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EDITORIAL

A New Update: Urology Best Practices for the Primary Care Physician (PCP)

In early 2008, the publishers and editors of the *Canadian Journal of Urology* met in Montreal to review the documents associated with the Journal supplement that we were preparing. We noted that a significant number of patients with urology-related problems initially present to the primary care physician (PCP). Unfortunately, the amount of formal urology education that these physicians receive in medical schools is minimal.

Over the last number of years there has been a major paradigm shift in the management of a number of urologic conditions. Many urologic conditions are initially treated medically rather than surgically.

We have also seen that a number of urologic presentations are linked to other medical conditions that can better be identified and managed by the PCP.

There was a knowledge gap.

The *Canadian Journal of Urology* supplement "Urology Update for Primary Care Physicians" was published in 2008. It was a joint effort between expert urologists and expert PCPs to create the "go-to" reference journal for the major PCP-identified urologic conditions such as benign prostatic hyperplasia, erectile dysfunction, andropause, overactive bladder, and prostate cancer.

We were very successful, as demonstrated by the positive feedback and international wide-spread use of the supplement by PCPs.

In the short time since the supplement was published, new study findings have been presented and published, which in some cases support and in other cases refute some of our recently accepted beliefs about these urologic conditions and our treatment approaches.

In November 2009 the Society of Urologic Surgeons of Ontario (SUSO) presented an Educational Day for Family Physicians, which was co-chaired by Dr. Alan Toguri (Urology) and Dr. John Axler (PCP). The profit from the SUSO update meeting went to the Ontario Medical Association student bursary fund. After each didactic presentation, PCPs had an opportunity in small group settings to discuss, reflect and question what had been presented with one of the urologists in attendance.

Presentations from this symposium, discussion points and questions raised by this recent group of PCPs and the content of the original supplement provided the basis and background for the articles contained in this 2010 urology update for PCPs.

We hope that this supplement, with the most up-to-date clinical study data, will provide PCPs with valuable and practical insights about the current approaches to diagnosis and management of these common urologic conditions.

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Erectile dysfunction and low testosterone: cause or an effect?

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BARKIN J. Erectile dysfunction and low testosterone: cause or an effect? The Canadian Journal of Urology. 2010;17(Supplement 1):2-11.

Studies have repeatedly confirmed that about 52% of men between the ages of 40 and 70 years have some degree of erectile dysfunction (ED). Other studies have shown that as a man ages, his testosterone level will naturally decrease. Over the last number of years, we have also seen that ED may be one of the earliest signs and markers of endothelial dysfunction. There appears to be an overlap between ED, metabolic syndrome, and symptomatic late onset hypogonadism (SLOH).

It is very important for the primary care physician to identify patients who are suffering from ED and/or hypogonadism, and to also identify any other existing comorbidities.
This article discusses the suggested work up, diagnosis, and management of men who present with either ED or symptoms and signs suggestive of hypogonadism (low testosterone). It also discusses the potential relationship between these conditions and metabolic syndrome.

Key Words: erectile dysfunction, low testosterone, diagnosis, management, metabolic syndrome, hypogonadism

Background

Over the last number of years, medical advances have led to improved survival and a longer lifespan. In the United States, from 2000 to 2030, the number of people age 65 and older is projected to increase from about 35 million to about 71 million, and the number of people aged 85 and older is projected to increase from 9.3 million to 19.5 million.[1] Because of the expected increased longevity of patients today, whenever a patient undergoes a medical or surgical intervention, there must be a strong consideration and discussion about the expected quality of life after the treatment.

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The human body today appears to have a built-in obsolescence. As men and women age, they undergo hormonal changes. Women undergo menopause, which is characterized by a fairly abrupt cessation of estrogen production, such that blood levels of estrogen drop to almost zero. Men, however, experience a gradual decrease in the production of androgens (such as testosterone), starting at about age 40.[2] Their testosterone levels never drop to zero. Because there is a more gradual decrease in the levels of androgenic hormones, and because there are always some hormones present, the clinical manifestations of this hormonal change vary among men.

Late onset hypogonadism (or lower than normal levels of testosterone that is a result of aging), can also be called andropause. If the man has symptoms, this condition can be called symptomatic late onset

hypogonadism (SLOH). Morales and Lunenfeld defined late onset hypogonadism as "a biochemical syndrome associated with advancing age and characterized by a deficiency in serum androgen levels with or without a decreased genomic sensitivity to androgens." They added that the condition "may result in significant alterations in the quality of life and adversely affect the function of multiple organs."[3]

Not all men experience the clinical symptoms associated with low testosterone. In one study, Wang and colleagues reported that about 20% of men over the age of 50 had some SLOH and might benefit from testosterone replacement therapy (TRT).[4]

Symptoms of hypogonadism most commonly include decreased libido and/or erectile dysfunction (ED). In 1993, a National Institute of Health consensus group defined ED as "the consistent (at least 3 month) inability to achieve or maintain an erection sufficient for satisfactory sexual performance."[5]

The Male Massachusetts Aging Study -- a prospective, population-based study of over 1100 white men who were aged 40 to 70 years at study entry and followed for up to 10 years --reported that about 52% of men aged 40 to 70 years experience some degree of ED.[6] ED can have a significant impact not only on a man's physical health and self-esteem, but also on his quality of life and relationship with his partner.

