Uropharmacology in primary care: 2010 update

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GOMELLA LG, LALLAS CD, PERKEL R, FOLIA C, HIRSCH I, DAS A, SHENOT P. Uropharmacology in primary care: 2010 update. The Canadian Journal of Urology. 2010;17(Supplement 1):35-51.

Many disorders such as erectile dysfunction, overactive bladder, hypogonadism and benign prostatic hypertrophy have traditionally been managed primarily by urologists. The development of newer agents to treat many of these conditions has allowed the primary care provider to manage many of these common conditions. The use of these newer medications has become commonplace in the primary care setting. This article will update some of the most commonly used urologic medications to optimize patient management strategies by the primary care provider or in coordination with the urologist.

Key Words: uropharmacology, overactive bladder, erectile dysfunction, benign prostate hypertrophy, prostate cancer, hypogonadism

Introduction

Advances in understanding the pathophysiology of a variety of urological diseases has allowed an unprecedented expansion in the pharmacologic options available to treat these conditions. The use of these medications for the treatment of urological diseases has become more commonplace in the office of the primary care physician. An understanding by primary care physicians of the pathophysiology and pharmacology of common urological diseases is important for the successful and safe management of these patients either as the primary caregiver or in coordination with the urologist. This review will provide a contemporary update of our original 2008 publication and will note changes in available medications as well as insight into the newer medications that may soon become available.[1] The medical management of common urological diseases such as benign and malignant diseases of the prostate, erectile dysfunction, overactive bladder and hypogonadism will be addressed.

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Symptomatic benign prostatic hyperplasia

Pathophysiology and pharmacology

Benign prostate hyperplasia (BPH) is a histologic diagnosis that is the precursor to benign prostate enlargement (BPE). BPE, subsequently, can lead to changes in voiding habits consistent with bladder outlet obstruction. Frequently, BPH is incorrectly used to refer to prostatic obstruction leading to urinary symptoms. Current terminology uses the global term symptomatic (sBPH) to encompass BPH, BPE and lower urinary symptoms (LUTS).[2]

LUTS are a group of irritative symptoms such as urgency, frequency and nocturia, or obstructive symptoms such as hesitancy, weak stream, intermittency or straining.[3] Often viewed as a disease of "inconvenience", sequelae of sBPH may sometimes include urinary retention, increased post void residual, bladder calculi, renal failure, hematuria, recurrent urinary tract infections and irreversible bladder dysfunction. It is important to recognize that the signs and symptoms of sBPH can also overlap with other urological pathology or insults to the central nervous system, including urethral stricture, bladder dysfunction, and neurological disorders including Parkinson disease and multiple sclerosis. If these conditions are suspected, a more complete neurologic and urologic evaluation is needed before initiating a pharmacotherapy regimen.

More than 50% of men over the age of 60 have sBPH. The incidence steadily increases with age greater than 60 and ultimately affects approximately 90% of men in their ninth decade of life.[4] Moderate to severe LUTS occur in 18%, 29%, and 50% of men in their 40's, 50's, and 60's, respectively, with a quarter of the men in each of those age groups progressing to require surgical intervention. Pharmacological management of sBPH is based on two concepts: reducing prostatic tone and decreasing the size of the prostate gland, thus leading to less resistance of flow.

An increase in smooth muscle tone of the prostate can be the primary cause of symptoms seen with sBPH. The prostate, human vasculature, and central nervous system are responsive to autonomic intervention via the neurotransmitter norepinephrine (NE), which then mediates various adrenoreceptors (AR). $Alpha_1$ AR have an important role in the urinary tract. In particular, the $alpha_{1A}$ subtype has received a great deal of attention because of its high concentration in the prostatic urethra, stroma and bladder neck.[5] Pharmacologically targeting these receptor subtypes can lead to a decrease in tone and lead to symptom relief.

An enlarged prostate gland may cause a decrease in urinary flow and can lead to sBPH. This is due to a mechanical outlet resistance from the prostate gland. Surgical therapies, minimally invasive therapies, and medical treatment may be used to reduce the size of the prostate and thus treat sBPH. Surgical debulking procedures include an open prostatectomy, transurethral resection of the prostate (TURP) and various laser therapies. Today, more commonly used minimally invasive therapies include radiofrequency ablation of the prostate and microwave therapy.[6] These techniques rely on controlled heating to treat sBPH.

Oral medical therapy to reduce the size of the prostate is often used to treat sBPH and typically involves some type of hormonal manipulation. Testosterone and dihydrotestosterone (DHT) are the predominant male hormones responsible for virilization and growth of the male genitalia. DHT is formed by two isoenzymes, types I and II, 5-α-reductase. Type I 5-α-reductase is predominantly concentrated in the lung and skin, with 10% found in the prostate. Type II 5-α-reductase is present in the stroma and basal epithelial cells of the prostate and is responsible for intraprostatic conversion of testosterone to DHT.[7] The conversion of testosterone to DHT by type II 5-α-reductase is mostly responsible for the growth of the prostate. DHT also indirectly modulates vascular derived endothelial growth factor (VEGF) with subsequent microvascular proliferation that contributes to the increased vascularity and troubling hematuria sometimes seen in sBPH.[8,9]

Alpha blockers

Alpha receptor blocking agents (alpha blockers) are competitive inhibitors of the alpha receptor. Blocking these receptors promotes bladder neck and prostatic urethral relaxation. Alpha blockers were among the first class of medications approved for the treatment of sBPH. Alpha blockers are generally subdivided depending on their degree of selectivity for the alpha AR and patient tolerability.[10] They are divided into first generation (phentolamine, phenoxybenzamine), second generation (prazosin [Minipress], doxazosin [Cardura], terazosin [Hytrin]), and third generation (tamsulosin [Flomax CR], alfuzosin [Xatral (Canada), Uroxatral (US)], silodosin [Rapaflo](US only)) agents.[10] Silodosin represents the latest agent in this class and is not available in Canada. Each subsequent generation within this class demonstrates increased specificity for the prostate and bladder neck alpha receptors.

First generation alpha blockers are no longer used in the management of sBPH because of their severe side effect profile due to a lack of selectivity toward the $alpha_1$ and $alpha_2$ ARs. This generation of medications historically caused palpitations, dizziness, impaired ejaculation, nasal stuffiness, and visual disturbances.

