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Management of Erectile Dysfunction: Focus on Levitra and Cialis

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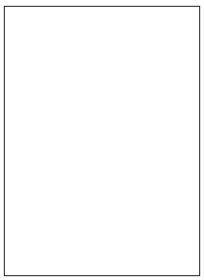
Goals. The goals of this lesson are to provide background information on erectile dysfunction and review the newest drugs, Levitra (vardenafil) and Cialis (tadalafil), approved for its treatment.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. explain the etiology and incidence of erectile dysfunction;
2. identify factors associated with its onset;
3. identify the pharmacologic classification and therapeutic considerations for the drugs discussed; and
4. select from a list, the indications, mechanism of action, adverse effects and toxicities, drug interactions, and benefits and limitations of the drugs presented.

Once a taboo topic for public discussion, the subject of erectile dysfunction (ED) is now commonplace. With two new drugs, Levitra (vardenafil) and Cialis (tadalafil), approved in 2003 to treat ED, pharmacists are likely to be included in these discussions. Erectile dysfunction is the most common male sexual dysfunction, and the leading complaint of males attending sex therapy clinics.



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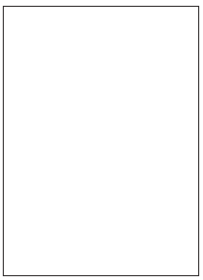

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Anatomy of the Human Penis

The penis is a highly vascular organ that consists of two parallel cylinders of erectile tissue located throughout the length of the penile shaft, the corpus cavernosum. A smaller cylinder, the corpus spongiosum, surrounds the urethra to form the glans penis at its terminus.

Blood supply into the penile tissues is provided by the paired cavernosal branches of the internal pudendal artery that divides into numerous terminal branches that open directly into the cavernous spaces.

Both autonomic and somatic nerves innervate the penis. Sympathetic and parasympathetic fibers of the autonomic system join in the pelvis to form the cavernous nerves that innervate the corpus cavernosum, corpus spongiosum, and glans penis to regulate blood flow during erection and detumescence (subsidence of swelling; i.e., moving toward flaccidity). Somatic fibers (the pudendal nerve) are responsible for penile sensation, and contraction and relaxation of the extracorporeal striated muscles.

Physiology of Erection

Penile erection requires a number of complex neuropsychological, hormone-mediated, and vascular interactions. When the penis is flaccid, blood flow into and out of the erectile bodies is in balance. Sympathetic activity via alpha-2-adrenergic receptors maintains contraction of both the penile arterial and cavernosal smooth muscles, which preserves high penile arterial resistance and flaccidity.

Upon arousal, parasympathetic activity initiates a series of biochemical actions beginning with increased formation and liberation of nitric oxide (NO), vasoactive polypeptide, and prostaglandin E_1. Nitric oxide, originally referred to as endothelium-derived relaxing factor, is a potent vasodilator released from endothelial cells that line blood vessels. Nitric oxide is believed to be the most important neurotransmitter in the erectile process. Its action promotes formation of cyclic guanosine monophosphate (cGMP), which in turn depletes intracellular calcium that leads to smooth muscle relaxation with erection.

Neuronal activity decreases following orgasm. The enzyme phosphodiesterase-5 (PDE-5) breaks down cGMP. Nitric oxide release is terminated and generation of cGMP within the cells ceases. By reducing intracellular levels of cGMP, PDE-5 therefore, inhibits vasodilation of the penile vasculature. Detumescence begins. Blood flow into the penis returns to baseline, and blood drains from the erectile tissues because the venous plexus of the

penis is no longer compressed. Erection is lost and the penis returns to its flaccid state.

Erectile Dysfunction

Erectile dysfunction is defined as the persistent inability to attain or maintain penile erection adequate for sexual intercourse. The term replaces the older descriptor *impotence* since the latter term often led to confusing and uninterpretable results in both clinical and basic science investigations. ED is a symptom complex which is frequently multifactorial in etiology.

Erectile dysfunction affects an estimated 152 million men worldwide, with 25 million or more in the U.S. There is a higher prevalence of complete ED in men with concomitant illnesses.

