Uropharmacology for the primary care physician

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Advances in the understanding of the pathophysiology of a variety of urological disorders have resulted in the development of novel medications to manage these diseases. While many disorders such as erectile dysfunction, overactive bladder, hypogonadism and benign prostatic hypertrophy have traditionally been managed primarily by urologists, the use of these newer medications has become commonplace in the primary care setting. For example, symptomatic benign prostatic hyperplasia therapy, while historically treated with primary surgical intervention, is now commonly initially managed with medical therapy. Prostate cancer patients are being treated with newer formulations of long term hormone therapy that range from monthly to yearly administration. Additionally, the open dialogue about erectile dysfunction can be directly traced to the development of oral therapy for this condition. Testosterone replacement therapy can be administered using a variety of oral, transdermal and intramuscular therapies in order to minimize side effects and provide a more consistent dosing pattern. Finally, overactive bladder, which is a significant problem socially, has many new medications available for its treatment. This article will review some of the newer classes of urological medications, provide an understanding of basic uropharmacology that may guide treatment recommendations, and provide insight into the potential adverse side effects and interactions of these useful medications.

Key Words: uropharmacology, urological medications

Introduction

Over the past several decades, improved understanding of the physiology that underlies various urological diseases and conditions has led to the development of many new medications. The use of these medications for the treatment of urological diseases has expanded from the urologist's office to the office of the primary care physician, who may provide both the initial evaluation and treatment. 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 their urological care. In this review, we focus on the significant advances in the medical management of common urological diseases such as benign and malignant diseases of the prostate, erectile dysfunction, overactive bladder and hypogonadism.

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Symptomatic benign prostatic hyperplasia

Pathophysiology and pharmacology

Benign prostate hyperplasia (BPH) is a term that is commonly, but incorrectly, used for prostatic

obstruction leading to urinary symptoms. BPH is a histologic diagnosis, the precursor to benign prostate enlargement (BPE). BPE can then lead to changes in voiding habits consistent with bladder outlet obstruction (BOO). This article will use symptomatic (sBPH) to encompass BPH, BPE and lower urinary symptoms (LUTS).[1,2] LUTS are constellation of irritative symptoms such as urgency, frequency and nocturia, or obstructive symptoms such as hesitancy, weak stream, intermittency or straining. While traditionally viewed as a disease of "inconvenience", sequelae of sBPH may sometimes include urinary retention, increased post void residual, bladder calculi, renal failure, hematuria, urinary tract infection 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 (e.g., urethral stricture, bladder dysfunction, neurological disorders including Parkinson disease and multiple sclerosis).

sBPH affects more than 50% of men over the age of sixty. The incidence steadily increases to approximately 90% as men reach their ninth decade of life.[1,2] 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 progressing to require surgical intervention.[1,2]

The smooth muscle tone of the prostate can be the primary cause responsible for 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. Within alpha$_1$ AR there are three subtypes that have been identified: alpha$_{1A}$, alpha$_{1B}$, and alpha$_{1D}$.[3] A considerable amount of attention has been placed on the alpha$_{1A}$ subtype because of its high concentration in the prostatic urethra, stroma and bladder neck. By pharmacologically targeting these receptor subtypes, a decrease in tone can be elicited and lead to symptom relief.

sBPH can also be the result of the mechanical impediment of urinary flow from an enlarged prostate gland. Testosterone and dihydrotestosterone (DHT) are the predominant male hormones responsible for virilizaton 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 (10% found in the prostate), and type II, 5-α-reductase is present in the stroma and basal epithelial cells of the prostate and is responsible for intraprostatic conversion.[4] The conversion of testosterone to DHT by type II 5-α-reductase is mostly responsible for the growth of the prostate. Interestingly, DHT also indirectly modulates vascular derived endothelial growth factor (VEGF), causing microvascular proliferation, and contributes to the increased vascularity and hematuria occasionally seen in patients with sBPH.[5,6] The management of sBPH today can include surgical debulking of the prostate with standard or newer "minimally invasive" technologies such as lasers or radio frequency ablation. Pharmacological management, which is typically the initial management approach, is based on two concepts: reducing prostatic tone and decreasing the size of the prostate gland, thus leading to less resistance of flow.