Second and third generation alpha blockers are more selective by targeting the alpha$_1$ and alpha$_{1A}$ subtypes, respectively. Canadian Urological Association (CUA) guidelines do not recommend first generation alpha blockers or prazosin in the treatment of sBPH.[11] The CUA guidelines note that second and third generation alpha blockers are similar in reducing the symptoms of BPH, increasing maximum urinary flow rate, and reducing post void residual, but vary in their degree of side effects and pharmacological profiles.

Cardiovascular symptoms such as hypotension, dizziness, fatigue, and first dose syncope are often associated with second generation alpha blockers. However, these adverse effects occur significantly less as compared to the first generation alpha blockers. These adverse events are thought to be due to interactions with alpha$_1$ receptors that control the tone of systemic blood vessels and those in the central nervous system (CNS). Second generation alpha blockers require titration over several weeks until maximum dosages are obtained. Terazosin and doxazosin represent the two major second generation alpha blockers. The important distinction between these medications is that terazosin has a peak plasma concentration that is delayed with fatty meals, while doxazosin is hepatically metabolized and should be used with caution in patients with liver pathology.[12]

Tamsulosin, alfuzosin, and silodosin, the third generation alpha blockers, have been found to have reduced cardiovascular side effects.[10] Unlike their second generation counterparts, these medications do not need to be titrated. Interestingly, alfuzosin is noted to be pharmacologically similar to the second generation but clinically it is has been found to be more uroselective, with minimal cardiovascular side effects. Tamsulosin and silodosin selectively target the bladder and prostatic urethra, having a high affinity for the alpha$_{1A}$ AR. These agents may cause ejaculatory dysfunction (anejaculation and/or retrograde ejaculation), which may be attributed to their affinity toward 5HT1A and D2 receptors centrally.[13] However, relative to surgical procedures such as resection of the prostate, the effects of these agents on ejaculatory function is far superior to surgical results. To improve absorption, alfuzosin, silodosin and tamsulosin (generic capsules) should be taken after the same meal daily.

Intraoperative floppy iris syndrome (IFIS) is an uncommon side effect of alpha blockers during cataract surgery. IFIS occurs during phacoemulsification cataract surgery and was first described in 2005.[14] The syndrome may lead to a more difficult cataract operation and an increased risk in surgical complications. IFIS is thought to be due to the interaction between alpha blockers and the heavily dominated alpha$_{1A}$ receptors in the iris, and has been reported with all alpha blockers, including tamsulosin, terazosin, doxazosin, and alfuzosin.[15] Stopping the alpha blocker may not always help. Up to 75% of cataract surgeons report IFIS in patients who stopped alpha blockers, see Table 1. Roughly 10% of ophthalmologists ask their patients to stop alpha blockers prior to surgery. Current recommendations concerning the use of alpha blockers in IFIS by major ophthalmic professional organizations are summarized in Table 1.

TABLE 1. **Current recommendations concern alpha blockers for symptomatic BPH and the Intraoperative Floppy Iris Syndrome (IFIS)**

American Society of Cataract and Refractive Surgery (ASCRS) and the American Academy of Ophthalmology (AAO) issued the following recommendations in 2009*

All alpha blockers can cause IFIS, but several studies suggest that IFIS is more likely to occur with the "selective" alpha blocker such as tamsulosin compared to the other "non-selective" alpha blockers. There are no data yet on IFIS with silodosin, but it is pharmacologically "selective" for the iris and prostate tissue similar to tamsulosin.

- Patients taking alpha blockers should inform their ophthalmologist before undergoing eye surgery.
- Prior to being started on an alpha blocker, patients with cataracts should be informed that alpha blockers may increase the difficulty of cataract surgery, and they may consider having surgery done before starting alpha blocker therapy.
- Many ophthalmologists recommend ophthalmologic evaluation in patients with a history of cataracts or decreased vision prior to starting tamsulosin.
- Discontinuation of tamsulosin prior to cataract surgery did not reduce the severity of IFIS in a prospective trial.
- Ophthalmologic surgeons may be able to modify surgical techniques in at-risk patients.

*Available on line at http://www.ascrs.org/press_releases/IFIS-Press-Release.cfm

TABLE 2. **Alpha blocker medications for symptomatic benign prostatic hyperplasia (sBPH)**

Name (Brand)	Dosage	Side effects/Notes
Second generation		
Terazosin (Hytrin)	1 mg-10 mg daily*	First dose syncope; dizziness; tachycardia; hypotension; headache; asthenia; rhinitis
Doxazosin (Cardura)	1 mg-8 mg daily*	Same as above
Third generation		
Alfuzosin (Xatral [Canada] Uroxatral [US])	10 mg daily with food	Dizziness; headache; minimal cardiovascular effect; less ejaculatory dysfunction than tamsulosin
Tamsulosin (Flomax CR, generic capsules)	Flomax CR: 0.4 mg daily (with or without food) Generic capsules: 0.4 mg-0.8 mg daily with food	Ejaculatory dysfunction; rhinitis
Silodosin (Rapaflo [US, not Canada])	8 mg daily;	Retrograde ejaculation 4 mg daily with CrCl 30-50 mL/min

*Dose titrated weekly to desired response

Finally, it should be noted that the alpha blockers may have an additional use in urology. Studies have shown that these agents may have utility as medical expulsive therapy in distal ureteral stones.[10] These agents are reviewed in Table 2.

5-alpha reductase inhibitors

An enlarged prostate gland can lead to sBPH, although the size of the prostate does not directly correlate with the degree of symptoms. Decreases in DHT have been shown to induce prostatic epithelial apoptosis and atrophy.[16] The 5-alpha reductase inhibitors (5-ARI) act by blocking the conversion of testosterone to DHT, an intracellular process mediated by the enzyme 5-alpha reductase. Finasteride [Proscar] and dutasteride [Avodart] are 5-ARI which have been shown to reduce the size of prostate. Finasteride is also available in a lower dosage to treat androgenetic alopecia [Propecia].

Finasteride is a type II 5-ARI that decreases serum DHT by 70%-90% within the prostate. This causes a reduction in prostate size by 20%-30% over a 6-12 month period.[17] This is accompanied by a decrease in prostate-specific antigen (PSA) by 42% and 50% at 3 and 6 months, respectively; a similar effect is seen with dutasteride.[18] The PSA change should be considered when screening for prostate cancer in patients that have been prescribed a 5-ARI, including lower dose finasteride for alopecia, with the new baseline PSA established at 6 months.

