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A review of men's health conditions and concerns

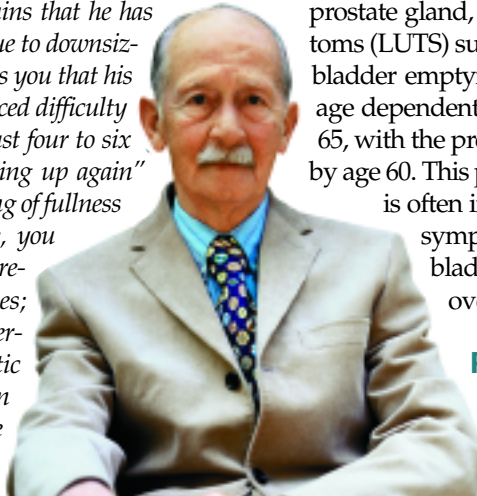
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A review of men's health conditions and concerns

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A 66-year-old Caucasian male, T.J., is a regular patient in your pharmacy with whom you have developed a trusting relationship. As he is here to pick up his monthly refills, T.J. explains that he has been under a tremendous amount of stress at work due to downsizing of his company. Upon further questioning, he tells you that his marriage has been "bumpy lately" as he has experienced difficulty achieving and maintaining erections for about the past four to six months. In addition, he believes his "prostate is acting up again" and reports nocturia, hesitancy, straining, and a feeling of fullness after voiding. As you glance at his patient profile, you notice he is taking aspirin for cardiovascular disease prevention; metformin and glipizide for diabetes; hydrochlorothiazide, ramipril, and atenolol for hypertension; tamsulosin (Flomax) for benign prostatic hyperplasia (BPH); and gemfibrozil and atorvastatin (Lipitor) for dyslipidemia. He thinks he needs to see his physician but wants your opinion first. What recommendations would you have for T.J.?



BENIGN PROSTATIC HYPERPLASIA

BPH is a benign neoplasm of the epithelial and stromal tissues of the prostate gland, which is often accompanied by lower urinary tract symptoms (LUTS) such as urinary frequency, urgency, weak stream, incomplete bladder emptying, and nocturia. Histological changes in the prostate are age dependent. In fact, the incidence of BPH peaks between ages 63 and 65, with the prevalence of histologically diagnosed BPH greater than 50% by age 60. This prevalence increases to 90% by age 85. Patient quality of life is often impacted by the presence of embarrassing and bothersome symptoms. If untreated, BPH can lead to the development of bladder stones, chronic kidney and bladder infections, and overflow incontinence.

Prostate gland tissue and pathophysiology

An understanding of normal prostate physiology is essential to understanding mechanisms surrounding the development of BPH. A normal prostate gland is heart-shaped and about the size of a walnut. It is locat-

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GOAL

To increase the pharmacist's and technician's familiarity with the clinical presentation, diagnosis, and treatments involved in the management of benign prostatic hyperplasia and erectile dysfunction

CREDIT

This lesson provides two hours of CE credit and requires a passing grade of 70%.*

OBJECTIVES

Upon completion of this article, the pharmacist and technician should be able to:

- ✓ Describe the epidemiology and pathophysiology of benign prostatic hyperplasia (BPH) and erectile dysfunction (ED)
- ✓ Discuss the risk factors and the clinical presentations of BPH and ED
- ✓ Explain anticipated physical examination and laboratory findings in a given patient with BPH and/or ED
- ✓ Counsel a patient receiving treatment for BPH and/or ED regarding administration, adverse effects, drug-drug interactions, and monitoring parameters
- ✓ Provide nonpharmacologic and pharmacologic recommendations for a patient with BPH and/or ED

*To receive credit you must score 70% or higher on the quiz and complete the evaluation. Upon successful completion, the University of Florida College of Pharmacy will mail Statements of Credit for written quizzes within 10 working days. Participants completing the program on-line may print a Statement of Credit after successfully completing the program.

ed below the bladder and surrounds the urethra, a structure that serves as a conduit for urine outflow from the body. The prostate gland is responsible for secreting components of semen, allowing the sperm to move freely. In addition, the prostate gland produces zinc-containing secretions with antibacterial effects to protect the urinary and reproductive tracts from pathogenic microorganisms.

Within the prostate, there are three types of prostate tissue: epithelial, stromal, and the capsule. Epithelial tissue, which is stimulated by androgens, is predominantly responsible for producing prostatic secretions and thereby contributes to the seminal fluid volume. Stromal tissue contains alpha-1 adrenergic receptors. When those receptors are stimulated by norepinephrine, smooth muscle contraction in the prostate gland leads to compression of the urethra and a reduction in bladder emptying. Once the urethra is compressed, urine outflow becomes difficult, often leading to the development of LUTS. Normally, the stromal to epithelial tissue ratio is 2:1; however, this ratio is as high as 5:1 in BPH patients. The capsule contains connective tissue and smooth muscle as well as alpha-1 adrenergic receptors.