Alpha-blockers

Alpha adrenergic antagonists competitively inhibit the alpha AR. Blocking these receptors promotes bladder neck and prostatic urethral relaxation. Alpha AR blocking agents (alpha-blockers) can be subdivided depending on their degree of selectivity for the AR and patient tolerability.[7,8] Correspondingly, there are first generation (phentolamine, phenoxybenzamine), second generation (prazosin [Minipress], doxazosin [Cardura], terazosin [Hytrin]), and third generation (tamsulosin [Flomax CR], alfuzosin [Xatral]) agents. Canadian Urological Association (CUA) guidelines do not recommend first generation alpha-blockers or prazosin in the treatment of sBPH.[9] The alpha-blockers were among the first class of medications approved for the treatment of sBPH.

First generation alpha-blockers are no longer considered in the management of sBPH because of their severe side effect profile, such as non-selectivity toward the alpha$_1$ and alpha$_2$ ARs, and irreversibility found in phenoxybenzamine. 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. According to the CUA guidelines, 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.[9]

Second generation alpha-blockers are commonly associated with cardiovascular symptoms such as hypotension, dizziness, fatigue, and first dose syncope, although these actually occur less than with first generation alpha-blockers. These adverse reactions are thought to be due to interactions with alpha$_1$

TABLE 1. **Alpha-blocker medications for symptomatic benign prostatic hyperplasia (sBPH)**

Name	Dosage	Side effects
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)	10 mg daily with food	Dizziness; headache; minimal cardiovascular effect; less ejaculatory dysfunction then 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

*Dose titrated weekly to desired response.

receptors that control the tone of systemic blood vessels and those in the central nervous system (CNS).[2] However, it is cautioned that alpha-blockers should not be used as the primary treatment for blood pressure management.[10] Second generation alpha-blockers require titration over several weeks until maximum dosages are obtained. Individually, these medications differ somewhat in their side effect profiles. Terazosin has a peak plasma concentration that is delayed with fatty meals. Doxazosin is hepatically metabolized, so caution should be used in patients with liver pathology.[11]

The third generation alpha-blockers tamsulosin and alfuzosin have been found to have minimal cardiovascular effects while exerting the desired effect of decreasing the symptoms associated with BPH. Unlike their second generation counterparts, both medications do not need to be titrated. Alfuzosin is noted to be pharmacologically similar to the second generation but clinically it is has been found to be more uroselective, exhibiting minimal cardiovascular side effects. Tamsulosin selectively targets the bladder and prostatic urethra, having a high affinity for the $alpha_{1A}$ AR. Alfuzosin and tamsulosin exhibit similar side effects, such as dizziness, but tamsulosin has been found to have higher rates of ejaculatory dysfunction (10%) (anejaculation and/or retrograde ejaculation), which may be attributed to an affinity toward 5HT1A and D2 receptors centrally.[12] To improve absorption, alfuzosin and tamsulosin (generic capsules) should be taken after the same meal daily. (Flomax CR tablets may be taken with or without food.)

An uncommon side effect of alpha-blockers is intraoperative floppy iris syndrome (IFIS), a condition that occurs during phacoemulsification cataract surgery and was first described in 2005.[13] The syndrome is characterized by a triad of events that may lead to a more difficult cataract operation and an increased risk of surgical complications of up to 49%.[14] The cause of IFIS is thought to be due to the interaction between alpha-blockers and the heavily dominated $alpha_{1A}$ receptors in the iris. Tamsulosin has been implicated in several case reports of causing IFIS.[13,14] In anecdotal studies, terazosin, doxazosin, and alfuzosin have also been implicated as culprits, but to a lesser degree.[15,16] Currently, it is recommended that one discontinue tamsulosin therapy for 1 to 2 weeks prior to cataract surgery.[13,17] Table 1.

5-alpha-reductase inhibitors

An enlarged prostate gland, although not directly correlated with degree of prostatic obstruction, can be a cause of sBPH. Finasteride [Proscar] and dutasteride [Avodart] are the two agents in the category of 5-alpha-reductase inhibitors (5-ARI). Finasteride is also available in a lower dosage to treat alopecia [Propecia].

