Pharmacology for common urologic diseases: 2011 review for the primary care physician

Xiaolong S. Liu, MD,[1] Christine Folia, PharmD,[2] Leonard G. Gomella, MD[1]

[1]Department of Urology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

[2]Agro Health Associates Inc., Burlington, Ontario, Canada

LIU XS, FOLIA C, GOMELLA LG. Pharmacology for common urologic diseases: 2011 review for the primary care physician. The Canadian Journal of Urology. 2011;18(Supplement 1):24-38.

Coordination of care between the urologist and primary care physician is critical to effective treatment of a variety of urologic conditions. Medical therapies for benign prostatic hyperplasia, erectile dysfunction, hypogonadism, overactive bladder, and prostate cancer are widely available and a basic understanding of the pathophysiology of these disease states as well as the pharmacology of existing treatment options are necessary to avoid complications and maximize efficacy associated with patient outcomes. Important regulatory decisions have been made concerning the approval and lack of approval of several important urologic medications. Major advances have been made in the therapy of castrate resistant prostate cancer as well as hormonal related skeletal events secondary to advanced carcinoma of the prostate. We provide a 2011 update of the available medications for treatment of several common urologic diseases.

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

Introduction

With continued research into the pathophysiology of urologic disease processes, advances in pharmacologic options for the management of these conditions have been fast growing. New medications for treatment of benign prostatic hyperplasia (BPH), erectile dysfunction (ED), hypogonadism, overactive bladder (OAB), and prostate cancer are continuously made available as trials demonstrating clinical efficacy and safety are published in the literature. While in past decades the use of these medications were more limited to the urologist's office, primary care physicians are now often comfortable in providing initial evaluation and treatment of many urologic disorders. A fundamental understanding of the pathophysiology and pharmacology of these conditions can lead to safe and effective management approaches for these patients. We provide a 2011 update on uropharmacology for the primary care physician and will give a review of the current available medications for the treatment of both benign and malignant urologic diseases noting the differences in products available in Canada and the United States (US).[1,2]

Address correspondence to Dr. Leonard G. Gomella, Department of Urology, Kimmel Cancer Center, Thomas Jefferson University, 1025 Walnut Street, Suite 1112, Philadelphia, PA 19107 USA

Benign prostatic hyperplasia

Pathophysiology

Benign prostatic hyperplasia (BPH) is technically a histologic diagnosis referring to smooth muscle and epithelial cell proliferation in the prostatic transition zone.[3] BPH can lead to benign prostate enlargement (BPE), further deteriorating into symptomatic voiding difficulties, specifically lower urinary tract symptoms (LUTS) or bladder outlet obstruction (BOO). LUTS can be generally described as a group of irritative or obstructive voiding symptoms including urgency, frequency, nocturia, hesitancy, weak stream, intermittency, or straining.[4] BOO can be the result of a constellation of findings commonly including urinary retention, bladder calculi, increased postvoid residuals, hematuria, recurrent urinary tract infections, and less commonly renal failure or irreversible bladder dysfunction. Currently, BPH, BPE, and LUTS can be grouped together under the term symptomatic BPH (sBPH) which is a result of increased resistance to urinary flow from an obstructing prostate gland.[5] It is important to keep in mind, however, that symptoms associated with sBPH can frequently overlap with other urologic pathology or central nervous system disorders including urethral stricture, bladder dysfunction, Parkinson's disease, or multiple sclerosis to name a few. When these pathologies are suspected further work up and different treatments may be required in symptomatic patients.

sBPH in the aging male population can present a significant burden to the healthcare community. The incidence increases with age, as greater than 50% of men over the age of 60 have sBPH, which ultimately affects 90% of men in their 90s.[6] Physicians must be keenly aware that LUTS is not limited to the older population as 18% of men in their 40s can begin to experience bothersome symptoms and may be candidates for treatment.

Pharmacologic management of sBPH is based on the physiologic concept of decreasing both the prostatic tone and glandular size of the prostate. This leads to reduced resistance to urinary flow and improved patient symptomatology. Prostate smooth muscle tone can be altered via alpha$_1$ adrenoreceptors (AR) which are heavily concentrated in the prostatic urethra, stroma, and bladder neck regions.[7] Alpha$_1$ ARs are under autonomic innervation via the neurotransmitter norepinephrine (NE). Medications targeting these receptors play a critical role in the management of sBPH. Prostate glandular size is predominantly controlled by the hormones testosterone and dihydrotestosterone (DHT). Testosterone is converted to DHT via two isoenzymes – 5-alpha reductase types I and II. Type II 5-alpha reductase is more concentrated in the prostatic stroma and epithelial cells while type I is present in only approximately 10% of the prostate. The conversion of testosterone to DHT mediated by type II 5-alpha reductase is the primary moderator of prostate glandular growth and is the target of pharmacologic therapies available for treatment of sBPH.

When medical management in these patients fails there are a multitude of surgical options available for sBPH. Minimally invasive therapies including radiofrequency needle ablation or transurethral microwave therapy can be offered to alleviate symptoms.[8] Other surgical options include monopolar or bipolar transurethral resection of the prostate (TURP), laser therapies such as holmium laser enucleation or ablation of the prostate (HoLEP or HoLAP), and open or laparoscopic simple prostatectomy. All improve urinary flow by eliminating outlet resistance from the prostate gland.[3]

Pharmacology

Alpha blockers

Alpha receptor blocking medications (alpha blockers) are one of the mainstays of medical management of sBPH and among the first class of medications approved for its treatment. Blocking these receptors can lead to bladder neck and prostatic urethral relaxation resulting in improved urine flow. As a whole, alpha blockers are subdivided based on their degree of selectivity for the alpha$_1$ AR subtype. See Table 1.[9]

First generation alpha blockers (phentolamine and phenoxybenzamine) are not recommended for use in the management of sBPH secondary to their side effect profile (e.g. palpitations, dizziness, impaired ejaculation, nasal congestion, and visual disturbances) and lack of selectivity to the alpha$_1$ AR. Second generation alpha blockers (prazosin [Minipress], doxazosin [Cardura], terazosin [Hytrin]) are becoming less commonly prescribed for use in sBPH as newer medications appear on the market. Doxazosin and terazosin require dose titration and close blood pressure monitoring. However, they are inexpensive and can be dosed once daily. Prazosin is not recommended by the Canadian Urological Association or the American Urological Association guidelines for treatment of sBPH secondary to its side effect profile.[10,11] Cardiovascular side effects including hypotension, dizziness, and first dose syncope can be seen with these medications but occur at a much lower frequency compared to

TABLE 1. **Alpha blockers for symptomatic benign prostatic hyperplasia (sBPH)**

Name (Brand)	Dose	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; 4 mg daily with CrCl 30-50 mL/min	Retrograde ejaculation

*Dose titrated weekly to desired response, monitor blood pressure

first generation alpha blockers. Third generation medications (tamulosin [Flomax CR], alfuzosin [Xatral (Canada), Uroxatral (US)], and silodosin [Rapaflo, US only]) do not require titration and have been found to be more uroselective than their second generation counterparts.[9] Silodosin [Rapaflo] was approved by the US Food and Drug Administration (FDA) in 2008 and represents the latest alpha receptor blocker drug available for use in men with sBPH. All third generation alpha blockers have fewer cardiovascular side effects compared to first and second generation alpha blockers but may cause anejaculation or retrograde ejaculation.[12] Physicians must be aware that these drugs should be taken after meals to improve absorption and maximize therapeutic efficacy.