The prostate gland undergoes two growth spurts throughout the male life cycle. At birth, the prostate is pea-sized and weighs approximately 1 gm. It slowly continues to grow until puberty, when there is an increase in the amount of endogenous testosterone and conversion to its active and very potent metabolite known as dihydrotestosterone (DHT) through the enzyme 5-alpha-reductase. Increased levels of DHT enhance the growth and development of the prostate gland, allowing it to mature to its normal adult size of approximately 20 gm. The size of the prostate is maintained through a balance of cell death and growth until the male reaches his 40s. At this time, a second growth spurt occurs, in which the prostate gland may double or triple in size.

Clinical presentation of BPH

Most men begin experiencing LUTS during the sixth decade of life, though some symptoms may be present as early as the fourth decade. It

is important to note prostate size does not necessarily correlate with symptom severity or degree of obstruction. Some men with very large prostates may experience very few symptoms, while other men with prostate glands that are not as enlarged may report significant bothersome symptoms. The signs and symptoms of BPH are believed to be caused by anatomical enlargement of the prostate gland, often referred to as *static factors*, and alpha-adrenergic-mediated muscle contractions referred to as *dynamic factors*.

The LUTS associated with BPH are often divided into obstructive and irritative symptoms. *Obstructive symptoms* result from reduced bladder emptying. Examples include urinary hesitancy, weak urine stream, straining, dribbling, and incomplete bladder emptying. *Irritative symptoms* typically occur with continuous bladder neck obstruction and include urinary frequency, urgency, nocturia, and enuresis. Because of long-standing obstruction and decreased emptying of the bladder, the detrusor muscle of the bladder hypertrophies in an attempt to compensate for the inability to expel urine efficiently.

Initially, this compensatory mechanism is beneficial, as the muscle is able to generate a contractile force to push urine past the obstruction; however, the hypertrophic detrusor muscle eventually decompensates and is unable to contract properly. As a result, urine stasis in the bladder continues to initiate the bladder-emptying response and leads to the irritative LUTS. With urine stasis, there is also an increased risk of infection. As BPH worsens, residual urine volumes may increase and can eventually lead to overflow incontinence.

Diagnosis of BPH

Several key components are essential to

ensure the correct diagnosis of BPH. A thorough assessment of symptoms and complete patient medical history will be important as part of the differential diagnosis. Conditions such as diabetes mellitus, heart failure, urinary tract infections, prostatitis, neurogenic bladder, and bladder cancer often have overlapping symptomology. The American Urological Association (AUA) recommends use of the AUA Symptom Index, which classifies patient symptoms as mild, moderate, or severe based on patient response to seven questions. This index is helpful in determining disease severity, response to treatment, and symptom progression in men not currently receiving pharmacotherapy (i.e., those under “watchful waiting”).

It is imperative that pharmacists obtain a complete medication history in order to determine the presence of agents that can cause LUTS. Medications with anticholinergic effects, such as antihistamines, tricyclic antidepressants (TCAs), and phenothiazines, reduce bladder contractility and can lead to urinary retention. This can be especially problematic for patients who have underlying difficulty urinating as a result of urethral compression. Testosterone replacement regimens used in the management of hypogonadism provide more substrate to be converted to the potent metabolite DHT. Alpha-adrenergic agonists such as pseudoephedrine, often used for the common cold and stress incontinence, result in smooth contractions through stimulation of the alpha-adrenergic receptors and worsening of BPH symptoms.

During a complete physical examination, patients with suspected BPH should undergo a digital rectal exam (DRE), which helps determine prostate size and assess for prostate cancer. As the posterior lobe of

Table 1

Pharmacotherapy regimens for BPH

Alpha-adrenergic antagonists

Alfuzosin (Uroxatral) 10 mg after the same meal each day
Doxazosin (Cardura) 1 mg at bedtime, up to 4-8 mg/day
Terazosin (Hytrin) 1 mg at bedtime, up to 2-10 mg/day
Tamsulosin (Flomax) 0.4 mg 30 minutes after the same meal each day, up to 0.8 mg/day if no response after two to four weeks of dosing

5-alpha reductase inhibitors

Dutasteride (Avodart) 0.5 mg daily
Finasteride (Proscar) 5 mg daily

the prostate gland is palpated during a DRE, tumors located in any other portion of the gland will likely not be detected. In order to definitively determine the size of the prostate gland, use of a transabdominal ultrasound is often employed.