Dutasteride, unlike finasteride, impedes both type I and type II 5-alpha enzymes and leads to almost total elimination of DHT in the serum. Both dutasteride and finasteride have been shown to have similar efficacy and tolerability. The half life of dutasteride is several weeks as compared to finasteride which is 8 hours. The 5-alpha reductase inhibitors are reviewed in Table 3.

TABLE 3. **5-alpha reductase inhibitor medications for symptomatic benign prostatic hyperplasia (sBPH)**

Name	Dose	Half-life	Mechanism	Side effects/Notes
Finasteride (Proscar)	5 mg daily	6-8 hours	Inhibits type II 5-AR	Decreased libido, sexual dysfunction, gynecomastia, and breast tenderness
Dutasteride (Avodart)	0.5 mg daily	3-5 weeks	Inhibits types I and II 5-AR	Same as above; approved for use with tamsulosin

5-AR = 5-alpha reductase

Large prospective randomized clinical trials have shown that 5-ARI can be utilized as a chemoprevention agent against prostate cancer. However, these agents are not currently approved by Health Canada or in the United States for this indication. The Prostate Cancer Prevention Trial (PCPT) examined the effects of finasteride on prostate cancer.[19] The results demonstrated an approximately 25% relative risk reduction in the incidence of prostate cancer over 7 years, with initial reports suggesting an increase in high grade prostate cancer when compared to placebo. The latest evidence suggests this observed increase in high grade cancers was influenced by the smaller post treatment prostate volumes, which improved the sensitivity of PSA, digital rectal exam, and prostate biopsies. There is speculation that there is also a selective inhibition of low grade cancer.[20]

A more recent prostate cancer prevention trial evaluated the effects of dutasteride compared to placebo in a higher risk group of men.[21] The initial results from the REDUCE (REduction by DUtasteride of prostate Cancer Events) trial suggest a prostate cancer risk reduction of approximately 23% seen over a 4 year period with dutasteride.[22]

The 5-ARI side effect profile can include decreased libido, sexual dysfunction, gynecomastia, and breast tenderness. These agents have utility in selected cases of bleeding from the prostate by indirectly inhibiting microvascular proliferation.[23] Both medications are considered to be teratogenic and should not be handled by women of childbearing age. Patients treated with dutasteride are asked not to donate blood for at least 6 months after stopping the drug due to the extended half life.

Combination sBPH therapy

Combination therapy with alpha blockers and 5-ARI should be considered in patients who have an enlarged prostate gland and symptoms consistent with bladder outlet obstruction. The Medical Therapy Of Prostatic Symptoms (MTOPS) trial demonstrated that combination therapy was found to be superior to both doxazosin and finasteride individually in preventing disease progression.[24] In addition, the need for surgical therapy was found to be significantly reduced with finasteride and combination therapy, but not with doxazosin as monotherapy. Similarly the Combination of Avodart and Tamsulosin (CombAT) trial demonstrated that combination treatment with dutasteride and tamsulosin provides significantly greater urinary symptom improvement for men with an enlarged prostate than either dutasteride or tamsulosin monotherapy over 24 months.[25] This combination of dutasteride with tamsulosin has recently been approved by Health Canada and in the United States by the FDA for sBPH. Although not available yet, a fixed dose combination of tamsulosin, with dutasteride is currently undergoing US FDA regulatory review.

Another combination therapy for sBPH that is under further study involves the addition of an antimuscarinic agent, to reduce detrusor contractility (see below), to an alpha blocker.[26] Combining alpha receptor antagonists with antimuscarinic agents has some utility in relieving symptoms of bladder outlet obstruction and detrusor overactivity. Theoretic concerns regarding the risk of acute urinary retention have been refuted in several recent clinical trials, however, further study is necessary before this can be widely adopted.

Erectile dysfunction

Pathophysiology and pharmacology

Erectile dysfunction (ED) is defined as the consistent inability to achieve or maintain an erection sufficient for sexual intercourse.[27] ED can be the early manifestation of serious underlying medical conditions commonly associated with cardiovascular or endocrine abnormalities. Additionally, ED may impact significantly on the psychosocial well-being of patients and partners. Approximately 50% of men over age 40 are affected by ED.[28] Multiple causes may be attributed to ED, including neurogenic, hormonal, arterial, cavernosal, and drug induced; collectively, these are classified as organic or psychogenic and/or mixed etiology.

A cascade of sequential psychological, neurovascular, smooth-muscular and chemical events are necessary to produce a normal erection. Originating with sexual stimulation, impulses from the parasympathetic nerve fibers lead to a release of nitric oxide from endothelial cells. Nitric oxide then enters corporal smooth muscle cells stimulating guanylyl cyclase that converts cyclic guanine triphosphate (cGTP) to cyclic guanosine monophosphate (cGMP). This in turn activates protein kinase and stimulates phosphorylation of proteins and opening of ion channels that eventually cause corporal smooth muscle relaxation and increased blood flow to the corporal sinusoids. A net decrease in venous outflow occurs with occlusion of subtunical venular plexus that are compressed against the wall of the tunica albuginea. The resultant increase in intracavernous pressure produces the penile rigidity necessary for erection. Detumescence occurs when cGMP is hydrolyzed by phosphodiesterase-type 5 (PDE-5) isoenzyme.[29] Eleven different isoenzymes of PDE have been identified in human tissue and are thought to explain the varied

side effect profiles of the different agents. PDE-5 is found primarily in the corpus cavernosum, platelets, and vascular and visceral smooth muscle.

Androgens are also instrumental for normal sexual function and erections. They have direct effects on libido, and also play a local role in the regulation of cGMP, PDE-5 and nitric oxide synthase expression.[30]

Oral therapy for erectile dysfunction

Multiple treatment options are available for erectile dysfunction including oral medical therapy, intraurethral agents, intracavernosal injections, vacuum tumescence devices and penile prosthesis. Sildenafil [Viagra], vardenafil [Levitra] and tadalafil [Cialis] are all oral phosphodiesterase inhibitors (PDE-5i).[31]

The erectogenic PDE-5i agents function by inhibiting the degradation of cGMP, enhancing the effect of nitric oxide and amplifying the relaxation of the cavernosal smooth muscle. The PDE-5i are generally comparable in their efficacy but differ in their pharmacokinetic and side effect profiles. Many of their adverse reactions can be attributed to interactions with other PDE isoenzymes. Sildenafil, for example, has a high affinity towards the PDE-6 isoenzyme, which is concentrated in the eye. This particular interaction may lead to a "blue haze", a side effect that is rarely seen with vardenafil or tadalafil. Vardenafil has been found to prolong the QT interval, and tadalafil may be associated with muscle pain in up to 9% of users.[32] Hearing loss has also been rarely reported with some of these agents.[33]

