CLINICAL PRACTICE

Erectile Dysfunction

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 65-year-old man presents to an outpatient clinic, reporting that he can no longer maintain an erection sufficient for intercourse. His medical history includes well-controlled hypertension and stable coronary artery disease. He smokes a pack of cigarettes daily. His medications include atenolol and low-dose aspirin (81 mg daily). On physical examination, his body-mass index (the weight in kilograms divided by the square of the height in meters) is 31; the examination is otherwise unremarkable, with normal external genitalia and no loss of body hair. How should he be evaluated and treated?

THE CLINICAL PROBLEM

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Erectile dysfunction is defined as the consistent inability to attain or maintain a penile erection of sufficient quality to permit satisfactory sexual intercourse.[1] The prevalence of this condition increases with age. In a large cross-sectional, community-based study,[2] among men between the ages of 40 and 49 years, the prevalence of complete or severe erectile dysfunction was 5%, and the prevalence of moderate erectile dysfunction was 17%; among men between the ages of 70 and 79 years, these rates were 15% and 34%, respectively. It has been estimated that the worldwide prevalence of erectile dysfunction will be 322 million cases by the year 2025.[3,4]

Erectile dysfunction was once considered to be psychogenic in origin and was frequently neglected by health care providers. More recently, there has been increasing recognition of the many physiological causes of the condition and of the potential for therapy to improve a patient's quality of life, self-esteem, and ability to maintain intimate relationships.[5]