Assessment of the prostate-specific antigen (PSA) level is often used as an indicator of prostate disorders. PSA is a glycoprotein produced and concentrated in the prostate gland. Large and inflamed prostate glands as well as malignant prostate tumors may secrete high levels of PSA. In addition, any disruption of the prostate gland, including a DRE, may increase PSA levels. Thus, this laboratory finding is not specific for BPH. Elevated levels may indicate BPH, prostatitis, or prostate cancer.

Because the prostate gland increases in size with age, PSA levels will increase as a reflection of this growth. When interpreting PSA levels, normal ranges are often age-adjusted to account for an age-dependent rise in PSA levels. In an effort to detect prostate cancer earlier, AUA recommends annual screening for prostate cancer beginning at age 50 and including both a PSA level and DRE. Men with a family history of prostate cancer or African-American men (who have a higher incidence of prostate cancer) may consider screening at age 45. However, it is important to note that even though BPH and prostate cancer may coexist, the presence of BPH does not increase the likelihood for developing prostate cancer.

Table 2

Medications associated with the development of ED

Type of drug	Examples
Antihypertensives	Beta-blockers, clonidine, guanethidine, methyl dopa, reserpine, thiazide diuretics
Antidepressants	Monoamine oxidase inhibitors, SSRIs, TCAs
Anticholinergics	Antihistamines, antiparkinsonian drugs, TCAs
Antipsychotics	Phenothiazines, risperidone
Hormonal agents	Luteinizing hormone-releasing hormone analogs, estrogens, anabolic steroids
Drugs of habituation or addiction	Alcohol, methadone, heroin, tobacco
Others	Allopurinol, amiodarone, carbamazepine, cholestyramine, cytotoxic agents, disulfiram, fibrates, omeprazole, phenytoin, statins, 5-alpha reductase inhibitors

AUA also recommends a neurologic examination in patients with suspected BPH to determine mental and ambulatory status as well as anal sphincter tone. Urinary flow rate and postvoid residual urine volume are considered optional evaluation tests to assess for urinary retention. In addition, a urinalysis by dipstick or microscopic examination is recommended to rule out urinary tract infections and to assess for hematuria. Routine assessment of the serum creatinine is no longer recommended by AUA, as the incidence of patients who develop renal insufficiency due to bladder obstruction is less than 1%.

Management options for BPH

Treatment goals for patients with BPH include reducing bothersome LUTS to improve quality of life and minimizing

disease progression. Options for the management of BPH include watchful waiting, pharmacotherapy, and surgical interventions. (Note: The latter option is beyond the scope of this article and will not be discussed.)

Watchful waiting: Watchful waiting is generally indicated for patients with a mild AUA symptom index score and those who are asymptomatic. This method involves no use of pharmacologic agents, as the adverse effects of the treatments often outweigh any potential benefits in these patients. During watchful waiting, patients may be educated regarding fluid restriction at bedtime to minimize nocturia and enuresis, the avoidance of caffeine and alcohol intake to reduce diuresis, scheduled toileting

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to minimize urinary leakage, and avoidance of exacerbating medications. Patients who are managed with watchful waiting typically undergo a thorough diagnostic workup every six to 12 months to assess disease progression.

Pharmacotherapy: Drugs used for the management of BPH exert effects through reducing static or dynamic factors. The 5-alpha reductase inhibitors interfere with testosterone's ability to stimulate the prostate gland, thereby minimizing the static factors associated with BPH. Alpha-adrenergic antagonists reduce the dynamic factors through relaxation of the smooth muscle in the prostate gland. Combination therapy involving an alpha-adrenergic antagonist and 5-alpha reductase inhibitor may be appropriate for patients with very large prostates (i.e., greater than 40 to 50 gm), elevated PSA levels, and bothersome LUTS.

BPH patients are typically initiated on a single agent, with an alpha-adrenergic antagonist frequently first line due to its quick onset of action, high efficacy rate, and minimal sexual adverse effects. Treatment with a 5-alpha reductase inhibitor may be an appropriate first-line agent in patients with prostate glands weighing more than 40 gm who are unable to tolerate the cardiovascular effects associated with alpha-adrenergic antagonists.

Alpha-adrenergic antagonists: Agents such as the alpha-adrenergic antagonists have been developed to reduce the excessive alpha-adrenergic tone of the prostate gland, thereby decreasing bothersome LUTS. In the late 1970s, phenoxybenzamine (Dibenzylamine), a nonselective alpha-1 and alpha-2 adrenergic antagonist, was found to be effective in reducing BPH symptoms. However, in a study involving 200 patients treated with phenoxybenzamine, 30% of patients experienced adverse effects and about 10% discontinued treatment due to side effects, mainly cardiovascular in nature.