Sildenafil and vardenafil have a serum half life of approximately 4 hours while tadalafil exhibits a half life of approximately 17.5 hours. The longer half life of tadalafil has not been correlated with prolonged adverse effects. Additionally, sildenafil and vardenafil are affected by fatty meal intake which can slow their time of onset. All three PDE-5 may exhibit symptoms of facial flushing, headache and rhinitis. Tadalafil has been recently approved for a daily dosing regimen (2.5 mg-5 mg) to avoid the theoretical inconvenience of "on demand" dosing.[34]

All PDE-5i are contraindicated with concurrent use of nitrates because of excessive systemic vascular smooth muscle relaxation causing pronounced vasomotor collapse and possible death. Patients with cardiac risk factors should be screened and grouped prior to initiation of treatment. Guidelines from the Princeton Consensus Conference have categorized patients into low, intermediate, and high risk based on their cardiovascular disease.[35] Low risk typically implies the ability to perform exercise of modest intensity without symptoms; intermediate risk indicates the need for further evaluation to reclassify risk as low or high; and high risk indicates that patients should defer sexual activity until cardiac assessment and/or treatment has been implemented.[36,37] Table 4 summarizes current oral medical therapy for ED.

Non-arteritic anterior ischemic optic neuropathy (NAION) is an adverse effect that has been recognized in patients taking PDE-5i. This is a sudden, painless, and

TABLE 4. **Oral phosphodiesterase-5 (PDE-5) inhibitors medications for erectile dysfunction**

Name	Dosage	Time to maximum plasma concentration	Serum	Affected half life	Side effects/Notes+ by food
Sildenafil (Viagra)	25 mg-100 mg 30-60 minutes before sexual activity, Max 1x day	60 minutes	4 hrs	Yes; delays onset	Visual disturbances ("blue halo")
Vardenafil (Levitra)	5 mg-20 mg 25-60 minutes before sexual activity Max 1x day	60 minutes	4 hrs	Yes; delays onset	Increase in QT interval; avoid use with other medications that prolong QT interval
Tadalafil (Cialis)	On-demand dosing: 10 mg-20 mg within 30 minutes Max 1x day Daily dosing: 2.5 mg-5 mg daily	120 minutes	17.5 hrs	No	Myalgia, back pain

+Class side effects include: headache, flushing, rhinitis, dyspepsia

irreversible ischemic event of the intraocular portion of the optic nerve.[38] Visual acuity is very often decreased to no light perception, and there may be a variety of visual field defects. Physical examination may reveal disc edema and a small cup to disc ratio, or absence of the cup entirely. The incidence occurs in 10/100,000 persons and is significantly more common in Caucasians. The World Health Organization (WHO) and Health Canada have concluded that there is no definitive evidence connecting NAION and PDE-5i, but patients should be advised to call a physician and stop the medication if any visual difficulties occur.[39] Physicians should also be aware of the symptoms of NAION and try to elicit a history of visual loss or NAION prior to prescribing PDE-5. A careful review of pooled data from clinical trials for all three PDE-5i, with well documented information regarding the dose and duration of exposure to the drug for a large number of patients, found no evidence for an increased risk of NAION or other adverse ocular events with PDE-5i use.[40]

Oral PDE-5i combined with androgen replacement therapy have a role in the treatment of a select number of ED patients. A threshold of testosterone is known to be necessary for normal erections. Hypogonadal men who do not initially respond to PDE-5i can respond to these agents with effective testosterone replacement therapy.[41]

Other issues are evolving concerning the use oral PDE-5i in urology. There are data to suggest that these agents may also enhance voiding in men with BPH.[42] Discussions are underway in some countries to consider making oral PDE-5i available over-the-counter (OTC) in pharmacies.[43]

Intraurethral therapy for erectile dysfunction

In the event that oral therapy is unsuccessful, local pharmacological options are available for patients with ED. Prostaglandin E1 (PGE1) stimulates adenyl cyclase to increase levels of cAMP; this stimulates adenylate cyclase, which ultimately causes arteriolar vasodilatation, direct smooth mucle relaxation and increased arterial blood flow leading to erection. Alprostadil [MUSE] is a synthetic PGE1 that is inserted into the urethra via an approximately 3 cm x 3 mm applicator whence it diffuses into the corpora cavernosa and corpus spongiosum by communicating veins. Efficacy overall exceeds 60%, while in patients with conditions less likely to respond to PDE-5i (i.e., post-prostatectomy or spinal cord injury), MUSE remains a viable option.[44] An advantage of intraurethral alprostadil is its local absorption, resulting in minimal systemic side effects and drug interactions. Intraurethral alprostadil may cause penile pain, warmth and burning, vaginal discomfort in partners, and hypotension. First-use self-administration in the office setting is advised. Table 5 outlines MUSE characteristics.

TABLE 5. **Transurethral (TU) and intracavernosal (IC) therapy for erectile dysfunction**

Name	Dosage	Mechanism of action	Side effects/Notes
Alprostadil TU (MUSE)	250 mcg-1000 mcg Max 2 administrations per 24 hrs	Synthetic PGE1 stimulates adenyl cyclase to increase cAMP	Painful erection, urethral pain and bleeding; can be delivered to partner; priapism (rare)
Alprostadil IC (Caverject, Edex†)	2.5 mcg-40 mcg* Max 1x daily and 3x weekly	Same as Alprostadil TU	Penile pain, fibrosis hematoma; priapism (rare)
Papaverine IC‡	15 mg-60 mg (monotherapy) 5 mg-20 mg (used in combination w/phentolamine)	Non-selective PDE inhibitor increases cAMP and cGMP	Priapism; corporal fibrosis
Phentolamine IC‡	0.5 mg-1 mg (used in combination w/papaverine)	Alpha blocker inhibits sympathetic tone to penis	Hypotension; reflex tachycardia

*Neurogenic ED may require lower starting dose. Severe vascular ED may require greater doses.
†Not available in Canada
‡Not approved by Health Canada for this use.