Intraoperative floppy iris syndrome (IFIS) continues to be discussed as an uncommon side effect of alpha blocker therapy in men undergoing cataract surgery. IFIS is thought to be secondary to an interaction between all alpha blockers including tamsulosin, terazosin, doxazosin, and alfuzosin, and $alpha_1$ ARs in the iris.[13] This may lead to an increased risk of surgical complications from cataract surgery. Patients with cataracts must be informed of these risks prior to starting alpha blocker therapy and may benefit from avoiding initiation of therapy until any planned cataract surgery is completed. Unfortunately, stopping alpha blockers does not always prevent the occurrence of IFIS in those who go on to have cataract surgery (up to 75% still present with IFIS). In June 2009, the American Academy of Ophthalmology and the American Society of Cataract and Refractive Surgery released their most current recommendations for patients taking alpha blockers and IFIS and are summarized in Table 2.

5-alpha reductase inhibitors

Prostatic glandular enlargement can lead to sBPH and bothersome LUTS. As previously discussed, gland growth and enlargement are under control of DHT via the isoenzymes 5-alpha reductase types I and II. The 5-alpha reductase inhibitors (5-ARI) finasteride [Proscar] and dutasteride [Avodart] have been shown to reduce prostate size and improve sBPH, Table 3.

Finasteride specifically inhibits the type II isoenzyme leading to decreases in serum DHT by 70%-90%. Over a 6-12 month period the prostate size can be reduced by 20%-30%.[14] Dutasteride blocks both type I and type II 5-alpha reductase leading to elimination of DHT to levels near zero in the serum.[14] Unfortunately, 5-ARIs can lead to decreased libido, sexual dysfunction, gynecomastia, and male breast tenderness. Both medications demonstrate similar efficacy and tolerability, and should not be handled by women of childbearing age as they are teratogenic. Additionally, both finasteride and dutasteride can be prescribed for prostate related bleeding as they inhibit microvascular proliferation (block vascular endothelial growth factor) and can be an effective treatment for refractory hematuria secondary to prostatic bleeding.[15]

TABLE 2. **Current recommendations concerning alpha blockers for symptomatic BPH and 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 June 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 place them at increased risk for surgical complications and should consider having surgery done before initiating 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

Recently, there have been several publications and studies analyzing the use of 5-ARIs as chemoprevention for prostate cancer. The Prostate Cancer Prevention Trial (PCPT) with finasteride demonstrated a 25% relative risk reduction in the incidence of prostate cancer over 7 years but suggested an increase in the detection of high risk disease compared to placebo.[16] More recently, the REDUCE (REduction by DUtsteride of prostate Cancer Events) trial showed results similar to the PCPT with prostate cancer risk reduction of approximately 23% over a 4 year period with the 5-ARI dutasteride.[17,18] While these results are promising, neither 5-ARI agent has been approved by Health Canada or in the United States for chemoprevention of prostate cancer. A major meeting of the US FDA Oncology Drugs Advisory Committee (ODAC) in December 2010 rejected the use of the entire class of 5-ARIs for prostate cancer risk reduction (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM239355.pdf).

Alpha blocker and 5-ARI combination therapy

The Medical Therapy of Prostatic Symptoms (MTOPS) trial was the first to demonstrate that combination therapy with an alpha blocker (doxazosin) and a 5-ARI (finasteride) was superior to either alone in preventing sBPH progression.[19] Specifically, the incidence of urinary retention and need for surgical therapy was reduced in those taking combination therapy. Similarly the CombAT (Combination of Avodart and Tamusloin) trial published in 2008 demonstrated a greater improvement in urinary symptoms in men with BPE on combination therapy compared to either

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

Name (Brand)	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
Dutasteride (Avodart)	0.5 mg daily	3-5 weeks	Inhibits types I and II 5-AR*	Same as above
Dutasteride/ Tamsulosin (Jalyn [US, not Canada])	0.5 mg dutasteride & 0.4 mg tamsulosin combination daily	9-13 hours (tamsulosin), 3-5 weeks (dutasteride)	Combination 5-ARI and alpha blocker	See dutasteride and tamsulosin

*5-AR = 5-alpha reductase

monotherapy alone over 24 months.[20] In 2010, Jalyn a single-capsule combination of dutasteride 0.5 mg and tamsulosin 0.4 mg was approved for use in the United States in men with sBPH based on two year study results from the CombAT trial, Table 3. Combination therapy should be considered in all men with symptoms as a result of BPE and BOO.

Erectile dysfunction

Pathophysiology

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance.[21] Approximately 50% of men over the age of 40 are affected by ED.[22] The etiology of ED covers the spectrum of medical pathology including neurogenic, cardiovascular, hormonal/endocrine, psychiatric, and pharmacologic induced. Treatment options are varied and should be tailored to patient specific requirements.

The pathophysiology to produce penile erection for sexual intercourse relies on a cascade of neurovascular events. Starting with appropriate sexual stimulation, parasympathetic nerve fibers cause endothelial cells to release nitric oxide (NO) which enter corporal smooth muscle inciting the conversion of cyclic guanine triphosphate (cGPT) to cyclic guanosine monophosphate (cGMP). This step stimulates penile corporal smooth muscle relaxation and increased blood flow producing penile rigidity necessary for erection and sexual function. Detumescence occurs when cGMP is hydrolyzed by the isoenzyme phosphodiesterase-type 5 (PDE-5).[23] Circulating androgens can also play a key role on libido and regulation of cGMP, PDE-5, and NO synthase expression.[24]