Both finasteride and dutasteride act by blocking the conversion of testosterone to DHT. Decreases in DHT have been shown to induce prostatic epithelial apoptosis and atrophy.[18] Finasteride is a type II 5-ARI that has been found to decrease serum DHT by 70%-90% within the prostate, causing a reduction in prostate size by 20%-30% over a 6-12 month period.[18,19] The loss of glandular tissue is responsible for a decrease in prostate-specific antigen (PSA) by

TABLE 2. **5-alpha-reductase inhibitor medications for symptomatic benign prostatic hyperplasia (sBPH)**

Name	Dose	Half-life	Mechanism	Side effects
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

42% and 50% at 3 and 6 months, respectively.[19] This PSA change should be considered when screening for prostate cancer in patients that have been prescribed a 5-ARI. 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, but differ in that dutasteride has a half life of several weeks, however this has not been shown to have any adverse consequences.[20,21] Table 2.

Data suggest that 5-ARI can be utilized as a chemoprevention agent against prostate cancer (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.[22] The results demonstrated a decreased incidence of prostate cancer, initially reported an increase in the incidence of high grade prostate cancer when compared to placebo. The latest evidence suggests that the observed increase in high grade cancers was influenced by the smaller post treatment prostate volumes that 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.[23,24]

To date, finasteride is the only medication in a prospective randomized trial to reduce the incidence of prostate cancer. A study is currently ongoing to determine if dutasteride can also reduce the risk of prostate cancer.[25]

The side effects of the 5-ARI family include decreased libido, sexual dysfunction, gynecomastia, and breast tenderness. Blood donations should be delayed by 6 months in men taking dutasteride due to the extended half life. The inhibition of DHT also has the added advantage of decreasing bleeding from the prostate by indirectly inhibiting microvascular proliferation.[5] Both medications are considered to be teratogenic and should not be handled by women of childbearing age.

Combination sBPH therapy

Concomitant 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 was a landmark study whose goal was to determine if clinical disease progression could be reduced by doxazosin and finasteride as mono- or combination therapy.[21] Combination therapy was found to be superior to both doxazosin and finasteride individually in preventing disease progression. 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 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.[26] This combination of dutasteride with tamsulosin was approved in 2008 in the United States by the FDA for sBPH.

Erectile dysfunction

Pathophysiology and pharmacology

Erectile dysfunction (ED) is the consistent inability to achieve and maintain an erection sufficient for sexual intercourse.[6] ED can have complex implications on the psychosocial well-being of patients. Additionally, ED may be the presenting symptom of cardiovascular or endocrine abnormalities. Approximately 50% of men over age 40 are affected by ED.[27-29] Multiple factors may be attributed to ED, including neurogenic, hormonal, arterial, cavernosal, and drug induced; collectively, these are classified as organic or psychogenic and/or a combination of the two.

A symphony of well-correlated psychological, neurovascular, muscular and chemical events are necessary to obtain an adequate erection. Simply put, during sexual stimulation, impulses from the

parasympathetic nerve fibers lead to a release of nitric oxide from endothelial cells. Nitric oxide then enters smooth muscle cells stimulating guanylyl cyclase and 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 an increase in smooth muscle tone and blood flow to the corporal sinusoids. A net decrease in venous outflow occurs due to occlusion of subtunical venular plexuses that are compressed against the wall of the tunica albuginea, resulting in an erection. Detumescence occurs when cGMP is hydrolyzed to GMP by phosphodiesterase type 5 isoenzyme (PDE5).[30] Eleven isoenzymes of PDE have been identified in human tissue.[13] PDE5 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 have a role in the regulation of cGMP, PDE5 and nitric oxide synthase expression.[31-33]