Intracavernosal therapy for erectile dysfunction

A very effective second line of treatment of ED is intracavernosal (IC) injection therapy. Alprostadil [Caverject, Edex (US only)] is a PGE1 that can be used safely and effectively in up to 70%-88% of non responders to oral agents and is the only approved intracavernosal agent.[45] Although the dose used is significantly lower than intraurethral therapy, the mechanism of action is identical. Side effects include pain at the injection site, fibrosis, hematoma, prolonged erection, and priapism. Papaverine is a nonselective PDEi that increases cAMP, which causes relaxation of corporal sinusoids. Papaverine has been found to be 55% effective when used as monotherapy. Bothersome side effects include a significantly high incidence of priapism (up to 35%), fibrosis of the corpora cavernosum (up to 33%), and occasional increases in serum aminotransferase.[44] Phentolamine is an alpha blocker that, when used alone, does not produce rigid erections, but is thought to have an effect on corporal smooth muscle cells which may increase the supply of nitric oxide to the cells and potentiate the effects of the IC medications previously mentioned.

Combining IC medications and their synergistic action results in high success rates and a lower risk of side effects, since lower doses of each agent can be used, however these combinations are not formally approved by the US FDA or Health Canada. Phentolamine and papaverine in combination have been shown to be highly successful. Success rates up to 87% have been reported, and with the addition of alprostadil (Tri-mix), success can increase to 92% in patients who were otherwise refractory to other medications.[46] Table 5 summarizes the characteristics of IC therapy.

Hypogonadism

Pathophysiology and pharmacology

Male serum testosterone begins to gradually decline toward the end of the third decade of life, after a surge in mid-teen years. The rate of decline continues at approximately 1% per year or approximately 10% per decade after the age of 40.[47] Common symptoms of hypogonadism include ED, diminished libido, depressed mood, fatigue, decreased lean body mass, anemia, and osteoporosis. ED may not only result from hypogonadism, but ED and hypogonadism often coexist.

The diagnosis of hypogonadism requires evidence of clinical symptoms that is supported biochemically; it is, therefore, based on a combination of clinical findings and laboratory examination. The laboratory examination should begin with a morning total serum testosterone. Serum testosterone exists in three components: 2% of testosterone is active and is unbound (free); 30% is bound to sex hormone binding globulin (SHBG) and is inactive; and the remainder is bound to albumin and is bioavailable.[48] The definition of hypogonadism is based on its cause and may be the result of primary or secondary etiologies. Primary hypogonadism occurs when there is failure of the testes to produce testosterone; secondary hypogonadism is due to insufficient production of LH and FSH by the pituitary gland. If suspected, the underlying causes for the hypogonadism should be investigated by consultation with an endocrinologist.

Testosterone replacement therapy

Testosterone replacement therapy (TRT) represents the primary therapy for patients with hypogonadism. Treatment may benefit sexual dysfunction and have positive effects on lean body mass, bone density, and mood.[49-51] Thus, even potent men with the stigmata and laboratory findings of hypogonadism may benefit from treatment. There are several methods by which testosterone can be administered. These include oral, intramuscular injection, and topical formulations.

Oral alkylated androgens (fluoxymesterone, methyltestosterone, etc.) are administered daily, and undergo rapid hepatic metabolism, oftentimes failing to achieve consistent therapeutic ranges in the serum. Inconsistent levels may lead to mood swings and sexual side effects. Liver toxicity, including hepatocellular adenomas, hemorrhagic cysts, and cholestatic jaundice have been associated with oral alkylated androgens.[52] Testosterone replacement with oral alkylated androgens has lost popularity over other administration routes in the United States, however the use of other oral medications, like testosterone undecanoate [Andriol], is still popular in other countries such as Canada.

Testosterone undecanoate is the only oral form of testosterone available in Canada. Liver toxicity is not observed with oral testosterone undecanoate, which avoids the first pass effect.[53] Oral testosterone undecanoate is administered daily and must be taken with food for optimal absorption.

Intramuscular injectable esters of testosterone, such as testosterone cypionate [Depo-Testosterone] and testosterone enanthate [Delatestryl] represent another alternative in testosterone administration. These medications are more conveniently dosed every 2-4 weeks, as opposed to the daily dosing of oral or topical formulations. However, they can be associated with supraphysiologic levels of testosterone and low nadirs,

TABLE 6. **Medications for male hypogonadism**

Name (brand name)	Route	Dosage	Notes*
Testosterone, buccal (Striant) [US, not Canada]	Buccal tablets	30-mg buccal tablets BID	Apply to gum over incisor; do not chew or swallow
Testosterone cypionate (Depo-Testosterone)	IM injection	200 mg-400 mg q 3-4 wks (100 mg-150 mg q 2 wks preferred)	
Testosterone enanthate (Delatestryl)	IM injection	100 mg-400 mg q 4 wks (100 mg-150 mg q 2 wks preferred)	
Testosterone gel (AndroGel 1%)	Topical	5 g-10 g daily	Apply to clean dry area on shoulder, upper arm, abdomen; 10 g/d max
Testosterone gel (Testim 1%)	Topical	5 g-10 g daily	Apply to clean dry area on shoulder, upper arm
Testosterone patch (Androderm)	Transdermal patch	2.5 mg-7.5 mg daily	Apply to clean dry area on back, arm; rotate site; remove for MRI; contains metallic components that can cause burn
Testosterone implant (Testopel) [US, not Canada]	Implantable pellets 75 mg/each	150 mg-450 mg (2-6 pellets) SC implant every 3-6 mo (implant [2] 75-mg pellets for each 25 mg testosterone required weekly; e.g.: For 75 mg/wk, implant 450 mg (6 pellets).	Implant in upper buttock under local anesthesia
Testosterone undecanoate (Andriol)[Canada, not US]	Oral	40 mg-160 mg daily, Divided in two doses	Take with food to ensure adequate absorption
Testosterone undecanoate (Nebido) [US, not Canada]	IM	1000 mg IM every 6-12 weeks	

*Monitor serum testosterone levels for all agents.

especially with extended dosing intervals.[48] These fluctuations may result in alterations in mood, and high levels of testosterone can lead to infertility through negative feedback suppression of LH and FSH.