Psychogenic vs. Organic Origin. Erectile dysfunction can be classed broadly into two categories by etiology: psychogenic (functional) and organic (physical). Evidence suggests that approximately 80 percent of cases are organic in nature, caused by physiological conditions, including cardiovascular disease and diabetes mellitus. Both psychogenic and organic factors may contribute to the condition. For example, after experiencing a myocardial infarction, patients may be apprehensive about performing sexual activity. In this case, cardiovascular disease (i.e., organic cause) initiated the ED which was worsened by apprehension (i.e., psychogenic cause).

Psychogenic ED (e.g., "performance anxiety") is usually episodic. The classical presentation is described by ED of sudden onset, often preceded by extreme stress.

Erectile dysfunction of organic origin is characterized by gradual onset of deterioration of rigidity and decreased frequency of erection. Men may no longer be able to achieve erection through fantasizing or masturbation. Attempts at intercourse are often unsuccessful during periods of fatigue or stress. Libido is often normal, but diminishes with any kind of ED.

Organic causes may be of vascular, neurologic or hormonal etiology. Vascular causes are most common with disorders of the arterial vasculature supply rather than venous outflow being at cause. Regardless, a psychogenic component frequently coexists to compound accurate diagnosis and assessment of the patient's condition. Descriptors including mild, moderate, or complete are often applied to ED, even though they are highly subjective and cannot be defined precisely.

Conditions Associated with Erectile Dysfunction

Conditions (i.e., risk factors) associated with ED are summarized broadly in Table 1. Aging is the most important independent factor. Young men are often capable of achieving erection within seconds simply by fantasizing. By age 40 or 50, this becomes increasingly difficult. Although the incidence of ED increases steadily with age, ED should not be considered an inevitable consequence of growing older. Many men well into their 80s and beyond report experiencing rigid erections and a healthy sex life.

Smoking almost doubles the probability of developing moderate to complete ED. Chronic alcoholism may affect erectile ability adversely through altered hormone metabolism and polyneuropathy. Medical disorders associated with ED include those that impair arterial blood supply to the erectile tissues or disrupt the neuronal circuitry. Patients with diabetes mellitus and/or cardiovascular disease, for example, experience high rates of ED.

Drugs that interfere with central neuroendocrine or local neurovascular control of penile smooth muscle have the potential to cause iatrogenic (i.e., treatment-related) ED (Table 2). The precise mechanism(s) for this adverse action for most causative agents is unknown even for those drugs reported to cause ED to greatest extent.

Table 1
Conditions Associated With Erectile Dysfunction

Aging/Lifestyle
cigarette smoking
chronic alcohol abuse
drug abuse
Chronic Disease
diabetes mellitus
heart disease
hypertension
lipid disorders/atherosclerosis
renal failure
liver disease
sickle cell anemia
idiopathic hemochromatosis
chronic obstructive pulmonary disease
leukemia
scleroderma
Endocrine Abnormalities
hypogonadism
hyperprolactinemia
hypothyroidism/hyperthyroidism
Neurogenic Causes
Alzheimer's disease
cerebrovascular accidents
epilepsy
head trauma/surgery
spinal cord trauma/surgery
multiple sclerosis
herniated disc
retroperitoneal lymph node dissection
Penile Injury/Disease
Peyronie's disease
priapism
anatomic abnormalities
Psychologic Issues
depression
widower's syndrome
anxiety
social stressors
performance anxiety
Trauma/Injury
pelvic or perineal trauma/surgery
pelvic radiation
prostate surgery
Nutritional
protein malnutrition
zinc deficiency
Infection
AIDS
brucellosis
trypanosomiasis
tuberculosis
Drugs
see table 2

Vardenafil and Tadalafil

Levitra (vardenafil) and Cialis (tadalafil), like Viagra (sildenafil),

are selective inhibitors of PDE-5 which inactivates cGMP. With release of NO into the penile smooth muscle following sexual stimulation, inhibiting PDE-5 enhances the activity of cGMP concentrations in the glans penis, corpus cavernosum, and corpus spongiosum. This promotes NO-induced smooth muscle relaxation, engorgement with blood, and firm erection. Because sexual stimulation is required to initiate the local release of NO, the inhibition of PDE-5 has no effect in the absence of sexual stimulation.