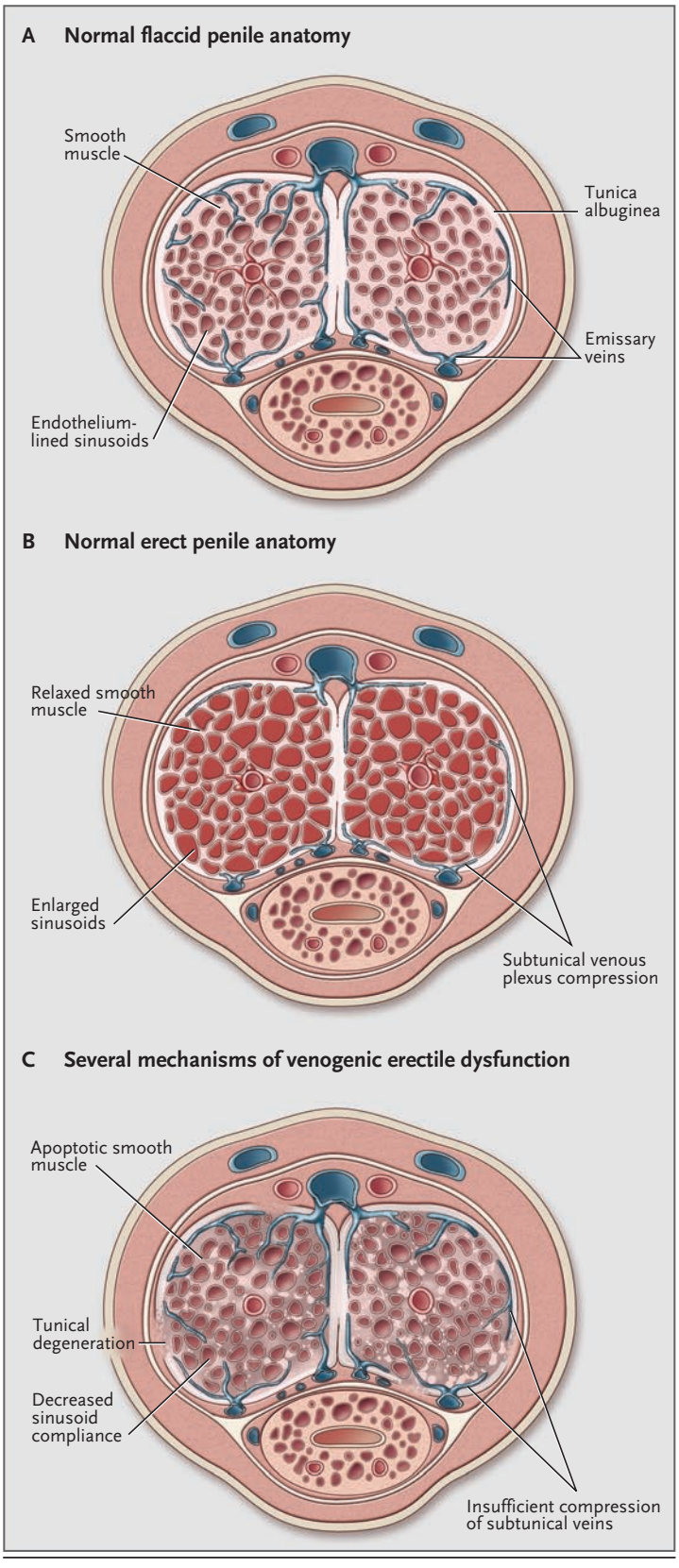
PHYSIOLOGICAL FACTORS

Sexual function is a complex process involving both biologic and psychological factors. Erections result from a combination of neurotransmission and vascular smooth-muscle responses that culminate in increased arterial inflow and signaling between endothelial-lined cavernosal sinusoids and the underlying smooth-muscle cells. Nitric oxide that is produced by the parasympathetic nonadrenergic, noncholinergic neurons and endothelial cells triggers a molecular cascade that results in the relaxation of smooth-muscle cells. This process occludes venous return through passive compression of the subtunical venules, resulting in an erection (Fig. 1). The ability to achieve or maintain an erection may be compromised by factors affecting any steps in this pathway (Fig. 2).

Conditions that are associated with erectile dysfunction include the metabolic syndrome,[6] lower urinary tract symptoms of benign prostatic hyperplasia,[7,8] cardiovascular disease,[9] central neuropathologic conditions (e.g., Parkinson's disease and

Figure 1. Physiological Mechanism of Penile Smooth-Muscle Relaxation.

The corpora cavernosa contain a network of smooth-muscle cells and endothelial cells surrounded by an expansible tunica albuginea. The sinusoid cavities are small in volume at rest as the smooth-muscle cells are tonically contracted (Panel A). With stimulation, smooth-muscle cells relax, which allows the sinusoids to engorge with blood and causes the penis to become tumescent. As the sinusoids expand, they compress the subtunical venous plexus, which causes an erection (Panel B). If there is insufficient relaxation of smooth-muscle cells (e.g., from a lack of endogenous nitric oxide associated with endothelial disease) and decreased sinusoid compliance, an inadequate number of smooth-muscle cells (e.g., cell apoptosis from diabetes or neuropathy), or tunical degeneration (e.g., Peyronie's disease), then insufficient compression of the subtunical veins results in erectile dysfunction (Panel C).



hemorrhagic or ischemic stroke), tobacco use (with the prevalence of erectile dysfunction twice as high among smokers as among nonsmokers),[10] diabetes mellitus,[11] and other endocrine disorders, including hypogonadism and hyperprolactinemia (Table 1). Atherosclerosis, with associated endothelial dysfunction, develops in the penile circulation as it does elsewhere; more than two thirds of patients with coronary artery disease have symptoms of erectile dysfunction before the onset of coronary symptoms.[9] For patients with diabetes, the risk of erectile dysfunction increases with the duration of the condition and with increasing levels of glycated hemoglobin.[11] Medications (both prescription and nonprescription) may cause or contribute to erectile dysfunction in as many as 25% of men who present for evaluation[12] (Table 2).

STRATEGIES AND EVIDENCE

EVALUATION

Erectile dysfunction may be the presenting symptom of serious medical problems. The evaluation should begin with a review of the patient's medical, sexual, and psychosocial history. The review of the medical history should include attention to previous events that may have affected vascular or neurologic function, such as pelvic trauma, surgery, or irradiation. Given the recognition of the relationship between lower urinary tract symptoms and erectile dysfunction, it is advisable to screen patients for irritative and obstructive voiding symptoms (e.g., with the International Pros-