Oral therapy for erectile dysfunction

Erectile dysfunction can be managed by medical therapy, intracavernosal injections, mechanical enhancements such as vacuum tumescence devices and penile prosthesis, with the oral agents having the biggest market share today. Sildenafil [Viagra], vardenafil [Levitra] and tadalafil [Cialis] are oral phosphodiesterase-5 inhibitors (PDE5i). PDE5i function by slowing the degradation of cGMP, enhancing the effect of nitric oxide and amplifying the relaxation of the cavernosal smooth muscles. The PDE5i are 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 PDE6 isoenzyme, which is concentrated in the eye. This particular interaction may lead to blue tinged vision, a side effect that is rarely seen with vardenafil or tadalafil. Vardenafil has been found to prolong the QT interval, and tadalafil has a high rate of muscle pain (up to 9% of users).[34]

Sildenafil and vardenafil have a serum half life of approximately 4 hours while tadalafil exhibits a half life of approximately 17.5 hours.[13] The longer half life of tadalafil has not been correlated with significant side effects. Additionally, sildenafil and vardenafil interact with fatty meals which can slow the time of onset. All three PDE5i may exhibit symptoms of facial flushing, headache and rhinitis. Recently, tadalafil has been approved for a daily dosing regimen to theoretically avoid the need for "on-demand" dosing.

PDE5i are contraindicated with concurrent use of nitrates because of excessive systemic vascular smooth muscle relaxation causing pronounced hypotension and possible death. Patients with cardiac risk factors should be screened and grouped prior to initiation of treatment.[35] Current guidelines from the Princeton Consensus Conference have categorized patients into low, intermediate, and high risk based on their cardiovascular disease. 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]

Non-arteritic anterior ischemic optic neuropathy (NAION) is an adverse effect that has been recognized in patients taking PDE5i. It has classically been described as a sudden, painless, and unilateral irreversible ischemic event of the intraocular optic nerve.[38] Interestingly, 10% of patients have been reported to experience ocular pain. On ocular examination, 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. Several cases have been reported since 2005.[39,40] Some risk factors of NAION include prolonged surgical procedures, hypovolemia, hemodilution through volume expansion, hypotension, and underlying vasculopathic diseases such as hyperlipidemia, hypertension, diabetes, and prothrombotic disorders.[41] Currently, the World Health Organization (WHO) and Health Canada have concluded that there is no definitive evidence connecting NAION and PDE5i, but patients should be advised to call a physician and stop the medication if any visual difficulties occur.[42] Physicians should also be aware of the symptoms of NAION and try to elicit a history of visual loss or NAION prior to prescribing PDE5i. Table 3.

Oral PDE5i 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. Patients that are hypogonadal and do not initially respond to PDE5i have been found to have sustainable erections after testosterone levels have been normalized and PDE5i are continued.[43,44]

Intraurethral therapy for erectile dysfunction

In the event that oral therapy is unsuccessful, other pharmacological options are available for patients

TABLE 3. **Oral phososphodiesterase-5 inhibitors medications for erectile dysfunction**

Name	Dosage	Time to maximum plasma concentration	Serum half life (hrs)	Affected by food	Notable side effects (other than headache, flushing, rhinitis, dyspepsia)
Sildenafil (Viagra)	25 mg-100 mg 30-60 minutes before sexual activity Max 1x day	60 minutes	4	Yes Delays onset	Visual disturbances
Vardenafil (Levitra)	5 mg-20 mg 25-60 minutes before sexual activity Max 1x day	60 minutes	4	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 Effective within 30 minutes Max 1x day Daily dosing: 2.5 mg-5 mg daily	120 minutes	17.5	No	Myalgia, back pain

with ED. Prostaglandin E1 (PGE1) stimulates adenyl cyclase to increase levels of cAMP; this stimulates adenylate cyclase, which ultimately causes arteriolar vasodilatation and increased arterial blood flow leading to erection. Alprostadil [MUSE] is a synthetic PGE1 that is inserted into the urethra and is then absorbed by the corpora cavernosum and spongiosum. Efficacy is approximately 60%, with lower reports in patients who are either post prostatectomy or have suffered a spinal cord injury.[20] One of the advantages of using intraurethral alprostadil is local absorption, and thus minimal systemic side effects and drug interactions. Intraurethral alprostadil may cause penile pain, warmth and burning, vaginal discomfort in partners, and hypotension. First-use office administration is advised. Table 4.