Pharmacology

Medical oral therapy for ED

The phosphodiesterase-5 inhibitors (PDE-5i) sildenafil [Viagra], vardenafil [Levitra], and tadalafil [Cialis] are common oral treatment options for ED, Table 4.[25] They function by inhibiting the degradation of cGMP by PDE-5 amplifying the effect of NO and preventing detumesence. All PDE-5i are comparable in efficacy but differ in their pharmacokinetics and side effect profiles. These differences are attributed to their interactions with the different PDE isoenzymes. Eleven different isoenzymes of PDE have been identified in human tissues. For instance, the PDE-6 isoenzyme is concentrated in the eye. Sildenafil has a high affinity for PDE-6 leading to a "blue haze" effect that is rarely seen with the other agents in this class. Vardenafil has been found to prolong the QT interval while tadalafil can be associated with muscle pain in 9% of patients.[26] All three PDE-5i can lead to facial flushing, headache, and rhinitis. These medications should be taken 20-60 minutes prior to the onset of sexual activity allowing time to reach maximum plasma concentration. In 2008, the FDA approved tadalafil as a once daily dosing regimen to prevent the inconvenience of "on demand" dosing.[27]

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

Name (Brand)	Dose	Time to maximum plasma concentration	Serum half life	Affected by food	Side effects/Notes ++
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 haze")
Vardenafil (Levitra)	5 mg-20 mg 25-60 minutes before sexual activity Max 1x day	60 minutes	4 hrs	Yes; delays onset	Increases QT interval; avoid use with other medications which have similar side effect
Tadalafil (Cialis)	10 mg-20 mg 30 min before sexual activity 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

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

Name (Brand)	Dosage	Mechanism of action	Side effects/Notes
Alprostadil TU (MUSE)	250 mcg-1000 mcg Max 2 administrations per 24 hrs	Synthetic PGE1 stimulates increased levels of cAMP	Painful erection; urethral pain; bleeding; bleeding; priapism (rare)
Alprostadil IC (Caverject, Edex†)	2.5 mcg-20 mcg* Max 1x daily and 3x weekly	Same as above	Penile pain, fibrosis hematoma; priapism (rare)
Papaverine IC‡	15 mg-60 mg (monotherapy) 5 mg-20 mg (combination therapy)	Non-selective PDEi increases cAMP and cGMP	Priapism; fibrosis
Phentolamine IC‡	0.5 mg-1 mg (combination therapy with papaverine)	Alpha blocker inhibiting sympathetic tone to penis	Hypotension; reflex tachycardia

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

All healthcare providers who prescribe PDE-5i must be aware that they are contraindicated with concurrent use of nitrates which can lead to pronounced vascular smooth muscle relaxation and possible death. Patients with cardiac risk factors who are taking nitrates or may require initiation of nitrate therapy should be informed of these risks and should seek other forms of treatment for their ED. Non-arteritic anterior ischemic optic neuropathy (NAION) has also been recognized as a rare side effect in patients taking PDE-5i. NAION is a sudden painless ischemic event of the optic nerve resulting in visual field defects and impaired light perception.[28] Health Canada and the World Health Organization have advised patients to contact their physician and stop PDE-5i medication immediately should any visual disturbances occur. Any previous history of NAION or visual difficulty should be documented prior to initiation of PDE-5i therapy in patients with ED.

Intraurethral and intracavernosal ED therapy

For those patients who are refractory to PDE-5i oral therapy, a variety of local pharmacologic options may be attempted. Similar to the PDE-5/cGMP mechanism, prostaglandin E1 (PGE1) stimulates adenyl cyclase to increase cyclic adenosine monophosphate (cAMP) levels leading to arteriolar vasodilation, penile smooth muscle relaxation, and penile erection. Alprostadil [MUSE] is a synthetic PGE1 analog available as a small pellet that can be inserted into the urethra where it then diffuses into both the corpora spongiosum and cavernosa, Table 5.[29] Minimal side effects and drug interactions are noted due to its local application and absorption. Rarely, penile pain, burning, and vaginal discomfort in sexual partners may be encountered.

Intracavernosal (IC) injection therapies such as alprostadil [Caverject, Edex (US only)], papaverine, and phentolamine can be effective second line options in patients with ED, Table 5. Alprostadil is an injectable PGE1 analog with a mechanism of action identical to its intraurethral counterpart.[29] Side effects include pain at the injection site, hematoma, and priapism (prolonged erection). Papaverine is a non-selective PDEi that can increase levels of cAMP. Both priapism (up to 35%) and corporal fibrosis (up to 33%) can result from its use.[30] Phentolamine is an alpha blocker that is used in conjunction (no effect when used alone) with the two previously mentioned IC therapies potentiating their effects on penile vasculature and smooth muscle. Combination IC medications such as Tri-mix (alprostadil, papaverine, and phentolamine) have been shown to produce synergistic action resulting in high success rates (up to 87%) for sexual function.[31] However, these combinations have not been officially approved for use by Health Canada or the US FDA.

Hypogonadism

Pathophysiology

Testosterone is primarily produced by the Leydig cell in the male testes. Its production is regulated by the

hypothalamic-pituitary axis, where low levels promote pituitary secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) thereby stimulating testosterone synthesis. Total serum levels of testosterone exist in three types: unbound (free and active, 2%), bound to sex hormone binding globulin (inactive, 30%), and the rest bound to albumin (bioavailable).[32] Levels begin to gradually decline by the end of the third decade of life. The rate of decline has been found to be approximately 10% per decade after the age of 40.[33] Therefore, aging males are subject to a variety of symptoms associated with low levels of testosterone.

The diagnosis of male hypogonadism requires the presence of both clinical symptoms and documented biochemical evidence of low serum testosterone. Patient symptoms of hypogonadism include ED, diminished libido, depressed mood, fatigue, anemia, and osteoporosis. Laboratory examination should be drawn with a morning total testosterone. Hypogonadism can be divided into two categories, primary or secondary depending on the etiology. Primary hypogonadism (congenital or acquired) occurs as a result of testicular failure to produce testosterone secondary to conditions such as cryptorchidism, bilateral testicular torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. Laboratory findings in these men include low serum testosterone concentrations with FSH and LH levels above the normal range. Secondary causes of hypogonadism are due to insufficient FSH and LH production by the pituitary gland. Hypogonadotropic hypogonadism (congenital or acquired) can be the result of idiopathic gonadotropin or luteinizing