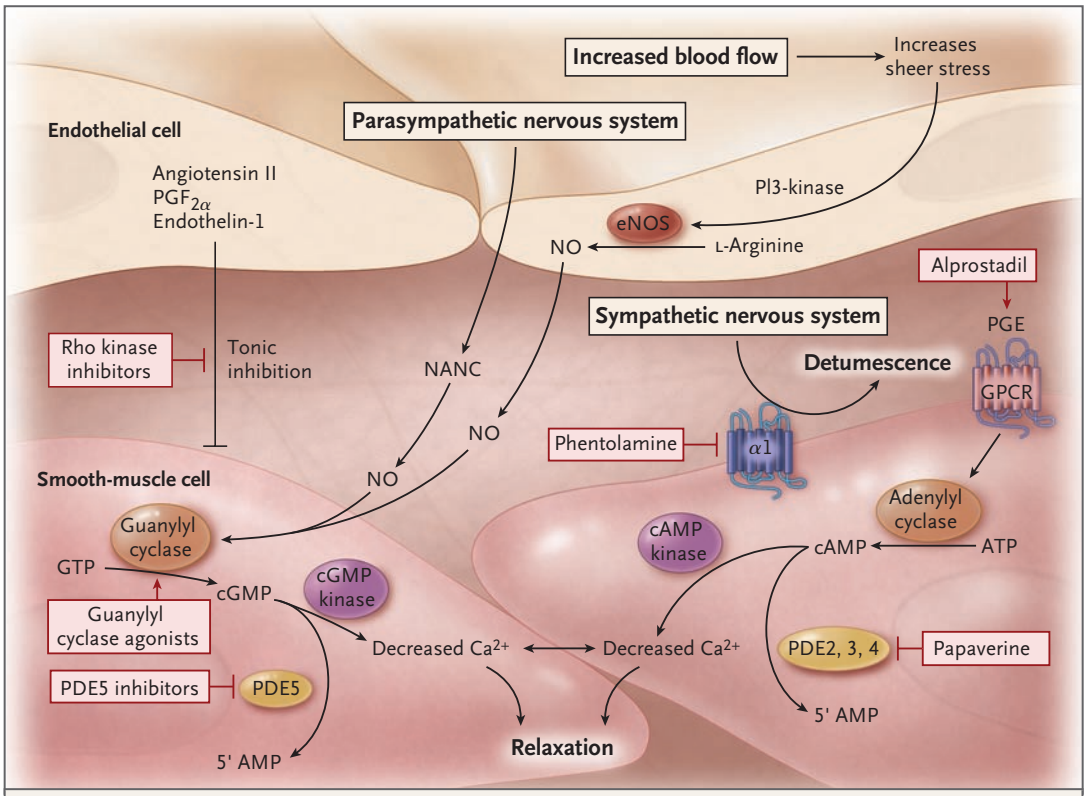


Figure 2. Molecular Mechanism of Penile Smooth-Muscle Relaxation.

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, nitric oxide is the neurotransmitter in nonadrenergic, noncholinergic (NANC) fibers; second, stimulation of endothelial nitric oxide synthase (eNOS) through cholinergic output causes increased production of nitric oxide. The nitric oxide produced in the endothelium then diffuses into the smooth-muscle cells. With the increase in nitric oxide content, the smooth-muscle cell decreases its intracellular calcium concentration through a pathway mediated by cyclic guanosine monophosphate (cGMP), which leads 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 nitric oxide is further sustained through the phosphatidylinositol 3 (PI3) kinase pathway. Active treatments (red boxes) include drugs that affect the cGMP pathway (phosphodiesterase [PDE] type 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 nitric oxide) and Rho kinase inhibitors (to inhibit tonic contraction of smooth-muscle cells mediated through endothelin). Parasympathetic outflow is impaired in patients with diabetes, depression, and central and peripheral neuropathic diseases that inhibit neural output; outflow is also impaired by destruction of the nonadrenergic, noncholinergic nerves themselves. Exposure to tobacco smoke and lower urinary tract symptoms of benign prostatic hyperplasia are associated with an increase in outflow from the sympathetic nervous system that inhibits relaxation forces. Lower urinary tract symptoms may also impair the nitric oxide content in the penis, prostate, and bladder and account for the association between such symptoms and erectile dysfunction. Diabetes, the metabolic syndrome, hyperlipidemias, atherosclerosis, and smoking also directly reduce the activity of nitric oxide synthase and induce apoptosis of endothelial and smooth-muscle cells. PGF denotes prostaglandin F, PGE prostaglandin E, GPCR G-protein–coupled receptor, α1 α-adrenergic receptor, and GTP guanosine triphosphate.

tate Symptom Score, a grading scale from 0 to 35, with scores of 8 to 19 indicating moderate symptoms).[7] Medications (including over-the-counter drugs) should be reviewed (Table 2), as should previous or current use of tobacco products, illicit drugs, and alcohol. The timing of the onset of erectile dysfunction should also be assessed; a gradual and progressive history suggests an organic cause, whereas a sudden onset of complete erectile dysfunction in the absence of trauma or other