TABLE 4. **Transurethral (TU) and intracavernosal (IC) medications for erectile dysfunction**

Name	Dosage	Mechanism of action	Side effects
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 (Caverjet)	2.5 mcg-20 mcg* Max 1x daily and 3x weekly	Same as Alprostadil TU	Penile pain, fibrosis hematoma; priapism (rare)
Papavarine IC†	15 mg-60 mg (monotherapy) 5 mg-20 mg (used in combination)	Non-selective PDE inhibitor increases cAMP and cGMP	Priapism; corporal fibrosis
Phentolamine IC†	0.5 mg-1 mg (used in combination)	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 approved by Health Canada for this use.

Intracavernosal therapy for erectile dysfunction

There are three intracavernosal (IC) injection therapies used for the treatment of ED. Alprostadil [Caverject] 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 officially approved intracavernosal agent.[45-47] 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.[20] 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.

Although not approved by Health Canada, combining IC medications has also been found to be effective in the treatment of ED, with high rates of success and a lower risk of side effects, since lower doses of each agent can be used. 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.[48-50] Table 4.

Hypogonadism

Pathophysiology and pharmacology

A patient with ED will sometimes have concurrent hypogonadism. 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.[51,52] Common symptoms of hypogonadism include ED, diminished libido, depressed mood, fatigue, decreased lean body mass, anemia, and osteoporosis.

The diagnosis of hypogonadism should be suspected based on clinical findings and laboratory examination. The work-up of the patient presenting with signs and symptoms of hypogonadism is beyond the scope of this article, but the laboratory examination should begin with a morning total serum testosterone. In the normal male blood, testosterone exists in three forms: 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.[31] The realm of hypogonadism includes primary and secondary etiologies. Primary hypogonadism occurs when there is failure of the testes to produce testosterone, and secondary hypogonadism is due to insufficient production of LH and FSH by the pituitary gland. If discovered, the underlying causes for the hypogonadism should be investigated by a specialist.

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.[53-55] Thus, men with the stigmata and laboratory findings of hypogonadism, even in the absence of sexual dysfunction, 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.[31,56] Testosterone replacement with oral alkylated androgens has lost popularity for other administration routes in the United States, however the use of other oral medications, like testosterone undecanoate [Andriol], is 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 testosterone undecanoate which avoids the first pass effect.[57] Oral testosterone undecanoate is administered daily and must be taken with food for optimal absorption.

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, especially with extended dosing intervals.[31] These fluctuations may

TABLE 5. **Medications for hypogonadism**

Name	Route	Dosage
Testosterone undecanoate (Andriol)	Oral	40 mg-160 mg daily
Testosterone cypionate (Depo-Testosterone)	IM injection	200 mg-400 mg q 3-4 weeks (100 mg-150 mg q 2 weeks preferred)
Testosterone enanthate (Delatestryl)	IM injection	100 mg-400 mg q 4 weeks (100 mg-150 mg q 2 weeks preferred)
Testosterone gel (Androgel 1%)	Topical	5 g-10 g daily
Testosterone gel (Testim 1%)	Topical	5 g-10 g daily
Testosterone patch (Androderm)	Transdermal patch	2.5 mg-7.5 mg daily

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.[31] 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. The most annoying side effects of these formulations are skin irritation and rash, which seems to be less common with the use of gels.[58]

New buccal preparations 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.[59]

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.[59] Some side effects reported with testosterone therapy include gynecomastia, erythrocytosis, testicular atrophy, and skin reactions (with topical formulations).[60] Table 5.