TABLE 6. **Testosterone replacement therapy (TRT) for male hypogonadism**

Name (Brand)	Route	Dose	Notes*
Testosterone (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 every 3-4 weeks (100 mg-150 mg every 2 weeks preferred)	
Testosterone enanthate (Delatestryl)	IM injection	100 mg-400 mg every 4 weeks (100 mg-150 mg every 2 weeks preferred)	
Testosterone gel (AndroGel 1%)	Topical	5 g-10 g daily (max)	Apply to clean dry shoulder area, upper arm, or abdomen
Testosterone gel (Testim 1%)	Topical	5 g-10 g daily (max)	Apply to clean dry area on shoulder or upper arm
Testosterone gel (Fortesta [US, not Canada])	Topical	10 mg-70 mg daily (max)	Apply to inner thigh area only
Testosterone topical solution (Axiron, [US, not Canada])	Topical	30 mg-120 mg daily (max)	Apply once daily to axillary region
Testosterone patch (Androderm)	Transdermal	2.5 mg-7.5 mg daily	Apply to clean dry area on back or arm; rotate site; remove for MRI as patch contains metal
Testosterone implant (Testopel) [US, not Canada]	Implantable pellets 75 mg/each	150 mg-450 mg SC implant every 3-6 months 2 pellets for each 25 mg testosterone required weekly	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
Testosterone undecanoate (Nebido) [US, not Canada]	IM injection	1000 mg every 6-12 weeks	

*Monitor levels of serum testosterone for all agents.

hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from trauma, tumors, or radiation. These men have low serum testosterone levels but have gonadotropins levels in the normal or low range. The expertise of an endocrinologist may be necessary when the diagnosis of hypogonadism is suspected.

Pharmacology

Primary therapy in patients with hypogonadism includes testosterone replacement therapy (TRT). Treatment with TRT may improve sexual function and have other effects on bone density and improved mood/libido.[34-36] General side effects of TRT include gynecomastia, erythrocytosis, and testicular atrophy. Several methods of testosterone delivery are available for use: oral, intramuscular (IM) injection, and topical formulations, Table 6. Oral alkylated androgens (e.g., fluoxymesterone, methyltestosterone) are administered daily and undergo hepatic elimination making it difficult to achieve consistent therapeutic levels in serum. This can result in unwanted mood swings and sexual side effects. Due to this method of metabolism, liver toxicity including hepatocellular adenomas, hemorrhagic cysts, and cholestatic jaundice have been reported.[37] Oral administration of alkylated androgens has lost its popularity in the United States secondary to its pharmacokinetics and list of side effects. In contrast, testosterone undecanoate [Andriol] is the only oral form available in Canada. This formulation avoids the first pass effect in the liver all but eliminating liver toxicity from its side effect profile.[38] IM injections (testosterone cypionate [Depo-Testosterone] and testosterone enanthate [Delatestryl]) can be dosed every 2-4 weeks but can be associated with supraphysiologic levels of hormone and low nadirs resulting in alterations in mood and infertility through negative feedback suppression of FSH and LH.[32] Transdermal patches [Androderm] and gels [AndroGel, Testim] can be directly applied to the skin and have been found to more closely follow physiologic cycles of serum hormone levels.[32] Fortesta™ (testosterone gel) was approved by the US FDA in December 2010 (not approved in Canada) and indicated for testosterone replacement in hypogonadal men and is approved for application to the inner thigh region. Axiron, a testosterone topical solution, is another formulation in this class approved in November 2010 by the US FDA also for TRT in hypogonadal men. Skin irritation or rash is a common side effect of the patch and less seen in the gel formulation.[39] Patients should wash their hands after any topical application of gels to prevent transmission of drug to others and should also be cautioned to allow the gel to dry completely before smoking as this formulation can be flammable.

Newer long acting testosterone derivatives have been released onto the US market in the last 2 years. Testosterone undecanoate [Nebido] IM can be administered at 6-12 week intervals.[40] Implantable pellets [Testopel] can be placed in the upper buttock under local anesthesia every 6 months. These modalities are safe, efficacious, and present convenient dosing intervals for TRT in the hypogonadal male.[32] Buccal preparations [Striant] have also demonstrated favorable results with a low side effect profile (mainly buccal irritation and bitter taste) but are not yet available in Canada.[41]

TRT in patients with a history of prostate cancer should be avoided. Its use for hypogonadal men after treatment of prostate cancer with radical prostatectomy has drawn interest.[42] However, primary care physicians should seek urologic consultation in this patient population prior to initiating treatment.

Overactive bladder

Pathophysiology

Physiologic bladder filling, storage, and emptying of urine is a complex neuromuscular interaction between the brain, spinal cord, and autonomic nervous system. The filling and storage phase is moderated by a sympathetic norepinephrine pathway and is normally characterized by low intravesical pressures protecting against vesico-ureteral reflux, incontinence, and bladder dysfunction.[43,44] Voiding is mediated by parasympathetic stimulation of detrusor smooth muscle leading to bladder contraction with a concomitant decrease in urethral resistance and relaxation of the external striated sphincter (inhibition of sympathetic tone to somatic nerves controlling the external sphincter).[45] The neurotransmitter acetylcholine interacts with muscarinic (M) receptors found within the bladder (mainly M2 and M3 receptors) resulting in bladder smooth muscle contraction during normal voiding.[45]

The International Continence Society (ICS) defines overactive bladder (OAB) as a syndrome characterized by urgency, with or without urgency incontinence, usually with frequency and nocturia.[46] Depending on survey methods and OAB definition, the prevalence of symptoms vary in population-based studies. However, OAB is estimated to affect 1 in 5 Canadian adults and increases in prevalence with aging.[47-49] The cost of OAB diagnosis and treatment has been estimated to approach $12 billion USD per year. The causes of

OAB commonly include neurologic conditions (e.g. stroke or multiple sclerosis), detrusor smooth muscle remodeling secondary to BPE, as well as several other idiopathic conditions.[44] Patients suffering from OAB can experience a significant decrease in quality of life and suffer from a multitude of resulting conditions (e.g. urinary tract infections, falls, skin irritation, etc).[50-53]

Pharmacology

Antimuscarinic medications are the mainstay of medical therapy for treatment of OAB, Table 7. They act by inhibiting M2 and M3 receptors located on detrusor smooth muscle cells within the bladder.[54] Antimuscarinics reduce urgency and increase bladder capacity but lack total selectivity for the bladder leading to a multitude of side effects limiting their efficacy. Dry mouth and constipation are the most common with gastroesophageal reflux, blurred vision, cognitive impairment, and sedation also reported. Octogenarians or those with baseline dementia who take anticholinergics must be warned of possible worsening cognitive impairment. This class of medications is contraindicated in any patient with narrow angle glaucoma or a history of urinary retention.