Eventually, it was discovered that two subtypes of the alpha-receptors existed. Alpha-1 receptors are responsible for smooth muscle tone in the prostate, while alpha-2 receptor interactions

mediate the cardiovascular effects. This led to the development of second-generation selective alpha-1 adrenergic antagonists such as doxazosin, prazosin, and terazosin. However, these agents not only block alpha-1 receptors in the prostate gland but also in the peripheral vasculature. For this reason, these agents are commonly noted to cause first-dose syncope, orthostatic hypotension, and dizziness. Adverse drug reactions may be minimized with bedtime administration, though patients who report frequent nocturia and/or enuresis may require further counseling and cautious use of these medications. In addition,

Table 3
Dosing regimens of medications used for ED

Drug name	Dosing range	Comments
PDE5 INHIBITORS		
Sildenafil	25-100 mg p.o. one hour prior to sexual activity	25 mg for elderly patients and patients with liver/renal dysfunction
Vardenafil	2.5-20 mg p.o. one hour prior to sexual activity	5 mg for elderly patients or those with moderate liver dysfunction; no dosing recommendations in severe liver dysfunction
Tadalafil	5-20 mg p.o. 30 minutes prior to sexual activity	5 mg for patients with renal impairment or receiving alpha-blocker therapy
PROSTAGLANDIN ANALOGS		
Intracavernosal alprostadil	2.5-60 mcg IC given 5-10 min before sexual activity	No more than one dose/24 hours and no more than three doses/week
Transurethral alprostadil	125-1,000 mcg TU 5-10 minutes before sexual activity	No more than two systems/24 hours; urinate prior to insertion

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slow titration of the dose over a period of seven to eight weeks is recommended to minimize cardiovascular adverse effects.

Another second-generation alpha-adrenergic antagonist, alfuzosin (Uroxatral), appears to have fewer cardiovascular adverse effects than other second-generation agents. This is believed to be attributed to its lack of high peak serum concentrations as it is available in an extended-release formulation.

Tamsulosin is considered to be a third-generation alpha-adrenergic antagonist and is selective for the alpha-1a receptor. This selectivity makes this therapy advantageous because the majority (70%) of alpha receptors in the prostate gland are of the alpha-1a subtype. The result is minimal effect on blood pressure. Patients treated with tamsulosin often report nasal congestion, fatigue, flu-like symptoms, and ejaculatory dysfunction.

Treatment with alpha-adrenergic antagonists is often attractive as obstructive symptom relief may be seen between 48 hours and three weeks after initiation. In fact, alpha-adrenergic antagonists generally improve AUA symptom scores by three to four points. Patients who discontinue treatment with alpha-adrenergic antagonists, most often due to the cardiovascular adverse effects of the second-generation agents, require tapering of the dose to avoid rebound hypertension. All alpha-adrenergic antagonists except phenoxybenzamine and prazosin are considered equally efficacious for managing BPH according to AUA, though their adverse effects differ. There are not enough data on prazosin to recommend using it to treat BPH symptoms, though it is believed that it exerts effects similar to other alpha-adrenergic antagonists.

Alpha-adrenergic antagonists are not designed to reduce the prostate size and volume and do not affect PSA levels. Therefore, the PSA level may be preserved as a marker for monitoring the development of prostate cancer.

Due to their ability to lower blood pressure, second-generation alpha-adrenergic antagonists have historically been used as antihypertensives.

In fact, in the 6th edition of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-6) guidelines for the management of hypertension, concomitant BPH and hypertension was considered a compelling indication for treatment with alpha-adrenergic antagonists. However, the ALLHAT study discovered that patients receiving doxazosin as monotherapy had a higher incidence of heart failure compared with those treated with an ACE inhibitor, calcium-channel blocker, and thiazide diuretic. For this reason, JNC-7 does not recommend monotherapy with an alpha-adrenergic antagonist for men with BPH who also have hypertension. BPH may be effectively managed with these agents, but patients should also receive another antihypertensive such as a thiazide diuretic to lower blood pressure.

5-alpha reductase inhibitors: The 5-alpha reductase inhibitors are used to reduce the static factors associated with BPH. These agents, which include finasteride and dutasteride (Avodart), block the conversion of testosterone to its potent metabolite, DHT, through inhibition of the 5-alpha reductase enzyme. Patients with large prostate glands and LUTS, especially those who are unable to tolerate the cardiovascular effects associated with alpha-adrenergic antagonists, may benefit from treatment with a 5-alpha reductase inhibitor. In fact, these agents reduce prostate size by about 25% and are generally ineffective in men without large prostates. Due to these effects on the prostate gland, 5-alpha reductase inhibitors reduce the risk for urinary retention as well as the need for prostate surgical interventions. However, it could take six to 12 months to see complete effects on symptom relief.

The use of 5-alpha reductase inhibitors is optional in men with large prostate glands who are asymptomatic. Treatment in this population of men is to prevent disease progression. However, the advantages and disadvantages associated with therapy need to be fully weighed.