Table 1. Risk Factors for Erectile Dysfunction.*

Risk Factor	Mechanism or Cause	Treatment
Metabolic syndrome	Endothelial dysfunction and down-regulation of nitric oxide synthase	Diet, exercise, and associated weight loss
Lower urinary tract symptoms of benign prostatic hyperplasia	Possible decrease in nitric oxide in the penis, bladder, and prostate	Use of a PDE5 inhibitor
Cardiovascular disease	Possible endothelial dysfunction in penile vasculature	Use of a PDE5 inhibitor with caution; contraindication with nitrate use
Tobacco smoking	Possible endothelial dysfunction, associated atherosclerosis, and sympathetic overactivity	Smoking cessation
Central neurologic conditions†	Disruption of descending neural control of proerectile processes	Medical treatment
Spinal cord injury	Dependent on the extent and location of the spinal lesion; nonsustained reflex erections commonly maintained	Use of a PDE5 inhibitor (depending on the level of injury)
Depression or social or marital stress	Unknown	Counseling, lifestyle change (e.g., weight loss, exercise), medical treatment
Endocrinologic conditions‡	Disruption of testosterone-mediated up-regulation of nitric oxide synthase; low testosterone levels from hyperprolactinemia-influenced changes in the hypothalamic–pituitary axis	Correction of underlying endocrine disorder; possible use of a PDE5 inhibitor
Diabetes mellitus	Vasculopathy from endothelial dysfunction and autonomic neuropathy	Appropriate glycemic therapy

* PDE5 denotes phosphodiesterase type 5.
† Neurologic conditions include Parkinson's disease, hemorrhagic or ischemic stroke, tumors, Alzheimer's disease, the Shy–Drager syndrome, and encephalitis.
‡ Endocrinologic conditions include hypogonadism, hypothyroidism, hyperthyroidism, and hyperprolactinemia.

obvious causes suggests a possible social or psychological cause.

Both the patient and his sexual partner should be interviewed regarding the sexual history. Erectile dysfunction should be distinguished from other sexual problems, such as premature ejaculation. Factors such as sexual orientation, the degree to which the patient is bothered by erectile dysfunction, performance anxiety, and details regarding sexual technique should be addressed. Standardized questionnaires are available to assess erectile dysfunction, including the International Index of Erectile Function and its validated and more easily administered abridged version, the Sexual Health Inventory for Men[13] (see Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). The five items on the latter inventory were selected in order to identify the presence or absence of erectile dysfunction and for consistency with the National Institute of Health's definition of the disorder.

On physical examination, signs of hypogonadism (including small testes, gynecomastia, and reduced growth of body hair and beard) warrant attention.[14,15] In addition, a digital rectal examination and an assessment of anal sphincter tone and bulbocavernous reflex (the contraction of the bulbocavernous muscle on the perineum after compression of the glans penis) are recommended to assess the integrity of the sacral neural outflow. Peripheral pulses should be palpated for signs of vascular disease.

Practice guidelines recommend the measurement of a morning serum testosterone level for men with erectile dysfunction,[1,14] although it should be recognized that the threshold level of testosterone for maintaining an erection is unknown and may depend on other factors (e.g., the level of luteinizing hormone).[14,15] An unequivocally low testosterone level warrants a repeat measurement of free or bioavailable testosterone, as well as the measurement of prolactin and luteinizing hormone. Measurements of glucose and

Table 2. Drugs Associated with Erectile Dysfunction.

Drug Class	Examples
Diuretics	Thiazides, spironolactone
Antihypertensive drugs	Calcium-channel blockers, beta-blockers, methyldopa, clonidine, reserpine, guanethidine
Cardiac or cholesterol drugs	Digoxin, gemfibrozil, clofibrate
Antidepressants	Selective serotonin-reuptake inhibitors, tricyclic antidepressants, lithium, monoamine oxidase inhibitors
Tranquilizers	Butyrophenones, phenothiazines
H_2 antagonists	Ranitidine, cimetidine
Hormones	Progesterone, estrogens, corticosteroids, luteinizing hormone–releasing hormone agonists, 5α-reductase inhibitors, cyproterone acetate
Cytotoxic agents	Methotrexate
Immunomodulators	Interferon-α
Anticholinergic agents	Disopyramide, anticonvulsants
Recreational drugs	Alcohol, cocaine

lipid levels, a complete blood count, and renal-function tests are also recommended on the basis of expert consensus.[16] Vascular assessments based on penile injection of prostaglandin E_1, duplex ultrasonography, biothesiometry, or nocturnal penile tumescence are not recommended in routine practice but can be helpful whenever information regarding the vascular supply is needed — for example, in the choice of surgical treatment (implantation of a prosthesis vs. penile reconstruction).[16]