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.[61,62] This low pressure protects against urinary 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 NE is released and stimulates 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.[63] 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 in the bladder detrusor, leading to contraction of bladder smooth muscle.[63]

Overactive bladder (OAB) is a medical condition characterized by symptoms of urgency, with or without urinary incontinence, accompanied by frequency and nocturia.[64] 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.[65-67] 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.[62] 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.[68-71]

Antimuscarinics

The medications primarily used in OAB are antimuscarinic agents. This group acts by blocking acetylcholine from interacting with the M receptor, and resulting in a decrease in uninhibited bladder contractions and a decrease in the force of contraction, leading to a reduction in both urgency and urge incontinence.[72] Side effects observed with this class of medications are attributed to interactions with the M receptor subtypes outside the bladder and are anticholinergic in nature. Dry mouth, constipation, gastroesophageal reflux, cognitive impairment, blurred vision, sedation, and tachycardia are not uncommon. Antimuscarinics are contraindicated in patients with narrow angle glaucoma and/or urinary retention.[61]

A naturally occurring antimuscarinic that has been in use for several years is hyoscyamine [Levsin]. It is a more general 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, Oxytrol, Uromax] and tolterodine [Detrol] are antimuscarinic agents that have been used traditionally in the United States and Canada. Newer medications, such as trospium [Trosec], darifenacin [Enablex], and solifenacin [Vesicare] have recently been introduced, and boast similar rates of efficacy. Both oxybutynin and tolterodine are available in short acting and extended release oral formulations, and oxybutynin is also available in a transdermal application. 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.[73] Tolterodine has greater affinity for M3, and oxybutynin has additional antispasmodic properties not seen with other antimuscarinic agents.

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 few CNS side effects secondary to its inability to cross the blood brain barrier.[74] Solifenacin and darifenacin have M3 selectivity. Both of these medications have been found to have high rates of constipation likely due

TABLE 6. **Medications for overactive bladder**

Antimuscarinics		
Name	**Dosage**	**Notes**
Oxybutynin (Ditropan, Ditropan XL, Oxytrol [patch], Uromax)	5 mg BID - QID (short acting); 5 mg-30 mg daily (extended release); Apply patch twice weekly – 1 patch delivers 3.9 mg/day (transdermal patch)	Antispasmodic properties
Tolterodine (Detrol, Detrol LA)	1 mg-2 mg BID (short acting) 2 mg-4 mg daily (long acting)	Special dosing for patients with hepatic dysfunction
Trospium (Trosec)	20 mg BID Take on empty stomach	Renal dosing; does not cross BBB (fewer cognitive side effects)
Solifenacin (Vesicare)	5 mg-10 mg daily	Renal and hepatic dosing; M3 selective
Darifenacin (Enablex)	7.5 mg-15 mg daily	M3>M2
Hyoscyamine (Levsin)		Less specific than newer medications, greater incidence of side effects. (rarely used)

BBB = Blood brain barrier; M = muscarinic receptor type

to interaction with M3 receptors in the colon.[75,76] In patients with renal impairment, trospium and solifenacin doses should be adjusted according to creatinine clearance. Table 6.

Hormonal therapy for prostate cancer

Pathophysiology and pharmacology

The treatment for prostate cancer varies depending on a multitude of factors related to the Gleason score, PSA, pathological stage, age of the patient, and the presence of symptoms. The treatment for low grade prostate cancer in a healthy young patient usually is monotherapy either via radical prostatectomy or radiation therapy. The need for hormonal therapy arises in conditions including local recurrence of prostate cancer, neoadjuvant or adjuvant treatment for high-risk disease, and in metastatic disease with or without symptoms.[77]

Normal prostate cells and malignant prostate cancer cells at least initially rely on androgen stimulation via androgen receptors for growth and vascular proliferation. Androgen withdrawal causes a retardation of prostate cell growth, thought to be from programmed cell death and ischemic injury from anoxia.[78,79] Thus, manipulation of the hormonal milieu plays a role in the treatment of prostate cancer, and decreases morbidity and increases survival.[80-82]

Androgen production relies on the interplay of the hypothalamic-pituitary axis and the testes to produce testosterone.[83] 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).[84]

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. 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.

LHRHA are found in a variety of formulations, and depending on the medication can be administered every 1 to 6 months. The available medications include leuprolide [Lupron, Eligard], goserelin [Zoladex] and triptorelin [Trelstar]. Associated side effects include hot flashes, decreased libido, erectile dysfunction, loss of bone mineral density, anemia, and mood changes.