Though efficacious, 5-alpha reductase inhibitors are associated with a rather extensive adverse-reaction profile, including ejaculation disorders, decreased libido, ED, gynecomastia, nausea, abdominal pain, and flatu-

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lence. The 5-alpha reductase inhibitors are teratogenic agents and are classified as Pregnancy Category X. Pregnant women or women of child-bearing age should avoid contact with 5-alpha reductase inhibitors due to the risk for percutaneous absorption. If absorbed, these agents can produce pseudohermaphroditic male offspring owing to the inhibition of external genitalia development. Thus, female R.Ph.s or caregivers who are of child-bearing age should use gloves when handling dutasteride and finasteride. For the same reason, women of child-bearing age should also avoid contact with the semen of males who are receiving treatment with 5-alpha reductase inhibitors.

Patients receiving 5-alpha reductase inhibitors should expect to see a 50% reduction in the PSA level as prostate size and volume are reduced. If this reduction is not noted, patients should first be assessed for medication compliance, as adverse reactions to this class of medications may lead to nonadherence. Once adherence has been confirmed, evaluation for prostate cancer may be warranted.

Combination therapy: Use of a 5-alpha reductase inhibitor in combination with an alpha-adrenergic antagonist is appropriate in patients with large prostate glands who have elevated PSA levels and bothersome LUTS. Combination therapy can provide symptom relief and minimize disease/symptom progression while also reducing urinary retention and the need for surgical interventions. The MTOPS study evaluated the long-term effects of treatment with doxazosin, finasteride, combination therapy (i.e., doxazosin and finasteride), and placebo in 3,047 men with symptomatic BPH. After an average of 4.5 years of treatment, the clinical progression was significantly lower in those receiving doxazosin, finasteride, and combination therapy compared with placebo. In addition, combination therapy provided a 66% reduction in BPH progression, which was statistically significant when compared with doxazosin monotherapy (39% reduction, $p < 0.001$) and finasteride monotherapy (34% reduction, $p = 0.002$). However, with combination therapy, there is an increased risk for adverse drug effects as well as increased pill bur-

den and cost for the patient (see Table 1).

ERECTILE DYSFUNCTION

Erectile dysfunction has been defined as “the inability to achieve or maintain an erection sufficient for satisfactory sexual performance.” This definition allows for subjective interpretation as what one male deems as satisfactory sexual performance may not be the same for another male. ED may occur intermittently or with every sexual encounter. In the Massachusetts Male Aging Study, the overall prevalence of some degree of ED was 52% in men between the ages of 40 and 70 years old. The prevalence of severe ED was reported at 9%. The incidence of ED increases with age, and the probability of complete ED triples between ages 40 and 70. In addition, Type 2 diabetes is associated with a twofold greater risk for developing ED compared with the normal population, and men with Type 1 diabetes have a threefold risk for the development of ED.

Erection physiology

When the penis is in a nonerect state, arterial blood flow into it is equivalent to venous outflow into the body. When stimulated, nerve signals travel from the brain down to the vasculature in the penis. This results in acetylcholine stimulation (i.e., parasympathetic nervous system activation) of nitric oxide (NO) production from the endothelial cells in the penis. NO in turn enhances the production of cyclic guanosine monophosphate (cGMP) through the enzyme guanylate cyclase. The production of cGMP reduces calcium concentrations to produce smooth muscle relaxation resulting in increased arterial blood flow into the two corpora cavernosa, sponge-like tissues that become engorged with blood and distended when the male is stimulated to yield an erection. The erection is maintained via compression of subtunical venules by the engorged corpora cavernosa to prevent blood flow back into the body.

Once ejaculation has occurred, the penis must return to a flaccid state. Norepinephrine (NE) is released, which, in turn, shuts off the

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parasympathetic nervous system. NE causes smooth muscle contractions and reduces arterial blood flow into the corpora cavernosa. Flaccidity is also promoted through catabolism of cGMP by phosphodiesterase type 5 (PDE5) into an inactive compound.

ED etiology and risk factors

Patients may be experiencing ED as a result of a physical cause. This is termed organic ED and may be the result of excessive alcohol intake; physical inactivity; surgical procedures such as a prostatectomy; smoking; chronic diseases such as diabetes, peripheral vascular disease, or arteriosclerosis; or medications such as beta-blockers, thiazide diuretics, selective serotonin reuptake inhibitors (SSRIs), and anticholinergics. See Table 2 for a more comprehensive list of drugs associated with ED.

Patients with cardiovascular disease or diabetes typically develop ED due to poor arterial blood flow into the penis, which results in difficulty achieving an erection, or due to poor intracavernosal trapping of blood which makes maintaining an erection difficult. Patients with organic ED often report a gradual onset of the condition, with an absence of morning erections. Pharmacologic treatment options are typically effective for this type of ED.