Among the first antimuscarinics was hyoscyamine [Levsin (US only)], a naturally occurring compound found in certain plants of the *Solanaceae* family. However, it is a non-selective antimuscarinic that has several systemic side effects limiting its use in light of the advent of newer medications. Oxybutynin [Ditropan, Ditropan XL, Oxytrol, Uromax] and tolterodine [Detrol, Detrol LA] have been historically the most widely used antimuscarinics for treatment of OAB. They are available in short acting and extended release forms, transdermal patches, and gel applications [Gelnique (US only)].[55] The extended release and transdermal formulations of

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

Name (Brand)	**Dose**	**Notes**
Darifenacin (Enablex)	7.5 mg-15 mg daily	Hepatic dosing; no change in dosing with renal insufficiency
Fesoterodine (Toviaz [US, not Canada])	4 mg-8 mg daily	Maximum 4 mg daily in renal insufficiency or if taking other CYP3A4 inhibitors
Hyosycamine (Levsin [US, not Canada])	0.125 mg every 6 hours	Less specific than newer medications, greater incidence of side effects
Oxybutynin IR (Ditropan)	5 mg BID or QID	Antispasmodic and local anesthetic properties
Oxybutynin ER (Ditropan XL/Uromax [Canada only]	5 mg-30 mg daily (extended release)	Not studied in renal or hepatic impairment
Oxybutynin gel (Gelnique 10% [US, not Canada])	1 gm to skin daily	Apply to abdomen; upper arms; thighs or shoulders; sites should be rotated; do not apply to same site for consecutive days
Oxybutynin transdermal Oxytrol [patch]	Apply twice weekly – 1 patch, delivers 3.9 mg/day	Not studied in renal or hepatic impairment
Solifenacin (Vesicare)	5 mg-10 mg daily	Reduce dose in renal or hepatic dysfunction
Tolterodine (Detrol, Detrol LA)	1 mg-2 mg BID (IR formulation) 2 mg-4 mg daily (ER formulation)	Special dosing for hepatic dysfunction
Trospium (Trosec [Canada], Sanctura [US}, Sanctura XR [US])	20 mg BID (IR formulation) 60 mg daily (ER formulation)	Reduce dose for renal insufficiency; dose not cross blood brain barrier (fewer cognitive side effects); take ER formulation 1 hour before meals

oxybutynin avoid first pass metabolism in the upper gastrointestinal tract leading to lower incidences of both dry mouth and constipation.[56] In addition, extended release forms of both oxybutynin and tolterodine have been shown to provide similar efficacy to their immediate release formulations but also demonstrated improved tolerability among patients.[57]

Newer generations of antimuscarinics that have been approved for use for OAB have demonstrated equal efficacy and improved side effect profiles compared to oxybutynin and tolterodine. Trospium [Sanctura (US), Trosec (Canada)] has been available for over 20 years in Europe and shows lower rates of dry mouth and CNS side effects secondary to its inability to cross the blood brain barrier.[58] Solifenacin [Vesicare] and darifenacin [Enablex] have been reported to have improved M3 receptor selectivity.[59,60] Both trospium and solifenacin should be dose titrated in those with baseline renal impairment. Fesoterodine [Toviaz (US only)] was the latest approved antimuscarinic (2009) for treatment of OAB. Its maximum dose of 8 mg/day has been shown to be more effective than maximum doses of tolterodine (4 mg/day) but can lead to more instances of dry mouth.[61,62]

The decision to prescribe one of the many antimuscarinics mentioned above can often be a difficult one for the primary care physician. With each demonstrating clinical efficacy, the decision should primarily hinge on patient tolerability of side effects. Each formulation has different side effect profiles and change in medication dose or mode of administration should not be frowned upon when treating patients with OAB. Most antimuscarinics are metabolized via the cytochrome P450 system which can create a risk for drug-drug interactions.[63] Drug prescription labels and safety information profiles should be checked by both the prescribing physician and pharmacy especially in those patients taking a multitude of medications for other medical conditions.

Prostate cancer

Pathophysiology

Similar to BPH, prostate cancer cellular growth is mediated by testosterone and DHT under control of the hypothalamic-pituitary axis.[64] Release of gonadotropin releasing hormone (GnRH) by the hypothalamus to the anterior pituitary promotes LH secretion and subsequent testosterone production in the testes. Physiologic negative feedback mechanisms regulate this system. Hormonal therapies for neoadjuvant/adjuvant prostate cancer treatment, local prostate cancer recurrence, or metastatic/high risk disease target this axis to achieve cancer control. Surgical bilateral orchiectomy has been the historical gold standard for hormone ablation with testosterone levels falling to < 20 ng/dL (0.69 nmol/L) postoperatively. Chemical or pharmacologic castration using LHRH agonists (LHRHA), LHRH antagonists (LHRHAN), and androgen receptor blockers (antiandrogens) can achieve testosterone levels < 50 ng/dL (1.73 nmol/L).[65] As more literature is published suggesting lower levels of testosterone improve outcomes in metastatic prostate cancer, different pharmacologic agents and formulations are continuously developed to achieve lower levels of androgen hormone.[66]

Pharmacology

LHRH agonists and antagonists

LHRHA therapy creates a pharmacologic negative feedback loop by constant stimulation of the anterior pituitary leading to decreased levels of LH and testosterone production. After the initial dose, there is a transient hormonal surge of LH that then becomes down-regulated after approximately 2 weeks.[64] This surge in LH and testosterone can be dangerous with advanced prostate cancer as bone pain from bony metastases, BOO, or neurologic compromise secondary to imminent spinal metastasis can all occur during this time period. Initial blockade with an antiandrogen can be helpful in this setting.

LHRHA can be administered every 1 to 6 months in a variety of different formulations. These include leuprolide [Lupron, Eligard], goserelin [Zoladex], buserelin [Suprefact], and triptorelin [Trelstar], Table 8a. Side effects of all LHRHA include hot flashes, decreased libido, erectile dysfunction, anemia, mood changes, and loss of bone mineral density.[67] LHRHAN such as degarelix [Firmagon] work by inhibiting binding of the LH receptor in the pituitary gland. Therefore, there is no hormonal surge as seen with LHRHA making it useful in those patients with impending cord compression or BOO from advanced prostate cancer.