Transdermal patches [Androderm] and gels [AndroGel, Testim] have been found to more closely mimic the circadian cycle of testosterone levels.[48] The patch and the gel can be directly applied to the skin. Transdermal formulations available in Canada should not be applied to the scrotum. When compared to injectable formulations, the transdermal patch shows less of an effect on LH and FSH levels, reducing chances of infertility. A common side effect of the patch is skin irritation and rash, which seems to be less common with the use of gel formulations.[54]

New buccal preparations [Striant] have been found to have favorable results, exhibiting adequate serum testosterone levels. These formulations have also demonstrated a low side effect profile, consisting mostly of buccal irritation and a bitter taste, and are not yet available in Canada.[55]

Testosterone therapy is contraindicated in patients with a history of prostate cancer. However, there is increasing interest in using testosterone supplementation in the hypogonadal man who has been rendered disease free following radical prostatectomy.[56] Some side effects reported with testosterone therapy include gynecomastia, erythrocytosis, testicular atrophy, and skin reactions (with topical formulations).[57] Patients should be instructed to cover topical gel sites with clothing and wash hands after application to prevent transfer of drug to others. In addition, patients should be advised that gels are flammable, and should therefore allow the gel to dry completely before smoking or going near an open flame.

Newly approved long-acting testosterone supplements have been recently released in 2009. Testosterone

undecanoate [Nebido (United States, not available in Canada)] 1000 mg IM may now be administered at 6-12 week intervals.[58] Implantable testosterone pellets may be also be utilized for long-acting testosterone replacement therapy for hypogonadal males. Testosterone implants [Testopel, 75 mg] are commercially available in the United States and are implanted in the upper buttock under local anesthesia every 6 months. These modalities are well-tolerated and maintain therapeutic serum testosterone levels during their respective dosing intervals.[58] Given their safety, efficacy and convenient dosing interval, long-acting testosterone formulations may offer a valuable addition to the armamentarium of testosterone replacement therapy. Table 6 lists the options for testosterone replacement therapy in the hypogonadal male.

Overactive bladder

Pathophysiology and pharmacology

The bladder functions as a reservoir for the storage and emptying of urine. These actions depend on the complex interplay between the brain, spinal cord, autonomic nervous system and organs of the genitourinary system. During filling, the bladder maintains a low intravesical pressure.[59,60] This low pressure protects against vesico-ureteral reflux, incontinence, and the deleterious effects of bladder dysfunction. Normal voiding is initiated by a coordinated bladder contraction, a decrease in urethral resistance, and relaxation of the external striated sphincter. In general, relaxation of the bladder during filling is moderated by the sympathetic pathway, in which norepinephrine (NE) is released, stimulating beta-adrenergic receptors that interact with adenlyate cyclase, eventually leading to smooth muscle relaxation of the bladder detrusor muscle.

Parasympathetic stimulation is responsible for voiding and leads to the contraction of detrusor smooth muscle and inhibition of sympathetic input from the bladder neck. It also causes inhibition of the somatic nerves to the striated sphincter.[61] Muscarinic (M) receptors are found within the bladder and throughout the body. The dominant subtype found in the detrusor muscle is the M2 receptor. The M3 subtype is also found in the bladder, as well as the salivary glands, brain, colon, and eye. During voiding, the neurotransmitter acetylcholine interacts with M2 and M3 receptors on the detrusor, leading to contraction of bladder smooth muscle.[61]

Overactive bladder (OAB) is a medical condition characterized by symptoms of urgency, with or without urinary incontinence, usually with frequency and nocturia.[62] It should be diagnosed only after other conditions such as urinary tract infection, bladder cancer or neurological disorder have been ruled out. OAB is thought to be caused primarily by abnormal detrusor activity from acetylcholine interaction with M3 receptor subtypes. OAB affects an estimated 1 in 5 Canadian adults and increases in prevalence with aging.[63-65] The cost of OAB has been estimated to be $12 billion (US) per year. The symptoms of OAB are commonly caused by uninhibited contractions of the detrusor muscle from altered innervation due to BPE, neurological conditions (e.g., stroke), as well as many idiopathic conditions.[60] OAB is also associated with a significant decrease in quality of life, an increased propensity for falls, dermatological conditions, and an increase in urinary tract infections.[66-69]

Antimuscarinics

The medications primarily used in OAB are antimuscarinic agents. This group acts by competitively inhibiting the binding of acetylcholine at muscarinic receptors M2 and M3 on detrusor smooth muscle cells and other structures within the bladder wall.[70] Antimuscarinic medications work primarily during the storage phase of bladder function to lessen urgency and increase bladder capacity. Currently used drugs lack total selectivity for the bladder, and the effects on other tissues may result in side effects, which can limit their usefulness. Side effects, as well as efficacy of antimuscarinic agents are dose-related. Dry mouth and constipation are common. Less common side effects include gastroesophageal reflux, cognitive impairment, blurred vision, sedation, and tachycardia. These agents are more likely to worsen cognitive impairment in the elderly and those with dementia (i.e., these patients are especially sensitive to the anticholinergic effects). Antimuscarinics are contraindicated in patients with narrow angle glaucoma and/or urinary retention.

A naturally occurring antimuscarinic that has been in use for many years is hyoscyamine [Levsin]. It is a non-selective antimuscarinic that can have several systemic side effects, such as dry mouth, somnolence, urinary retention, and more seriously, tachycardia and psychosis. Its use, however, has decreased with the advent of newer, more specific medications.

Oxybutynin [Ditropan, Ditropan XL, Oxytrol, Uromax] and tolterodine [Detrol, Detrol LA] are antimuscarinic agents that have been most widely utilized to treat OAB in the United States and Canada. Both oxybutynin and tolterodine are available in short acting and extended release oral formulations, and oxybutynin is also available in transdermal patch and gel applications [Gelnique, United States only, not available in Canada].[71]

TABLE 7. **Antimuscarinic medications for overactive bladder**

Name (Brand name)	Dosage	Notes
Darifenacin (Enablex)	7.5 mg-15 mg daily	Hepatic dosing; No change in dosing with renal impairment
Fesoterodine (Toviaz [US, not Canada])	4 mg-8 mg daily	Maximum 4 mg daily in renal insufficiency (CrCl < 30 ml/min) or if taking potent CYP3A4 inhibitors
Hyoscyamine (Levsin)	0.125 mg every 6 hours	Less specific than newer medications, greater incidence of side effects (rarely used).
Oxybutynin immediate release (Ditropan)	5 mg BID - QID (immediate release);	Antispasmodic and local anesthetic properties
Oxybutynin extended release (Ditropan XL/Uromax)	5 mg-30 mg daily (extended release)	Not studied in renal or hepatic impairment
Oxybutynin transdermal Oxytrol [patch]	Apply patch twice weekly – 1 patch	Not studied in renal or hepatic impairment delivers 3.9 mg/day (transdermal patch)
Oxybutynin gel, 10% (Gelnique[US, not Canada])	Apply 1 gm to skin daily	Apply to abdomen, upper arms/shoulders or thighs. Application sites should be rotated. Do not apply to the same site on consecutive days.
Solifenacin (Vesicare)	5 mg-10 mg daily	Renal and hepatic dosing reduction
Tolterodine (Detrol, Detrol LA)	1 mg-2 mg BID (Immediate release) 2 mg-4 mg daily (Extended release)	Special dosing for patients with hepatic dysfunction
Trospium (Trosec [Canada] Sanctura [US})	20 mg BID	Renal dosing (20 mg daily); does not cross easily pass BBB (fewer cognitive side effects); No known drug-drug interactions
(Sanctura XR [US])	60 mg daily	Take 1 hour before meals (empty stomach)

