including lubrication complaints) remain the most common pre senting problems when surveyed in a community-based population. TABLE 409-4 Risk Factors for Female Sexual Dysfunction Neurologic disease: stroke, spinal cord injury, parkinsonism Trauma, genital surgery, radiation Endocrinopathies: diabetes, hyperprolactinemia Liver and/or renal failure Cardiovascular disease, especially hypertension Psychological factors and interpersonal relationship disorders: sexual abuse, life stressors Medications Antiandrogens: cimetidine, spironolactone Antidepressants, alcohol, hypnotics, sedatives Antiestrogens or GnRH antagonists Antihistamines, sympathomimetic amines Antihypertensives: diuretics, calcium channel blockers

Alkylating agents Anticholinergics Abbreviation: GnRH, gonadotropin-releasing hormone.

■ ■PHYSIOLOGY OF THE FEMALE SEXUAL RESPONSE The normal female sexual response requires the presence of estrogens. A role for androgens is also likely but less well established. In the CNS, estrogens and androgens work synergistically to enhance sexual arousal and response. A number of studies report enhanced libido in women during preovulatory phases of the menstrual cycle, suggesting that hormones involved in the ovulatory surge (e.g., estrogens) increase desire. Sexual motivation is heavily influenced by context, including the environment and partner factors. Once sufficient sexual desire is reached, sexual arousal is mediated by the central and autonomic nervous systems. Cerebral sympathetic outflow is thought to increase desire, and peripheral parasympathetic activity results in clitoral vaso congestion and vaginal secretion (lubrication). The neurotransmitters for clitoral corporal engorgement are similar to those in the male penile tissues, with a prominent role for neural, smooth-muscle, and endothelial released nitric oxide (NO). A fine network of vaginal nerves and arterioles promotes a vaginal transudate. The major transmitters of this complex vaginal response are not certain, but roles for NO and vasoactive intestinal polypeptide (VIP) are sup ported. There are doubts concerning the construct of a linear relation ship between initial desire, arousal, vasocongestion, lubrication, and orgasm. Caregivers should consider a paradigm of a positive emotional and physical outcome with one, many, or no orgasmic peak and release. Although there are anatomic differences as well as variation in the density of vascular and neural beds in males and females, the primary effectors of sexual response are strikingly similar. Intact sensation is important for arousal. Thus, reduced levels of sexual functioning are more common in women with peripheral neuropathies (e.g., diabetes). Vaginal lubrication is a transudate of serum that results from the increased pelvic blood flow associated with arousal. Vascular insuffi ciency from a variety of causes may compromise adequate lubrication and result in dyspareunia. Cavernosal and arteriole smooth-muscle relaxation occurs via increased NO synthase (NOS) activity and produces engorgement in the clitoris and the surrounding vestibule. Orgasm requires an intact sympathetic outflow tract; hence, orgasmic disorders are common in female patients with spinal cord injuries. APPROACH TO THE PATIENT Female Sexual Dysfunction Many women do not volunteer information about their sexual response. Open-ended questions in a supportive atmosphere are helpful in initiating a discussion of sexual integrity. Once a com plaint has been voiced, a comprehensive evaluation should be performed, including a medical history, a psychosocial history, a physical examination, and limited laboratory testing. The history should include the usual medical, surgical, obstet ric, psychological, gynecologic, sexual, and social information. Past experiences, intimacy, knowledge, and partner availability should also be ascertained. Medical disorders that may affect sexual health should be delineated. They include diabetes, cardiovascu lar disease, gynecologic conditions, obstetric history, depression, anxiety disorders, and neurologic disease. Medications should be reviewed as they may affect arousal, libido, and orgasm. The need for counseling and recognizing life stresses should be identified. The physical examination should assess the genitalia, including the clitoris. Pelvic floor examination may identify prolapse or other disorders. Laboratory studies are needed, especially if menopausal status is uncertain. Estradiol, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) are usually obtained, and dehydro epiandrosterone (DHEA) should be considered as it reflects adrenal androgen secretion. A complete blood count, liver function assess ment, and lipid studies may be useful, if not otherwise obtained. Complicated diagnostic evaluation such as clitoral Doppler ultraso nography and biothesiometry require expensive equipment and are of uncertain utility. It is important for the patient to identify which symptoms are most distressing.

The evaluation of FSD previously occurred exclusively in a psychosocial context. However, inconsistencies between diagnos tic categories based only on psychosocial considerations and the emerging recognition of organic etiologies have led to a new classification of FSD. This diagnostic scheme is based on four components that are not mutually exclusive: (1) hypoactive sexual desire—the persistent or recurrent lack of sexual thoughts and/or receptivity to sexual activity; hypoactive sexual desire may result from endocrine failure or may be associated with psychological or emotional disorders; (2) sexual interest arousal disorder—the persis tent or recurrent inability to attain or maintain sexual excitement; (3) orgasmic disorder—the persistent or recurrent loss of orgasmic potential after sufficient sexual stimulation and arousal; and (4) sexual pain disorder—persistent or recurrent genital pain associ ated with noncoital sexual stimulation. This newer classification emphasizes “personal distress” as a requirement for dysfunction and provides clinicians with an organized framework for evaluation before or in conjunction with more traditional counseling methods. Sexual Dysfunction CHAPTER 409 TREATMENT Female Sexual Dysfunction GENERAL An open discussion with the patient is important as couples may need to be educated about normal anatomy and physiologic responses, including the role of orgasm, in sexual encounters. Physiologic changes associated with aging and/or disease should be explained. Couples may need to be reminded that clitoral stimula tion rather than coital intromission may be more beneficial. Behavioral modification and nonpharmacologic therapies should be a first step. Patient and partner counseling may improve communication and relationship strains. Lifestyle changes involv ing known risk factors can be an important part of the treatment process. Emphasis on maximizing physical health and avoiding life styles (e.g., smoking, alcohol abuse) and medications likely to pro duce FSD is important (Table 409-3). The use of topical lubricants may address complaints of dyspareunia and dryness. Contributing medications such as antidepressants may need to be altered, includ ing the use of medications with less impact on sexual function, dose reduction, medication switching, or drug holidays. HORMONAL THERAPY In postmenopausal women, estrogen replacement therapy may be helpful in treating vaginal atrophy, decreasing coital pain, and improving clitoral sensitivity (Chap. 407). Menopause and its transition represent significant risk factors for the development of vulvovaginal atrophy–related sexual dysfunction. Available vaginal estrogen preparations include conjugated equine estrogens, estra diol vaginal cream, a sustained-release intravaginal estradiol ring, or a low-dose estradiol tablet. Vaginal estrogen preparations with the lowest systemic absorption rate may be preferred in women with history of breast cancer and severe vaginal atrophy. Vaginal lubricants and moisturizers applied on a regular basis have an efficacy comparable to that of local estrogen therapy and should be offered to women wishing to avoid the use of vaginal estrogens. If a hormonal supplement is chosen, then estrogen replacement in the form of local cream is the preferred method as it avoids sys temic side effects. Androgen levels in women decline substantially before menopause. However, low levels of testosterone or DHEA are not effective predictors of a positive therapeutic outcome with androgen therapy. The widespread use of exogenous androgens is not supported by the literature except in select circumstances (premature ovarian failure or menopausal states) and in secondary arousal disorders. Atrophic vaginitis is very common in postmenopausal women and is most commonly treated with estrogen-based treatments. However, many women are hesitant to use estrogen-based

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