On a related note, there are significant concerns over the long term use of any LHRHA or LHRHAN inducing osteoporosis and increasing fracture risk in men. Strategies to reduce this risk are becoming commonplace in the management of this chemically induced hypogonadism. Bisphosphonates are used to treat or prevent those prostate cancer patients at risk for hormonal induced osteoporosis, osteopenia, or pathologic fracture.[68,69] Historically, zoledronic acid [Zometa] was the first approved agent for preventing

TABLE 8a. **LHRH agonist and LHRH antagonists as hormonal therapy for prostate cancer**

Name (Brand)	Class	Administration	Notes
Buserelin (Suprefact [Canada only])	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	Can cause initial hormonal surge
Degarelix (Firmagon)	LHRH antagonist	240 mg SC in 2 divided doses initially, the 80 mg SC every 28 days	No hormonal surge; administer in abdominal wall
Goserelin acetate (Zoladex, Zoladex LA)	LHRH agonist	3.6 mg SC monthly (28 days); 10.8 mg SC every 3 months (13 weeks)	Can cause initial hormonal surge; SC resorbable implant
Histrelin (Vantas)	LHRH agonist	SC implant 50 mg every 12 months	Remove implant at reinsertion; local anesthesia, place in upper inner arm
Leuprolide (Lupron Depot)	LHRH agonist	7.5 mg IM monthly 22.5 mg IM every 3 months; 30 mg IM every (16 weeks)	Can cause initial hormonal surge
Leuprolide gel (Eligard)	LHRH agonist	7.5 mg monthly; 22.5 mg every 3 months; 30 mg every 4 months; 45 mg every 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)	Off US market for new patients since 2008
Triptorelin (Trelstar, Trelstar LA)	LHRH agonist	3.75 mg IM monthly 11.25 mg IM every 3 months 22.5 mg IM every 6 months (US only)	Can cause initial hormonal surge

skeletal events in men with metastatic prostate cancer, Table 8b.[70] More recently in 2010, denosumab [Xgeva (US only)], a human monoclonal antibody against the receptor activated of nuclear factor k-B ligand (RANKL) was studied in a randomized phase III trial versus zoledronic acid to treat men with bone metastases from castrate-resistant prostate cancer, Table 8b.[71,72] Denosumab demonstrated a delay to the primary endpoint (defined as time to first on-study skeletal-related event – occurrence of a pathologic fracture, bone radiation or surgery, or spinal cord compression) by 18% with a difference of 3.6 months. Physicians should be aware of skeletal related events in their patients with metastatic prostate cancer and

TABLE 8b. **Medications for prevention of skeletal related events secondary to advanced or castrate resistant prostate cancer (CRPC) and newer agents for treatment of CRPC**

Name (Brand)	Dose	Mechanism	Side effects/Notes
Zoledronic acid (Zometa)	4 mg IV infusion over 15 min every 3-4 weeks	Bisphosphonate	Reduce dose in patients with renal insufficiency; rare reports of osteonecrosis of the jaw; given with Vitamin D and calcium supplementation (indicated for treatment of bone metastases only in Canada)
Denosumab (Xgeva [US, not Canada])	120 mg every 4 weeks SC	Monoclonal antibody targeting RANKL	Severe hypocalcemia can be seen; reports of osteonecrosis of the jaw; given with Vitamin D and calcium supplementation (Note there is different formulation/ dosing than denosumab [Prolia] used in female osteoporosis)
Docetaxel (Taxotere)	75 mg/m^2 IV infusion over 1 hour every 3 weeks Given in combination with 5 mg prednisone oral twice daily	Suppresses microtubule assembly dynamics	Should not be given in patients with elevated LFTs or who are neutropenic; severe fluid retention can also result
Cabazitaxel (Jevtana [US, not Canada])	25 mg/m^2 IV infusion over 1 hour every 3 weeks Given in combination with 10 mg prednisone oral once daily	Same as for docetaxel	Contraindicated in neutropenic patients or those with previous hypersensitivity; renal and GI toxicity reported
Sipuleucel-T (Provenge [US, not Canada])	Leukapheresis process 2-3 days prior to each dose to collect patient's own immune cells; IV infusion in 3 doses given 2 weeks apart	Utilizes patients own immune cells to target cancer cells	Fevers; chills; fatigue; weakness; respiratory issues; dizziness; headache; GI upset all reported

might consider offering medical therapy in these instances. It should also be noted that denosumab is also approved as the brand name Prolia (Canada and US) for post-menopausal osteoporosis at a different dosage (60 mg every 6 months versus 210 mg every 4 weeks for Xgeva).

Antiandrogens

Antiandrogens are oral agents that block the androgen receptors required for prostate cancer progression and growth, Table 8c. There are two different classes of antiandrogens: non-steroidal (flutamide [Euflex], nilutamide [Anandron], and bicalutamide [Casodex]) and steroid antiandrogens (cyproterone acetate [Androcur, Canada only]). As previously discussed, antiandrogens are frequently prescribed to prevent the hormonal surge associated with initial LHRHA administration. Complete androgen blockade for treatment of advanced prostate cancer with combination LHRHA or LHRHAN and antiandrogen therapy has been debated and should be patient specific determined by a cost-benefit analysis.[73] Antiandrogen monotherapy for prostate cancer should be avoided by the general practitioner and used only in highly select

TABLE 8c. **Antiandrogen hormonal therapy for prostate cancer**

Name (Brand)	Class	Administration	Notes
Flutamide (Euflex [Canada], Eulexin [US])	Nonsteroidal antiandrogen	250 mg PO every 8 hours 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, Androcur Depot [Canada, not US]	Steroidal antiandrogen	100 mg-300 mg PO daily, divided into 2-3 doses (after meals) 300 mg IM weekly or 300 mg IM q2weeks (if orchiectomized)	Follow LFTs; not available in US

LFTs = liver function tests

cases where well-informed patients wish to remain sexually active by avoiding LHRHA therapy.[74] Liver function tests must be monitored periodically in those taking antiandrogens as they are metabolized by the cytochrome P450 system in the liver.

Castrate resistant prostate cancer

There have been several developments in the treatment of advanced prostate cancer over the last year that warrant further discussion. Castrate resistant prostate cancer (CRPC) is the cause of death in most men with advanced disease. The above mentioned androgen ablation therapies are used as the standard of care for metastatic prostate cancer. However, many patients develop CRPC defined as progressive disease despite castrate levels of serum testosterone (i.e. < 50 ng/dL or < 1.73 nmol/L).[75] This advanced disease state is now termed CRPC or metastatic CRPC (mCRPC). The historic term of "hormone refractory prostate cancer" is now considered to be a misnomer since it has been recognized that there is actually increased production of intra-tumoral androgens in patients with CRPC.

Prior to 2004, chemotherapy for CRPC was limited to palliative care with mitoxantrone [Novantrone]. Two trials in 2004 established docetaxel [Taxotere] as the standard of care for CRPC.[76,77] In 2010 cabazitaxel [Jevtana (US only)], a novel taxane, was approved for the treatment of patients with mCRPC who failed docetaxel-based chemotherapy, Table 8b.

Sipuleucel-T [Provenge (US only)] is a first of its kind therapeutic cancer vaccine that uses patients' own immune cells to stimulate an immune response against prostate cancer cells, Table 8b.[78] Sipuleucel-T is indicated for the treatment of patients with mCRPC with either minimal or no symptoms. Studies showed a significant improvement in median overall survival with sipuleucel-T compared with placebo of about 4 months.[78] Administration requires a series of three leukophoresis procedures as well as processing of the cells at a production facility where the patient's own dendritic cells are modified for subsequent reinfusion.