TREATMENT

Therapies currently used for the treatment of erectile dysfunction include oral therapy with a phosphodiesterase type 5 inhibitor (the most commonly used therapy), injection therapies, testosterone therapy, penile devices, and psychotherapy. In addition, limited data suggest that the treatment of underlying risk factors and coexisting illnesses — for example, with weight loss, exercise, stress reduction, and smoking cessation — may improve erectile function.[17] Decisions regarding therapy should take into account the preferences and expectations of patients and their partners.

Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase type 5 inhibitors are considered to be the first-line therapy for the treatment of erectile dysfunction. These agents improve erectile function by increasing penile cyclic guanosine monophosphate (cGMP), resulting in relaxation of smooth-muscle cells (Fig. 2).

Several randomized trials have demonstrated the efficacy of this class of medications. A meta-analysis of 14 randomized trials involving 2283 men showed that treatment with sildenafil (at all doses tested) significantly increased the proportion of patients who had at least one episode of intercourse (83%), as compared with placebo (45%), with a risk ratio of 1.8 in the placebo group (95% confidence interval, 1.7 to 1.9).[18] Another randomized trial showed that treatment with sildenafil (at a dose of 100 mg) increased the proportion of men who had a successful episode of intercourse, as compared with placebo (51% vs. 30%, $P<0.05$).[19]

There are no compelling data to support the superiority of one phosphodiesterase type 5 inhibitor over another.[16] Comparisons of efficacy among various agents in this class are limited because of the exclusion of patients who did not have a response to sildenafil in studies of tadalafil and vardenafil and because of differences among study subjects in such factors as smoking status, baseline erectile function, race, and age. In a meta-analysis of 11 randomized trials involving 2102 men, tadalafil (at a dose of 10 or 20 mg) led to significant improvement in erectile function (as assessed with the International Index of Erectile Function) and significant increases in the proportion of sexual attempts leading to successful intercourse (34% with 10 mg of tadalafil, 46% with 20 mg of tadalafil, and 8% with placebo; $P<0.001$ for all comparisons).[20] Similar improvement in erectile function was reported in a meta-analysis of randomized trials of vardenafil (at doses of 5 mg, 10 mg, and 20 mg).[21]

Patients may not have a response to a phosphodiesterase type 5 inhibitor for several reasons. Figure 3 reviews potential reasons for failure of these medications, as well as common adverse events. Some patients may not be able to tolerate phosphodiesterase type 5 inhibitors because of adverse events related to vasodilatation in nonpenile tissues expressing phosphodiesterase type 5 or from the inhibition of homologous nonpenile isozymes (i.e., phosphodiesterase type 6 in the retina). Abnormal vision that is attributed to the effects of phosphodiesterase type 5 inhibitors on retinal phosphodiesterase type 6, reported only