BBB = Blood brain barrier; M = muscarinic receptor type

When comparing the extended release to the short acting forms of oxybutynin and tolterodine, the extended release formulations have demonstrated similar efficacy and improved tolerability.[72] Tolterodine has greater affinity for M3, and oxybutynin has additional antispasmodic and local anesthetic properties not seen with other antimuscarinic agents. Most antimuscarinic agents are metabolized by the P450 enzyme system to active and/or inactive metabolites.[73] This metabolic conversion creates a risk for drug–drug interactions, resulting in either reduced or increased plasma concentration/effect of the antimuscarinic and/or interacting drug. Oxybutynin is metabolized in the liver to N-desethyloxybutynin. It is this active metabolite that is thought to be responsible for many of the adverse effects associated with the use of oxybutynin.[74]

Extended release (ER) and transdermal oxybutynin delivery systems avoid absorption in the upper gut to diminish first pass metabolism. This is thought to be one reason that these preparations of oxybutynin are associated with decreased antimuscarinic side effects.[75] The use of ER or transdermal oxybutynin delivery systems result in serum levels of N-desethyloxybutynin lower than those of oxybutynin immediate-release (IR), with lower incidences of dry mouth and constipation. In addition, ER formulations avoid peaks in drug levels that may increase side effects.

Newer medications, such as trospium [Sanctura (United States),Trosec (Canada)], darifenacin [Enablex], and solifenacin [Vesicare] boast similar rates of efficacy. Trospium has been available in Europe for more than 20 years and exhibits proven effectiveness. Advantages

seen with this medication include lower rates of dry mouth, and the potential for fewer CNS side effects secondary to its inability to cross the blood brain barrier.[76] Solifenacin and darifenacin have relative M3 selectivity while sparing the M1 receptors believed to be involved in central nervous system function. Both agents have proven effective in large trials, however anticholinergic side effects such as dry mouth and constipation are still common.[77,78] In patients with renal impairment, trospium and solifenacin doses should be adjusted according to creatinine clearance. Fesoterodine [Toviaz (United States only, not available in Canada)] was approved for OAB in the United States in 2009. It is a prodrug that is rapidly hydrolyzed to its active moiety 5-hydroxymethyl tolterodine, which is also the active metabolite of tolterodine [Detrol]. Although tolterodine has a maximum dose of 4 mg/day due to concerns about a potential for QT prolongation, fesoterodine did not prolong the QT interval in clinical trials. Its maximum approved dose (8 mg/day) has been more effective than the maximum approved dose of tolterodine (4 mg/day), but also causes more dry mouth.[79,80]

A meta-analysis of all approved antimuscarinics concluded that tolterodine IR caused less dry mouth than oxybutynin IR, and that in general, ER formulations caused less dry mouth than IR formulations.[81] Newer antimuscarinic agents appear to offer reduced incidence of side effects compared to oxybutynin IR. Each agent has demonstrated efficacy for the treatment of OAB symptoms, but their pharmacokinetic and adverse event profiles differ somewhat. There are few studies to guide the clinician in choosing a first line antimuscarinic agent for the treatment of OAB and empiric dosing with a change in medication or mode of administration may be necessary to optimize treatment results and minimize side effects. Table 7 summarizes the antimuscarinic medications for OAB.

Hormonal therapy for prostate cancer

Pathophysiology and pharmacology

The use of hormonal therapy is the mainstay for metastatic prostate cancer. Hormonal therapy is also used for conditions such as local recurrence of prostate cancer, or neoadjuvant or adjuvant treatment for high-risk disease, usually in combination with radiation therapy.[82] Androgen withdrawal causes a retardation of prostate cell growth, thought to be from programmed cell death and ischemic injury from anoxia.[83] Thus, manipulation of the testosterone axis plays an important role in the treatment of prostate cancer.[84]

Androgen production relies on the interplay of the hypothalamic-pituitary axis and the testes to produce testosterone.[84] Androgen homeostasis is achieved by pulsatile release of gonadotropin releasing hormone (GnRH) by the hypothalamus to the anterior pituitary gland every 90-120 minutes. The interaction between GnRH and LH receptors in the pituitary gland promotes the release of LH into the systemic blood circulation. LH induces testosterone production by binding to receptors on Leydig cells in the testes. Negative feedback of GnRH is exerted by testosterone through androgen receptors on the hypothalamus and pituitary glands. Currently there are three forms of pharmacological agents to induce the androgen deprived state for the treatment of prostate cancer: LHRH agonists (LHRHA); LHRH antagonists (LHRHAN); and androgen receptor blockers (antiandrogens).[85]

Recent interest has been directed toward the optimum level of testosterone that is necessary in the management of advanced prostate cancer.[86] Surgical orchiectomy is considered the "gold standard" for hormonal ablation with testosterone levels consistently measured at < 20 ng/dL (0.7 nmol/L). Traditional LHRH analogue therapy achieving testosterone levels of < 50 ng/dL (1.74 nmol/L) have been considered the standard for "chemical castration". Growing literature suggests that the lowest levels may enhance the therapeutic outcomes in metastatic prostate cancer.[87] As newer agents are developed for the management of advanced prostate cancer, more attention is being given to which agents and formulations may achieve the lowest levels of serum testosterone.

LHRH manipulation

LHRHA exert a non-pulsatile, constant stimulation on the anterior pituitary, which in turn decreases LH and testosterone production. During treatment, LH release is transiently increased up to 2 weeks after the initial dose, which is referred to as hormonal surge.[84] LH receptors are then down-regulated and testosterone production is inhibited. Hormonal surge can sometimes be dangerous, such as with severe bone pain from bone metastasis, ureteral or bladder outlet obstruction, and when neurological compromise is imminent from metastatic disease. Blockade with the initial use of an antiandrogen can be useful. Another consideration in this setting could be the use of an LHRHAN (see below).