Abarelix [Plenaxis] is a LHRHAN that inhibits binding onto the LH receptor in the pituitary gland. This drug that was taken off the US market due to financial considerations and but may still be used in men who were treated before the May 2005 action. It has limited availability outside of the United States but is not available in Canada. Unlike LHRHA, there is no hormonal surge. However, the use of this medication is limited by a 3.7% chance of anaphylaxis and the possibility of an increased QT interval.[85]

Antiandrogens

Antiandrogen therapy is used to block the androgen receptor. The two classes of antiandrogens are non-steroidal (flutamide [Euflex], nilutamide [Anandron] and bicalutamide [Casodex]), and steroidal (cyproterone acetate [Androcur]). In many cases, antiandrogens are administered for 2 weeks prior to beginning LHRHA in order to reduce any adverse effects of the hormonal surge. The role of antiandrogen therapy before initiating LHRHA or use long term in combination with LHRHA (known as total androgen blockade) has been debated and may be determined by patient risk factors and cost benefit ratios.[86] 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.[84] All of these agents can cause gynecomastia. Table 7.

TABLE 7. **Medications for prostate cancer**

Medications	Class	Administration	Notes
LHRH manipulation			
Leuprolide (Lupron Depot 1 month, Lupron Depot 3 month, Lupron Depot 4 month)	LHRH agonists	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 (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
Goserelin acetate (Zoladex 3.6, Zoladex LA 10.8)	LHRH agonist	3.6 mg SC monthly (28 days); 10.8 mg SC q 3 months (13 weeks)	Can cause initial hormonal surge
Triptorelin (Trelstar, Trelstar LA)	LHRH agonist	3.75 mg IM monthly 11.25 mg IM q 3 months (LA)	Can cause initial hormonal surge
Androgen receptor blockade			
Flutamide (Euflex)	Nonsteroidal antiandrogen	250 mg PO q8h w/LHRH analog	Follow LFTs
Nilutamide (Anandron)	Nonsteroidal antiandrogen	Start: 300 mg PO daily x30 days, then 150 mg PO daily w/LHRH analog or orchiectomy	Follow chest x-ray and consider baseline PFTs; Follow LFTs
Bicalutamide (Casodex)	Nonsteroidal antiandrogen	50 mg PO daily w/ LHRH analog	Follow LFTs
Cyproterone acetate (Androcur)	Steroidal antiandrogen	100 mg-300 mg daily, divided into 2-3 doses (take after meals)	Follow LFTs

LFTs = liver function tests; PFTs = pulmonary function tests

Conclusions

Overall, the treatment of urological disease and dysfunction can be complicated and somewhat overwhelming to the patient. A basic understanding of medications and their inherent properties is important for successful treatment that may be supervised by the primary care physician. Also, the primary care physician should be aware of the contraindications and interactions of pharmacological interventions and have an understanding of when further urological consultation is warranted. In this common but potentially complicated area of clinical medicine, a successful working partnership between the primary care physician and urologist is important.

Disclosure

Dr. Leonard Gomella is a consultant for GlaxoSmithKline and TAP Pharmaceuticals. He is a member of the Speakers' Bureau for Astra Zeneca. □

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DISCUSSION

Question (Dr. Rosenberg):
What are the consequences of using antimuscarinic agents that cross blood brain barrier?

Answer (Dr. Gomella):
This class of agents is commonly used to treat overactive bladder, a condition characterized by urgency, with or without urinary incontinence, frequency and nocturia. These agents can have central nervous system side effects that may include cognitive impairment, sedation and rarely frank psychosis. Some of the later more selective forms of antimuscarinic agents such as trospium may have less central effects due to its reduced ability to cross the blood-brain barrier.

Question (Dr. Laroche):
Please discuss the use of antimuscarinics in terms of their impact on QT abnormalities (i.e. Canadian and US guidelines and possible contraindications)?

Answer (Dr. Gomella):
We have an increased appreciation of the potential effects of drugs on the myocardium including agents with antimuscarinic activity. This has increased the need for the evaluation of new drugs for cardiac safety issues. Due to the potential of these medications inducing QT abnormalities they should be cautiously prescribed in patients with a known history of QT prolongation or in patients using antiarrhythmic agents that affect the QT interval.