Stress or a highly stressful situation is typically the culprit for psychogenic ED. Most patients report intermittent ED associated with a sudden onset. Morning erections are maintained, and treatment strategies are often targeted at stress reduction and behavioral modifications.

ED diagnosis

When a patient presents with suspected ED, obtaining complete medical, medication, and sexual histories is essential. A medical history may point to underlying diseases such as diabetes or arteriosclerosis, which may be contributing to the clinical presentation. In addition, it is important to note that ED may be the first sign of underlying cardiovascular disease. The medication history can help determine whether medica-

tions are the causative agents of ED, especially since it is estimated that up to 25% of ED cases are attributed to drugs. A sexual history may shed light on the frequency of the problem along with quality of erections. Abstinence for long periods of time has also been linked to the development of ED.

A physical examination can help to rule out any prostate or penile abnormalities, such as Peyronie's disease, that may be contributing to erection difficulties. Laboratory tests such as blood glucose levels, lipid profiles, thyroxine levels, and testosterone levels may be beneficial in ruling out underlying diseases as the identifiable cause of ED. Standardized questionnaires such as the International Index of Erectile Function may be useful as a screening tool for ED as well as to assess ED severity.

Management options for ED

According to AUA, patients with organic ED may receive first-line treatment with a PDE5 inhibitor or vacuum erection device. If these options are unsuccessful, use of a prostaglandin analog such as alprostadil may be attempted. If all therapies are exhausted with minimal to no efficacy, surgical interventions such as penile prostheses or revascularization may be warranted. Treatment of psychogenic ED focuses on behavioral modifications.

Nonpharmacologic recommendations: Patients with ED may benefit from lifestyle modifications such as reducing and/or maintaining moderate alcohol consumption, smoking cessation, increasing physical activity, and losing weight. Stress and anxiety reduction, though often difficult, may be especially beneficial for patients with psychogenic ED.

PDE5 inhibitors: Perhaps the most commonly prescribed medications for ED are the PDE5 inhibitors. Ever since sildenafil (Viagra) was introduced in 1998, use of these agents has skyrocketed. They inhibit the PDE5 enzyme—hence their name—to reduce the breakdown of cGMP. This in turn allows for NO-mediated vasodilation of the vasculature in the penis to enhance the erection process. In general, the PDE5 inhibitors are con-

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sidered equally efficacious but have differences with regard to onset and duration of action.

Sildenafil should be administered one hour prior to sexual intercourse; its effects last up to four hours after administration. Patients should not use more than one dose per day. Meals, especially with those high in fat, can reduce the absorption of sildenafil. Thus, patients are advised to avoid taking sildenafil within two hours of a meal.

Vardenafil (Levitra) was the second PDE5 inhibitor to make it to market and is very similar to sildenafil. The dose of vardenafil should also be taken one hour prior to sexual intercourse, with effects lasting up to four hours. Fatty foods reduce the absorption, and patients should not take vardenafil within three hours of a meal.

Tadalafil (Cialis) is quite different from its two predecessors. Tadalafil has a quicker onset of action and may be taken approximately 30 minutes prior to sexual intercourse. In addition, it has a much longer half life, ranging from 24 to 36 hours, and is often referred to as the “weekend Viagra.” Food does not appear to affect tadalafil’s absorption. For these reasons, patients may prefer tadalafil, to allow for more spontaneity.

Patients taking PDE5 inhibitors may experience headache, facial flushing, nasal congestion, dyspepsia, and dizziness because these medications inhibit the PDE5 enzyme in extragenital tissues. Sildenafil also inhibits phosphodiesterase type 6, which is located in the retina. This inhibition can lead to a loss of blue-green color discrimination, photosensitivity, and blurred vision. Tadalafil inhibits phosphodiesterase type 11, located in skeletal tissue, which may lead to the development of back and muscle pain. There is a small risk for priapism, or painful and prolonged erections, the incidence of which is slightly higher with tadalafil use due to its longer duration of action.

PDE5 inhibitors may also cause ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attacks, myocardial infarctions, hypertension, and sudden cardiac death. Thus, patients with a significant cardiovascular history, including a myocardial infarction within the past

two weeks, heart failure, unstable angina, uncontrolled hypertension, and arrhythmias, should undergo a thorough evaluation preferably by a cardiologist prior to receiving a PDE5 inhibitor. In 2005, the Food & Drug Administration required updated labeling for all PDE5 inhibitors to include the risk for vision loss known as nonarteritic anterior ischemic optic neuropathy (NAION). This type of vision loss typically occurs in one eye and is caused by reduced blood flow to the optic nerve. Patients who experience vision loss in one or both eyes should stop treatment with PDE5 inhibitors and seek immediate medical attention.