Clinical Trials. In one clinical trial with vardenafil, 762 men (mean age 57, range 20-83 years) were evaluated. There was significant improvement at three months with the drug improving the rates of achieving an erection sufficient for penetration at doses of 5 mg, 10 mg, and 20 mg (65 percent, 75 percent, and 80 percent, respectively) vs. 52 percent response for placebo. Men taking vardenafil were able to achieve and maintain an erection sufficient to complete successful intercourse (51 percent on 5 mg, 64 percent on 10 mg, and 65 percent on 20 mg doses, respectively, compared to 32 percent with placebo).

Several studies were conducted with tadalafil with the objective of determining the optimal use of tadalafil in the treatment of ED. In one clinical study, the percentage of patients achieving successful erections within 30 minutes of dosing was determined. Two hundred twenty-three patients were randomized to tadalafil 10 mg or 20 mg, or to placebo. Using a stopwatch, patients recorded the time following dosing at which a successful erection was obtained. A successful erection was defined as at least one erection in four attempts that led to successful intercourse. At or prior to 30 minutes, 38 percent and 52 percent of patients in the tadalafil 10 mg and 20 mg groups, vs. 35 percent of patients with placebo, reported successful erections as defined above.

Adverse Effects. Vardenafil was administered to over 4430 men (mean age 56, range 18-89 years) during controlled and uncontrolled clinical trials worldwide. More than 2200 men received the drug for six months or longer, and 880 patients were treated for at least one year. When vardenafil was taken as recommended, the following adverse events were reported by ≥2 percent of patients treated with the drug and more frequently on drug than placebo: headache, flushing, rhinitis, dyspepsia, sinusitis, flu syndrome, dizziness, increased creatine kinase, and nausea. The discontinuation rate due to adverse events was 3.4 percent for vardenafil compared to 1.1 percent for placebo.

Tadalafil was administered to over 5700 men (mean age 59, range 19-87 years) during clinical trials worldwide. Over 1000 received the drug for a year or longer; over 1300 were treated for ≥six months. When tadalafil was taken as recommended, the following adverse events were reported in ≥2 percent of patients treated with 10 or 20 mg tadalafil and more frequently on drug than placebo: headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and limb pain. In Phase 3 clinical trials, the discontinuation rate due to adverse effects in patients treated with tadalafil was 3.1 percent, compared to 1.4 percent in placebo-treated patients.

Rare events of erections greater than four hours and priapism (painful erections lasting longer than six hours) are reported for PDE-5 inhibitors, including Levitra and Cialis. The patient should seek immediate medical assistance in the event that an erection persists longer than four hours. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

Phosphodiesterase inhibitors have caused rare instances of dose-related changes in color discrimination such as seeing a blue tinge or having difficulty differentiating between blue and green. A single study involving 25 men who received 40 mg doses of Levitra, and a single study involving 59 men who received 40 mg doses of Cialis, failed to show altered visual acuity.

Drug Interactions. Administration of Levitra or Cialis with nitrates (dosed regularly and/or intermittently) is contraindicated.

Table 2
Representative Drugs Associated with Erectile Dysfunction

Diuretics
thiazides
spironolactone
Antihypertensives
methyldopa
clonidine
reserpine
beta-adrenergic blockers
guanethidine
verapamil
Cardiac
clofibrate
gemfibrozil
digoxin
Tranquilizers
phenothiazines
butyrophenones
barbiturates
Antidepressants
tricyclic antidepressants and other antidepressants
MAO inhibitors
lithium
H_2-receptor antagonists
cimetidine
ranitidine
Hormones
estrogens
progesterone
corticosteroids
gonadotropin-releasing hormone agonists
Cytotoxic Agents
cyclophosphamide
methotrexate
Miscellaneous
disopyramide
anticonvulsants
ketoconazole
metoclopramide
roferon-A
baclofen
carbonic anhydrase inhibitors
NSAIDs
amphetamines
opiates
finasteride

Phosphodiesterase inhibitors may potentiate their hypotensive effects including rapid heart rate.

The drugs are also contraindicated in patients taking alpha-adrenergic receptor antagonists since co-administration can produce hypotension. There is a single exception – administration of Cialis (but not Levitra) is approved for concomitant administration in patients taking 0.4 mg once-daily doses of tamsulosin (Flomax).