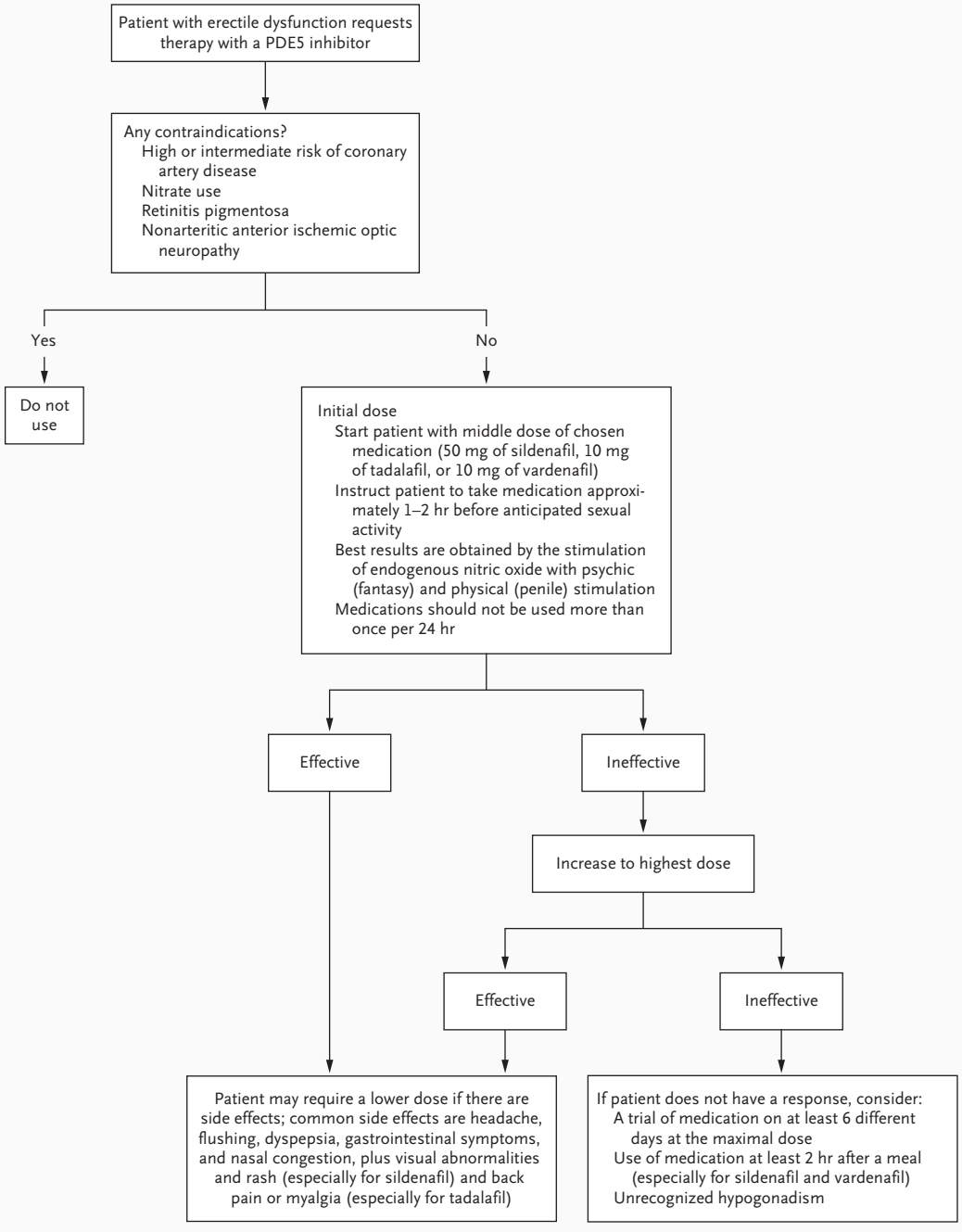


Figure 3. Algorithm for the Use of Oral Phosphodiesterase Type 5 (PDE5) Inhibitors.
Data are adapted from Montague et al.[16]

with sildenafil, is of short duration and is not thought to be of clinical significance. A more serious concern is the possibility that phosphodiesterase type 5 inhibitors may cause nonarteritic anterior ischemic optic neuropathy; although data in support of such an association are limited, it is prudent to avoid the use of these agents in men with a history of this condition.[22] Patients who are receiving phosphodiesterase type 5 inhibitors should be informed about the low risk

of changes in visual acuity. If such changes occur, patients should be referred to an ophthalmologist. Changes in visual acuity should not be confused with the harmless "blue haze" caused by the above-mentioned inhibition of phosphodiesterase type 6 in the retina.

A related concern, especially given the frequent coexistence of erectile dysfunction and coronary artery disease, is the possibility that treatment with a phosphodiesterase type 5 inhibitor might precipitate coronary ischemia. Treating erectile dysfunction, whatever approach is used, may slightly increase the risk of myocardial infarction simply because of a modest increase in physical exertion during intercourse (3 to 4 metabolic equivalents) and the associated increase in sympathetic activity with attendant increases in blood pressure and heart rate.[23] The absolute risk of myocardial infarction during intercourse is estimated at 20 chances per million per hour in patients with ischemic heart disease. Nonetheless, it is prudent to evaluate a patient's cardiovascular status before initiating treatment.[24,25] Since the use of phosphodiesterase type 5 inhibitors concurrently with nitrates may induce hypotension, this combination is strictly contraindicated. Additional recommendations for managing erectile dysfunction in patients with coronary artery disease are summarized in Table 3.[23,26]