Drug-drug interactions should also be taken into consideration when using PDE5 inhibitors. Patients taking nitrate-containing products such as sublingual nitroglycerin, isosorbide mononitrate, and isosorbide dinitrate should not be treated with PDE5 inhibitors. Nitrates cause hypotension and supply extra sources of NO to enhance vasodilation. For these reasons, nitrates in combination with PDE5 inhibitors can lead to severe hypotension.

BPH and ED often coexist. In fact, some drugs used for the treatment of BPH, such as tamsulosin and 5-alpha reductase inhibitors, may contribute to the clinical presentation of ED. It is recommended that patients receiving alpha-adrenergic antagonists, especially second-generation agents, separate the dosing of the alpha-adrenergic antagonist from the PDE5 inhibitor by at least four hours to avoid hypotension. Tamsulosin is associated with minimal effects on blood pressure, and, currently, the drug may be given concomitantly with tadalafil though it is believed it may be given safely with any PDE5 inhibitor.

Prostaglandin analogs: For patients who have an inadequate response to PDE5 inhibitors or vacuum erection devices, use of a prostaglandin analog may be appropriate. Alprostadil acts like endogenous prostaglandin E1 to increase cyclic adenosine monophosphate concentrations and, ultimately, increase arterial blood flow into the corpora cavernosa. Currently two formulations of alprostadil exist including intracavernosal (IC) alprostadil (Caverject) and transurethral (TU) alprostadil

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(MUSE).

The IC formulation involves injection of alprostadil into one of the corpora cavernosa approximately five to 10 minutes before sexual activities. The effects of IC alprostadil should last no longer than one hour. Patients experiencing an erection lasting longer than one hour should seek immediate medical attention. Prolonged erections, defined as greater than four hours, and priapism, defined as erections greater than six hours, have been reported to occur in 4% and 0.4% of patients, respectively, who are receiving treatment with intracavernosal alprostadil. Other potential adverse effects include corporal fibrosis, which may be due to alprostadil itself and/or poor injection technique; penile pain, which generally resolves on its own though it may persist once ejaculation has occurred; injection site hematomas, which may be minimized by applying pressure to the injection site after administration; and dizziness and hypotension owing to some systemic absorption of alprostadil.

Alprostadil may also be administered via insertion of a pellet containing the medication into the urethra five to 10 minutes prior to sexual intercourse. Patients receiving MUSE (medicated urethral systems for erections) should be instructed to urinate prior to insertion of the medication, as it is designed to dissolve in the residual urine. After MUSE administration, the penis should be massaged for about five minutes to enhance absorption. Like IC therapy, TU alprostadil is associated with the risk for priapism, dizziness, and hypotension. In addition, patients may also experience urethral bleeding and pain. Female partners of patients receiving TU alprostadil may experience vaginal irritation due to transfer of the medication during intercourse (see Table 3).

Back to T.J.

Based on his current clinical presentation, T.J. should follow up with his

physician. It is quite possible that he is experiencing clinical progression of BPH, and his prostate gland may have increased in size. If this is the case, he may require treatment with a 5-alpha reductase inhibitor to reduce the size of the prostate and modestly improve LUTS. With the addition of a 5-alpha reductase inhibitor, there is a risk for a worsening of ED symptoms.

T.J.'s problem of achieving and maintaining erections has several potential factors, including stress, diabetes, arteriosclerosis, and treatment with medications such as a thiazide diuretic, beta-blocker, tamsulosin, gemfibrozil, and atorvastatin. Obtaining information regarding initiation of the medications may provide further insight to the onset of ED symptoms. Stress reduction may be important for improving T.J.'s symptoms, especially if his symptoms began when his stress level increased. It is possible that potentially switching beta-blocker therapy for another antihypertensive and tamsulosin for a second-generation alpha-adrenergic antagonist may reduce ED symptoms.

If his physical examination does not reveal any significant findings, especially cardiovascular findings, T.J. would most likely benefit from treatment with a PDE5 inhibitor. Selection of the appropriate PDE5 inhibitor may depend on patient preference, any underlying comorbidities such as renal and liver dysfunction, and insurance coverage, though all three agents are considered equally efficacious. With concomitant alpha-adrenergic antagonist therapy, counseling regarding possible hypotension may be warranted when receiving PDE5 inhibitor therapy, even though tamsulosin is associated with minimal effects on blood pressure. Patient education tailored to fit the needs of the patient can be beneficial in managing patients with BPH and ED.

References are available upon request.

TEST QUESTIONS

Mark the most appropriate answer. The answer form follows the test questions.