Ritonavir (Norvir) and indinavir (Crixivan) – both strong inhibitors of CYP3A4 – increase plasma concentrations of Levitra. To reduce the chance of an adverse reaction in patients taking Norvir or Crixivan, a maximum single dose of 2.5 mg Levitra should not be exceeded. Dosing should be limited to a single 2.5 mg dose of Levitra taken in a 72-hour period by patients also taking Norvir. Men taking Crixivan, ketoconazole 400 mg daily, or itraconazole (Sporanox) 400 mg daily should not exceed doses of Levitra greater than 2.5 mg once daily. For patients taking erythromycin, ketoconazole or itraconazole 200 mg daily, a single dose of 5 mg Levitra should not be exceeded in a 24-hour period.

Ketoconazole (400 mg daily) increases Cialis 20-mg single-dose exposure (AUC) by 312 percent and C_{max} by 22 percent, compared to the values for Cialis 20 mg alone. Norvir (200 mg twice daily) increases Cialis 20 mg single-dose exposure (AUC) by 124 percent with no change in C_{max}, compared to the values for Cialis 20 mg alone. Based upon these results, in patients taking concomitant potent CYP3A4 inhibitors, the dose of Cialis should not exceed 10 mg, and should not be taken more frequently than once every 72 hours.

Dosage and Administration. The recommended starting dose of Levitra for most patients is 10 mg, taken orally approximately 60 minutes before sexual activity. The usual dosage spans the range of 5 mg to 20 mg based on efficacy and side effects. A lower dose, 2.5 mg, may be appropriate for patients taking other drugs that interact with Levitra. A starting dose of 5 mg Levitra is recommended for patients ≥65 years of age. The recommended dosing frequency is one dose per day. Levitra can be taken with or without food.

No dose adjustment is required for patients with mild hepatic impairment. A starting dose of 5 mg is recommended for patients with moderate hepatic impairment, with maximum dose up to 10 mg. Levitra has not been evaluated in patients with severe hepatic impairment. No dose adjustment is required for patients with mild, moderate, or severe renal impairment. Levitra has not been evaluated in patients on renal dialysis.

The cardiovascular status of patients should be assessed before starting on Levitra. It is not recommended for men who have suffered a myocardial infarction or stroke within the past six months, or persons with significant hypotension or uncontrolled hypertension, unstable angina, severe liver impairment, end-stage renal disease requiring dialysis, or retinitis pigmentosa, a hereditary, degenerative retinal disorder. The drug should be used cautiously in patients with anatomical deformity of the penis, such as Peyronie's disease, and men predisposed to priapism, such as in sickle cell anemia, multiple myeloma, or leukemia.

Levitra is available as orange, film-coated round tablets containing 2.5, 5, 10, or 20 mg vardenafil.

The recommended initial dose of Cialis in most patients is 10 mg, taken prior to anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients, taken without regard to food. While the FDA-approved dosage does not address when to take Cialis, the manufacturer's patient information leaflet states that in some men, improved sexual activity was apparent 30 minutes after taking a dose with erectile function improved up to 36 hours following dosing, compared to placebo.

For patients with mild or moderate hepatic impairment, the dose of Cialis should not exceed 10 mg once daily. The drug is not recommended in patients with severe hepatic impairment. No dose adjustment is required in patients with mild renal insufficiency. For patients with moderate renal insufficiency, a starting dose of 5 mg, not more than once daily, is recommended, and the maximum dose should be limited to 10 mg, not more than once every 48 hours. A maximum dose of 5 mg is recommended for patients with severe renal insufficiency on hemodialysis.

Until further information is available, Cialis is not recommended in patients with a myocardial infarction within the last 90 days, or patients with unstable angina or angina occurring during sexual intercourse. It is not recommended in persons with stroke or Class 2 or greater heart failure in the last six months, or patients with uncontrolled arrhythmias, hypotension, or uncontrolled hypertension. In addition, it is not recommended in patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa.

Cialis is supplied as yellow, film-coated almond-shaped tablets containing 5, 10, or 20 mg tadalafil.