Conclusion

With the increased prevalence of many common urologic diseases as the average age of the adult population in North America shifts upward, the primary care physician will continue to play an increasing role in the treatment of patients with both malignant and benign urologic conditions. Treatment of sBPH, ED, hypogonadism, OAB, and prostate cancer require frequent interaction and management discussions between the urologist and the patient's general practitioner to maximize therapeutic efficacy and limit medical toxicity. With a basic understanding of urologic pathophysiology as well as pharmacologic mechanisms of action, dosing regimens and side effect profiles of common urologic medical therapies, primary care physicians are better armed to engage their patients in a discussion regarding treatment options for a number of urologic disease processes. □

References

1. Gittens PR, Lallas CD, Pe ML, Perkel R, Folia C, Gomella LG. Uropharmacology for the primary care physician. *Can J Urol* 2008; 15(Suppl 1):78-91;discussion 91.
2. Gomella LG, Lallas CD, Perkel R, Folia C, Hirsch I, Das A, Shenot P. Uropharmacology in primary care: 2010 update. *Can J Urol* 2010; 17(Suppl 1):35-51.
3. Auffenberg G, Helfan B, McVary K. Established medical therapy for benign prostate hyperplasia. *Urol Clin North Am* 2009;36(4):443-459.
4. Laborde EE, McVary KT. Medical management of lower urinary tract symptoms. *Rev Urol* 2009;11(Suppl 1):S19-S25.
5. Burnett AL, Wein AJ. Benign prostatic hyperplasia in primary care: what you need to know. *J Urol* 2006;175(3 Pt 2):S19-S24.
6. Bushman W. Etiology, epidemiology, and natural history of benign prostatic hyperplasia. *Urol Clin North Am* 2009;36(4):403-415.
7. Lepor H. Pathophysiology of benign prostatic hyperplasia: insights from medical therapy for the disease. *Rev Urol* 2009;11(Suppl 1):S9-S13.
8. Van Hest P, D'Ancona F. Update in minimal invasive therapy in benign prostatic hyperplasia. *Minerva Urol Nefrol* 2009;61(3):257-268.
9. Roehrborn CG. Efficacy of alpha-adrenergic receptor blockers in the treatment of male lower urinary tract symptoms. *Rev Urol* 2009;11(Suppl 1):S1-S8.
10. Nickel JC, Herschorn S, Corcos J et al; Canadian Prostate Health Council; Canadian Urological Association Guidelines Committee. Canadian guidelines for the management of benign prostatic hyperplasia. *Can J Urol* 2005;12(3):2677-2683.
11. McVary KT, Roehrborn CG, Avins AL et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol* 2011;185:1794-1804.
12. Kaplan SA. Side effects of alpha-blocker use: retrograde ejaculation. *Rev Urol* 2009;11(Suppl 1):S14-S18.
13. Issa SA, Hadid OH, Baylis O, Dayan M. Alpha antagonists and intraoperative floppy iris syndrome: A spectrum. *Clin Ophthalmol* 2008;2(4):735-741.
14. Aggarwal S, Thareja S, Verma A, Bhardwaj TR, Kumar M. An overview on 5alpha-reductase inhibitors. *Steroids* 2010;75(2):109-153.
15. Memis A, Ozden C, Ozdal OL, Guzel O, Han O, Seckin S. Effect of finasteride treatment on suburethral prostatic microvessel density in patients with hematuria related to benign prostate hyperplasia. *Urol Int* 2008;80(2):177-180.
16. Thompson IM, Goodman PJ, Tangen CM et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349(3):215-224.
17. Gomella LG. Chemoprevention using dutasteride: the REDUCE trial. *Curr Opin Urol* 2005;15(1):29-32.
18. Andriole GL, Bostwick D, Brawley O et al. The influence of dutasteride on the risk of biopsy-detectable prostate cancer: outcomes of the REduction by DUtasteride of prostate Cancer Events (REDUCE) study. *N Engl J Med* 2010;362(13):1192-1202.
19. McConnell JD, Bruskewitz R, Walsh P et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. *N Engl J Med* 1998;338(9):557-563.
20. Roehrborn CG, Siami P, Barkin J et al. CombAT Study Group. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. *J Urol* 2008;179(2):616-621.
21. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994;151(1):54-61.
22. Grover SA, Lowensteyn I, Kaouache M et al. The prevalence of erectile dysfunction in the primary care setting. *Arch Intern Med* 2006;166:213-219.
23. Lue TF. Erectile dysfunction. *N Engl J Med* 2000;342(24):1802-1813.
24. Morelli A, Corona G, Filippi S, Ambrosini S, Forti G, Vignozzi L. Which patients with sexual dysfunction are suitable for testosterone replacment therapy? *J Endocrinol Invest* 2007;30(10):880-888.
25. Eardley I, Donatucci C, Corbin J et al. Pharmacotherapy for erectile dysfunction. *J Sex Med* 2010;7(1 Pt 2):524-540.
26. Seftel AD, Farber J, Fletcher J et al. A three-part study to investigate the incidence and potential etiologies of tadalafil-associated back pain or myalgia. *Int J Impot Res* 2005;17(5):455-461.
27. Wrishko R, Sorsaburu S, Wong D, Strawbridge A, McGill J. Safety, efficacy, and pharmacokinetic overview of low-dose daily administration of tadalafil. *J Sex Med* 2009;6(7):2039-2048.
28. Mathews MK. Nonarteritic anterior ischemic optic neuropathy. *Curr Opin Ophthalmol* 2005;16(6):341-345.
29. Heidelbaugh JJ. Management of erectile dysfunction. *Am Fam Physician* 2010;81(3):305-312.
30. Montorsi F, Salonia A, Deho F et al. Pharmacological management of erectile dysfunction. *BJU Int* 2003;91(5):446-454.
31. Hatzimouratidis K, Hatzichristou DG. A comparative review of the options for treatment of erectile dysfunction: which treatment for which patient? *Drugs* 2005;65(12):1621-1650.
32. Morales A, Buvat J, Gooren LJ et al. Endocrine aspects of sexual dysfunction in men. *J Sex Med* 2004;1(1):69-81.
33. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab* 2001;86(2):724-731.
34. Seftel AD, Mack RJ, Secrest AR, Smith TM. Restorative increases in serum testosterone levels are significantly correlated to improvements in sexual functioning. *J Androl* 2004;25(6):963-972.
35. Wang C, Swerdloff RS, Iranmanesh A et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab* 2000;85(8):2839-2853.
36. Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J Clin Endocrinol Metab* 2003;88(6):2673-2681.
37. Bagatell CJ, Bremner WJ. Androgens in men--uses and abuses. *N Engl J Med* 1996;334(11):707-714.
38. Jockenhovel F. Testosterone therapy--what, when and to whom? *Aging Male* 2004;7(4):319-324.
39. Lazarou S, Morgentaler A. Hypogonadism in the man with erectile dysfunction: what to look for and when to treat. *Curr Urol Rep* 2005;6(6):476-481.
40. Gooren LJ. Advances in testosterone replacement therapy. *Front Horm Res* 2009;37:32-51.
41. Korbonits M, Kipnes M, Grossman AB. Striant SR: a novel, effective and convenient testosterone therapy for male hypogonadism. *Int J Clin Pract* 2004;58(11):1073-1080.
42. Morgentaler A. Rapidly shifting concepts regarding androgens and prostate cancer. *Scientific World Journal* 2009;27(9):685-690.
43. Erdem N, Chu FM. Management of overactive bladder and urge urinary incontinence in the elderly patient. *Am J Med* 2006;119(3 Suppl 1):29-36.
44. Brading AF. A myogenic basis for the overactive bladder. *Urology* 1997;50(6A Suppl):57-67.
45. Ouslander JG. Management of overactive bladder. *N Engl J Med* 2004;350(8):786-799.