Injection Therapies

The intracavernous or transurethral injection of vasoactive medications may also be used to treat erectile dysfunction. Alprostadil is a stable form of prostaglandin E_1 that increases the concentration of cyclic adenosine monophosphate (cAMP) and decreases the intracellular calcium concentration, resulting in relaxation of smooth-muscle cells (Fig. 1B). In randomized trials, as compared with placebo, intracavernous injection of alprostadil increased the proportion of men with "full rigidity,"[27] as well as the proportion of men with erections (50% vs. none in the placebo group; P<0.001).[28] In a meta-analysis of four trials, the efficacy of intracavernous injections of alprostadil was more than 70%.[29] Trimix, a combination of prostaglandin E_1 phentolamine (an α_1-adrenergic antagonist) and papaverine (a nonspecific phosphodiesterase inhibitor), has been used for injection therapy when prostaglandin E_1 alone failed to induce an adequate erection; the rate of response to this combined therapy was approximately 90%.[30]

The transurethral delivery of alprostadil by means of suppositories, an approach known as medicated urethral system for erection (MUSE), is a second-line method of penile injection in which the drug is absorbed through the urethral mucosa and into the corpus cavernosum. A systematic review of MUSE therapy in three randomized trials involving 1828 men showed that transurethral delivery of alprostadil significantly increased the proportion of men with at least one successful episode of intercourse, as compared with placebo (65% vs. 18%, P<0.001).[29] This treatment was reported to be effective in up to 43% of men with erectile dysfunction who did not have a response to sildenafil.[31]

Because there is a small risk of priapism with intracavernous injection therapy (1%) or of technical problems associated with self-injection, it is generally recommended that the first dose be administered under the supervision of a health care provider. Penile ache has been reported with both intracavernous and transurethral injections (incidence, 5%), and leg ache or a burning sensation in the urethra has been reported with MUSE. Penile fibrosis is a rare complication of both therapies. Contraindications to such therapies include a history of priapism, sickle cell disease or trait, multiple myeloma, and thrombocytopenia; for MUSE specifically, contraindications are urethral stricture and urethritis.

Testosterone Therapy

Despite the uncertainties associated with the diagnosis and clinical implications of a low testosterone level, testosterone-replacement therapy is commonly recommended for men with erectile dysfunction in whom a low bioavailable testosterone level has been confirmed.[14,16] In a meta-analysis of 16 studies, improvement in erectile dysfunction was significantly more common in men with hypogonadism who were treated with testosterone than in those who received placebo (57.0% vs. 16.7%).[32] In nine studies that included data on the cause of erectile dysfunction, the response rate was significantly higher among men with primary testicular failure (64%) than among those with a secondary cause of erectile dysfunction (44%). Transdermal testosterone therapy resulted in significantly higher response rates than did either intramuscular or oral administration (80.9%, 51.3%, and 53.2%, respectively).

Men who receive testosterone should be reevaluated after 1 to 3 months and at least annu-

ally thereafter for testosterone levels, erectile function, and adverse effects, which may include gynecomastia, sleep apnea, development or exacerbation of lower urinary tract symptoms due to benign prostatic hyperplasia, prostate cancer, reduced levels of high-density lipoprotein cholesterol, erythrocytosis, elevations in liver enzyme levels, and reduced fertility.[4,15] Periodic reevaluation should include a complete blood count and measurement of prostate-specific antigen, as well as a digital rectal examination.[33] Therapy should be discontinued in patients who do not have a response within 3 months.

Penile Devices

Penile devices may be considered in men who do not have a response to the above-mentioned therapies or who have contraindications to either drug or injection therapies. Such devices have not been studied in randomized trials, and data to evaluate results are derived largely from case series.