- BPH peaks in incidence in men between the ages of:
 - 50 and 53
 - 55 and 58
 - 63 and 65
 - 66 and 69
- The prevalence of histologically diagnosed BPH by age 85 is:
 - 50%
 - 75%
 - 85%
 - 90%
- Dynamic factors associated with the clinical presentation of BPH refer to:
 - Alpha-adrenergic mediated muscle contractions
 - Anatomical enlargement of the prostate gland
 - Compression of the urethra, leading to reduced bladder emptying
 - Stimulation of epithelial tissue by testosterone
- Examples of obstructive symptoms of BPH include all of the following *except*:
 - Dribbling
 - Straining
 - Nocturia
 - Urinary hesitancy
- Which of the following is true regarding PSA levels and DREs?
 - A DRE can definitively determine the size of the prostate gland.
 - Annual screening for prostate cancer is recommended beginning at age 50 for men and includes a DRE and PSA level testing.
 - Elevated PSA levels are specific and diagnostic only for BPH.
 - PSA levels are age-adjusted to account for an age-dependent decline in PSA.
- Watchful waiting:
 - Generally involves a diagnostic workup for BPH every two to five years
 - Involves use of no pharmacologic agents
 - Is indicated for men with a moderate to severe AUA symptom index score
 - Is recommended for men with bothersome BPH symptoms to improve their quality of life
- Second-generation alpha-antagonists such as terazosin, doxazosin, alfuzosin, and prazosin are typically associated with:
 - Pruritus
 - Nasal congestion
 - NAION
 - Orthostatic hypotension
- Which of the following would be an appropriate counseling point for a patient receiving dutasteride?
 - Dutasteride should be administered at bedtime to minimize first-dose syncope.
 - Since dutasteride does not affect PSA levels, patients require only one DRE per year.
 - Symptom relief is very quick and may be seen as early as 48 hours after initiating therapy.
 - Treatment may cause adverse effects such as abdominal pain, gynecomastia, and ED.
- Women of child-bearing age should use caution when handling:
 - Alprostadil
 - Doxazosin
 - Finasteride
 - Tamsulosin
- The 5-alpha reductase inhibitors are used to:
 - Reduce the static factors associated with BPH
 - Reduce the dynamic factors associated with BPH
 - Increase prostate size
 - Improve ED
- The Massachusetts Male Aging Study found an overall prevalence of some degree of ED in:
 - 9% of men
 - 40% of men
 - 52% of men
 - 90% of men
- The risk for the development of ED in patients with Type 2 diabetes, compared with the normal population, is:
 - Twofold
 - Threefold
 - Fivefold
 - Tenfold

TEST QUESTIONS

- 13.** During an erection:
- Acetylcholine is responsible for the catabolism of cGMP
 - Compression of the subtunical venules by the engorged corpora cavernosa allows the erection to be maintained
 - Elevated calcium concentrations cause smooth muscle contractions to produce an erection
 - Venous outflow into the body is greater than arterial blood flow into the penis
- 14.** Causes of organic ED include all of the following *except*:
- Diabetes
 - Physical inactivity
 - Smoking
 - Stress
- 15.** Medications associated with ED include all of the following *except*:
- Atenolol
 - Dutasteride
 - Famotidine
 - Fluoxetine
- 16.** A first-line agent for the management of organic ED in the absence of any contraindications to therapy is:
- Alprostadil
 - Dutasteride
 - Sildenafil
 - Testosterone
- 17.** Which of the following would be an appropriate counseling point for a patient receiving treatment with tadalafil?
- The effects of tadalafil last for approximately four hours.
 - Muscle and/or back pain may result from treatment with tadalafil.
 - In order to improve its absorption, tadalafil should not be taken within two hours of a fatty meal.
 - The medication must be administered at least one hour prior to sexual activity.
- 18.** Unilateral vision loss may occur with which class of medications?
- Alpha-adrenergic antagonists
 - 5-alpha reductase inhibitors
 - Prostaglandin E1 analogs
 - PDE5 inhibitors
- 19.** M.B. is a 65-year-old African-American man who presents with a prescription for tadalafil 10 mg. He is receiving the following medications: tamsulosin, hydralazine, isosorbide dinitrate, metoprolol succinate, furosemide, and spironolactone. You decide to call his physician regarding this prescription because:
- Tadalafil cannot be safely given in combination with tamsulosin due to the risk for hypotension
 - M.B. is receiving treatment with isosorbide dinitrate, which can lead to severe hypotension
 - Spironolactone in combination with tadalafil can lead to severe hyperkalemia
 - The dose of tadalafil is too high for any patient
- 20.** Intraurethral alprostadil may cause:
- Corporal fibrosis
 - Hematoma development
 - NAION
 - Vaginal irritation in female partners

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ANSWER FORM

MEN'S HEALTH CONDITIONS AND CONCERNS

APRIL 2, 2007 ACPE # 012-999-07-083-H01

Test questions start on preceding page

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