LHRHA are found in a variety of formulations, and depending on the medication can be administered every 1 to 6 months. The available injectable medications include leuprolide [Lupron, Eligard], goserelin [Zoladex], buserelin [Suprefact] and triptorelin [Trelstar]. Buserelin is also available as a nasal spray in Canada but not in the

TABLE 8a. **Medications for the hormonal therapy of prostate cancer - LHRH agonists and antagonists**

LHRH agonists and antagonists

Name (Brand name)	Class	Administration	Notes
Buserelin (Suprefact)	LHRH agonist	SC: 500 mcg q8h X 7 days then 200 mcg daily; Depot 2-month: 6.3 mg implant every 8 weeks Depot 3-month: 9.45 mg implant every 12 weeks Intranasal: 400 mcg (200 mcg into each nostril) 3 times/day	Not available in the US. Can cause initial hormonal surge
Degarelix (Firmagon [US, not Canada])	LHRH antagonist	240 mg SC in 2 divided doses initially, the 80 mg SC every 28 days	No hormonal surge; Requires two 3 mL (40 mg/mL) injections first month, then one 4 mL (80 mg) injection monthly; administer in abdominal wall.
Goserelin acetate (Zoladex, Zoladex LA)	LHRH agonist	3.6 mg SC monthly (28 days); 10.8 mg SC q 3 months (13 weeks)	Can cause initial hormonal surge; SC resorbable implant
Histrelin implant (Vantas [US, not Canada])	LHRH agonist	SC implant 50 mg every 12 months	Remove implant at reinsertion; local anesthesia, place in upper inner arm
Leuprolide (Lupron Depot 1 month, Lupron Depot 3 month, Lupron Depot 4 month)	LHRH agonist	7.5 mg IM monthly 22.5 mg IM q 3 months; 30 mg IM q 4months (16 weeks)	Can cause initial hormonal surge
Leuprolide gel (Eligard 7.5 mg, Eligard 22.5 mg, Eligard 30 mg, Eligard 45 mg)	LHRH agonist	7.5 mg SC monthly; 22.5 mg SC q 3 months; 30 mg SC q 4 months; 45 mg SC q 6 months	Can cause initial hormonal surge; requires refrigerated storage
Leuprolide implant (Viadur [US, not Canada])	LHRH agonist	SC implant every 12 months (contains 65 mg leuprolide)	Remove implant at reinsertion Off US market for new patients since 2008
Triptorelin (Trelstar, Trelstar LA)	LHRH agonist	3.75 mg IM monthly 11.25 mg IM q 3 months (LA)	Can cause initial hormonal surge; 6 month formulation under 2010 US FDA review

TABLE 8b. **Medications for the hormonal therapy of prostate cancer - Anti-androgens**

Anti-androgens			
Name (Brand name)	**Class**	**Administration**	**Notes**
Flutamide (Euflex [Canada], Eulexin [US])	Nonsteroidal antiandrogen	250 mg PO q8h w/LHRH analog	Follow LFTs
Nilutamide (Anandron [Canada]) (Nilandron [US])	Nonsteroidal antiandrogen	Start: 300 mg PO daily x30 days, and then consider 150 mg PO daily w/LHRH analog or orchiectomy	Follow chest x-ray Follow LFTs baseline PFTs;
Bicalutamide (Casodex)	Nonsteroidal antiandrogen	50 mg PO daily w/ LHRH analog	Follow LFTs
Cyproterone acetate (Androcur) [Canada, not US]	Steroidal antiandrogen	100 mg-300 mg daily, divided into 2-3 doses (after meals)	Follow LFTs; not available in US

LFTs: liver function tests

United States, Table 8a. Side effects include hot flashes, decreased libido, erectile dysfunction, loss of bone mineral density, anemia, and mood changes.[88] There is significant interest in using bisphosphonates to treat and or prevent hormonal therapy induced osteoporosis in the United States and Canada.[89,90]

Degarelix [Firmagon, United States only, not available in Canada)] is a new LHRHAN that inhibits binding onto the LH receptor in the pituitary gland.[91] There is no hormonal surge and this unique property makes it particularly useful for conditions such as impending cord compression or urinary tract obstruction in advanced prostate cancer.

Antiandrogens

These oral agents block the androgen receptor. There are two general classes of antiandrogens: non-steroidal antiandrogens (flutamide [Euflex], nilutamide [Anandron] and bicalutamide [Casodex]), and steroidal antiandrogens (cyproterone acetate [Androcur]). In many cases, antiandrogens are administered starting 2 weeks prior to beginning LHRHA in order to reduce any adverse effects of the LHRHA-induced hormonal surge. The role of antiandrogen therapy before initiating LHRHA or use long term in combination with LHRHA (known as total or complete androgen blockade) has been debated and may be determined by patient risk factors and cost benefit ratios.[92] In certain countries, antiandrogens are part of "step up therapy" where by the dose of an agent such as bicalutamide is progressively increased up to a dose of 150 mg/day, allowing a delay before LHRHA therapy is initiated. This antiandrogen monotherapy is considered to be a treatment only in highly selected, well-informed patients who wish to remain sexually active.[93]

All antiandrogens are metabolized by the liver and induce cytochrome P450, which can result in liver toxicity, therefore liver function tests must be monitored periodically. Also, gynecomastia and mastodynia are not uncommon. Individual medications have different pharmacological properties. Flutamide may cause an increase in gastrointestinal symptoms and has a half life of up to 6 hours while nilutamide has a half life of up to 1 week and may cause impaired dark adaptation and interstitial pneumonitis.[85] See Table 8b for a comparison of oral antiandrogens.

Conclusions

The expanded use of current mediations and development of newer agents and delivery systems to treat urological conditions requires a partnership between the urologist and primary care physician to avoid complications and optimize patient outcomes. The joint management of patients with prostate disease, erectile dysfunction, hypogonadism and overactive bladder must be done with basic understanding of the pathophysiology of the disease processes, mechanisms of action of the specific medications and their inherent benefits and potential side effects.

Disclosure

Dr. Leonard Gomella is a consultant or investigator for GlaxoSmithKline, Watson, Ferring and Astra Zeneca Pharmaceuticals.
Drs. Das, Hirsch, Perkel, Lallas and Shenot have no disclosures.
Dr. Folia is a consultant to Solvay and AstraZeneca. □

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