Vacuum erection devices induce penile rigidity by means of a vacuum, which traps blood in the penis with an elastic band placed around its base. Data from small series suggest that approximately 35% of men are satisfied with the results of such devices.[34]

More commonly used is a penile prosthetic device, which is surgically implanted into the penis. There are two general types of prostheses: malleable and inflatable. The choice of prosthesis is dependent on the preference of the patient and should take into account the patient's body habitus and manual dexterity, which may have an effect on the ability to manipulate the device. Owing to the permanence of prosthetic devices, patients should be advised first to consider less invasive options for treatment. Limited evidence suggests that many patients and their partners are highly satisfied with this approach.[35]

Psychotherapy

Psychosexual therapy involves such techniques as sensate focus (nongenital massage), sensory-awareness exercises, correction of misconceptions regarding sexuality, and therapy for interpersonal difficulties (e.g., open communication about sexual issues, scheduling of physical intimacy, and behavioral interventions). These approaches may be useful for patients in whom erectile dysfunction has psychogenic or social components, although data from randomized trials are scant and inconsistent. For example, one small, randomized, controlled trial showed that counseling had no significant effect on the percentage of patients who had successful intercourse,[36] whereas in another randomized trial, counseling was associated with a significant improvement in sexual functioning, satisfaction with sexual life, and social skills.[37]

Table 3. Princeton Guidelines for the Treatment of Erectile Dysfunction in Men with Coronary Artery Disease.*

Risk Level	Treatment Recommendation
Low — Asymptomatic coronary artery disease and <3 of the following risk factors: controlled hypertension, mild stable angina, successful coronary revascularization, previous uncomplicated myocardial infarction, mild valvular disease, and congestive heart failure (left ventricular dysfunction with or without NYHA class I)	Possible use of a PDE5 inhibitor
Indeterminate — Coronary artery disease and ≥3 of the following risk factors: moderate angina, recent myocardial infarction (>2 wk but <6 wk), left ventricular dysfunction or congestive heart failure (NYHA class II), and noncardiac sequelae of atherosclerotic disease such as cerebrovascular accident or premature ventricular depolarization	Further evaluation by a cardiologist
High — Unstable angina and any of the following risk factors: uncontrolled hypertension, congestive heart failure (NYHA class III or IV), very recent myocardial infarction (<2 wk), high-risk arrhythmias, hypertrophic obstructive or other cardiomyopathy, and moderate-to-severe valvular disease	No treatment until cardiac status is stabilized

* According to the consensus-panel guidelines, the patients' cardiovascular risk factors and previous history of cardiovascular disease are used to assign risk levels and guide therapy. PDE5 denotes phosphodiesterase type 5, and NYHA New York Heart Association. Data are adapted from Jackson et al.[23]

GUIDELINES

Treatment recommendations for erectile dysfunction have been published by guideline committees of the American Urological Association[16,38] and the Endocrine Society; the latter has also published recommendations for the use of testosterone therapy.[14,15] The recommendations in this review are consistent with these guidelines.

AREAS OF UNCERTAINTY

The pathophysiology of erectile dysfunction remains incompletely understood. Drugs affecting a variety of signaling pathways that are involved in erectile dysfunction (e.g., Rho kinase inhibitors, guanylyl cyclase agonists, and phosphodiesterase

type 5 inhibitors with an increased onset of action) are currently being developed. Novel delivery methods, such as gene therapy to alter the relaxability of penile smooth muscles by up-regulating the maxi-K channel (a potassium-ion channel), are being investigated in phase 1 clinical trials.

SUMMARY AND RECOMMENDATIONS

Erectile dysfunction should be evaluated by taking a careful medical history (with attention to cardiovascular disease, diabetes or other features of the metabolic syndrome, manifestations of hypogonadism, previous pelvic surgery or trauma, and medications) and physical examination, looking for evidence of underlying disorders such as hypogonadism and vascular disease. Limited laboratory testing is recommended, including the measurement of testosterone, glucose, and lipid levels. Switching from a medication that is associated with erectile dysfunction to an alternative that is not should be considered. In the case in the vignette, for example, the beta-blocker might be changed to an angiotensin-converting–enzyme inhibitor in order to assess whether the patient's symptoms would improve in the absence of the beta-blocker. In addition, weight loss and exercise should be recommended, and smokers should be counseled to discontinue.

The selection of specific treatments should involve both the patient and his partner. In the absence of contraindications to the use of phosphodiesterase type 5 inhibitors (e.g., the use of nitrates or a history of priapism), these agents are generally prescribed as first-line therapy. Injection and device therapies should be reserved for patients who do not have a response to phosphodiesterase type 5 inhibitors or in whom these drugs are contraindicated or poorly tolerated (i.e., about a third of men who receive such drugs). Psychosexual counseling may be helpful in cases of erectile dysfunction with psychogenic or social components.

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