46. Abrams P, Blaivas JG, Stanton SL, Andersen JT. The standardisation of terminology of lower urinary tract function. The International Continence Society Committee on Standardisation of Terminology. *Scand J Urol Nephrol Suppl* 1988;114:5-19.
47. Stewart WF, Van Rooyen JB, Cundiff GW et al. Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003;20(6):327-336.
48. Hannestad YS, Rortveit G, Sandvik H, Hunskaar S. A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT study. Epidemiology of Incontinence in the County of Nord-Trondelag. *J Clin Epidemiol* 2000;53(11):1150-1157.
49. Corcos J, Schick E. Prevalence of overactive bladder and incontinence in Canada. *Can J Urol* 2004;11(3):2278-2284.
50. Hu TW, Wagner TH, Bentkover JD et al. Estimated economic costs of overactive bladder in the United States. *Urology* 2003;61(6):1123-1128.
51. Langa KM, Fultz NH, Saint S, Kabeto MU, Herzog AR. Informal caregiving time and costs for urinary incontinence in older individuals in the United States. *J Am Geriatr Soc* 2002;50(4):733-737.
52. Jackson S. The patient with an overactive bladder--symptoms and quality-of-life issues. *Urology* 1997;50(6A Suppl):18-22;discussion 23-14.
53. Thom DH, Haan MN, Van Den Eeden SK. Medically recognized urinary incontinence and risks of hospitalization, nursing home admission and mortality. *Age Aging* 1997;26(5):367-374.
54. Scarpero HM, Dmochowski RR. Muscarinic receptors: what we know. *Curr Urol Rep* 2003;4(6):421-428.
55. Staskin DR, Robinson D.Oxybutynin chloride topical gel: a new formulation of an established antimuscarinic therapy for overactive bladder. *Expert Opin Pharmacother* 2009;10(18):3103-3111.
56. Sand PK. The evolution of transdermal therapy for overactive bladder. *Current Urol Reports* 2009;10:338-341.
57. Chu FM, Dmochowski RR, Lama DJ, Anderson RU, Sand PK. Extended-release formulations of oxybutynin and tolterodine exhibit similar central nervous system tolerability profiles: a subanalysis of data from the OPERA trial. *Am J Obstet Gynecol* 2005;192(6):1849-1854.
58. Doroshyenko O, Jetter A, Odenthal KP, Fuhr U. Clinical pharmacokinetics of trospium chloride. *Clin Pharmacokinet* 2005;44(7):701-720.
59. Haab F, Stewart L, Dwyer P. Darifenacin, an M3 selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder. *Eur Urol* 2004;45(4):420-429.
60. Cardozo L, Lisec M, Millard R et al. Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol* 2004;172(5 Pt 1):1919-1924.
61. Nitti VW, Dmochowski R, Sand PK et al. Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. *J Urol* 2007;178(6):2488-2494.
62. Sand PK, Morrow JD, Bavendam T, Creanga DL, Nitti VW. Efficacy and tolerability of fesoterodine in women with overactive bladder. *Int Urogynecol J Pelvic Floor Dysfunct* 2009;20(7):827-835.
63. Guay DR. Clinical pharmacokinetics of drugs used to treat urge incontinence. *Clin Pharmacokinet* 2003;42:1243-1285.
64. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. *JAMA* 2005;294(2):238-244.
65. Pinthus JH. Androgen deprivation therapy for prostate cancer. *AUA Update Series* 2006;25(Lesson 15):134-139.
66. Gomella LG. Effective testosterone suppression for prostate cancer: is there a best castration therapy? *Rev Urol* 2009;11(2):52-60.
67. Gomella LG, Johannes J, Trabulsi EJ. Current prostate cancer treatments: effect on quality of life. *Urology* 2009;73(5 Suppl):S28-S35.
68. Saad F, Abrahamsson PA, Miller K. Preserving bone health in patients with hormone-sensitive prostate cancer: the role of bisphosphonates. *BJU Int* 2009;104(11):1573-1579.
69. Lau YK, Lee E, Prior HJ, Lix LM, Metge CJ, Leslie WD. Fracture risk in androgen deprivation therapy: a Canadian population based analysis. *Can J Urol* 2009;16(6):4908-4914.
70. Saad F, Gleason DM, Murray R et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;94(19):1458-1468.
71. Silver DA. Denosumab reduces the incidence of new vertebral fractures in men with prostate cancer. *Curr Osteoporos Rep* 2010;8(1):1-3.
72. Fizazi K, Carducci M, Smith M et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomized, double-blind study. *Lancet* 2011;377:813-822.
73. Chodak G, Gomella L, Phung de H. Combined androgen blockade in advanced prostate cancer: looking back to move forward. *Clin Genitourin Cancer* 2007;5(6):371-378.
74. Baltogiannis D, Giannakopoulos X, Charalabopoulos K, Sofikitis N. Monotherapy in advanced prostate cancer: an overview. *Exp Oncol* 2004;26(3):185-191.
75. Chen Y, Sawyers CL, Scher HI. Targeting the androgen receptor pathway in prostate cancer. *Curr Opin Pharmacol* 2008;8(4):440-448.
76. Petrylak DP, Tangen CM, Hussain MH et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351(15):1513-1520.
77. Tannock IF, de Wit R, Berry WR et al. TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351(15):1502-1512.
78. Kantoff PW, Higano CS, Shore ND et al. IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363(5):411-422.