Primary care physicians and other clinicians need to be aware of three important aspects of ED. First, comorbidities and risk factors associated with ED are very similar to those that are associated with endothelial or vascular dysfunction. Second, men with ED may also have low testosterone levels (or late onset hypogonadism), and men who have late onset hypogonadism may also have ED. Lastly, hypogonadism, ED, and metabolic syndrome appear to be closely related.

Erectile dysfunction

The vascular mechanism of ED

The endothelium (blood vessel lining) responds to stimuli so that the blood vessel either opens (vasodilation) or closes (vasoconstriction). Testosterone may activate the enzyme that produces nitric oxide. Production of nitric oxide increases the production of cyclic guanosine monophosphate (cGMP), which causes vasodilatation. Phosphodiesterase-type 5 (PDE-5) enzymes break down cGMP, and PDE-5 inhibitors block the breakdown of PDE-5.[7]

Risk factors for ED

The most common risk factors for endothelial dysfunction are hypercholesterolemia, hypertension, increasing age, diabetes, tobacco use, and hereditary predisposition.[8]

Recent studies have suggested that erectile dysfunction may be one of the most common manifestations of endothelial dysfunction. Several studied have identified risk factors for ED that are similar to the risk factors for endothelial dysfunction.

The Male Massachusetts Aging Study identified multiple risk factors for ED: diabetes, heart disease, hypertension, low high-density lipoprotein (HDL) levels, depression, high levels of anger, and smoking (in patients who also had heart disease or hypertension).[6]

In a study published in 2003, Safarinejad and colleagues report that tobacco use was associated with a 2.4-fold increased risk of ED. Coronary artery disease (CAD) and peripheral vascular disease (PVD)--both signs of endothelial dysfunction--were also strongly associated with ED: CAD was linked with a 1.61-fold increased risk and PVD was linked with a 2.44-fold increased risk. Other factors linked with ED--other than the male sex and increasing age--included diabetes (3.72-fold increased risk), hypercholesterolemia (1.71), hypertension (1.69), and use of therapeutic and recreational drugs (3.71).[8]

A study by Kaiser and colleagues suggests that vascular ED may be an early marker for endothelial dysfunction. The researchers compared 30 men who had a mean age of 46, Doppler- proven ED, and no clinical evidence of cardiovascular disease (CVD) with 27 age-matched controls. They found that the men with ED had significantly lower brachial artery flow-mediated vasodilation, which suggests that men with ED have a peripheral vascular abnormality associated with the nitric oxide pathway.[9]

Similarly, a study by Montorsi and colleagues suggests that vascular ED may be an early marker for CVD. The researchers looked at 300 men with angiography-confirmed CAD. They found that 147 men (49%) had coexisting ED, and in 67% of these men, the ED had preceded symptoms of CAD.[10]

Diabetes is a risk factor for both ED and endothelial dysfunction. A study by Gazzaruso and colleagues suggests that in men with diabetes, ED might be a marker for silent CAD. They compared 133 diabetic men who had silent CAD seen on angiography versus 127 diabetic men with no evidence of myocardial ischemia. One third of the patients with silent CAD had ED, whereas only 5% of those without silent CAD had ED.[11]

Several other studies also suggest that there is a strong relationship between endothelial dysfunction, PVD, coronary ischemia, and ED. The clinical implication is that it is very important for the family care practitioner to ask patients about possible ED as part of history-taking during a physical examination. If the family care practitioner detects ED, especially in a younger man, he or she should consider referring the patient for a cardiac work up to detect possible cardiac disease.

Patient management

History

When taking the history of a patient with ED, it is very important for clinicians to obtain answers to the following questions. How old was the patient when he first experienced ED? Was the onset of ED acute or gradual? What physical, physiologic, metabolic, iatrogenic, or psychological factors may have contributed to ED? For example, was the man feeling guilty because he was having an extramarital affair? Does the man experience ED only with his wife, only at home, and not when he is on holiday? The clinician also needs to determine if the patient has risk factors for the development of ED such as diabetes, neurologic disorders, tobacco use, excessive alcohol intake, obesity, lack of exercise, or the use of recreational or pharmaceutical drugs. It is also important to ask the patient about lower urinary tract symptoms (LUTS) that may be a sign of benign prostatic hyperplasia (BPH). Symptoms of frequency, urgency, nocturia, hesitancy, and dribbling are the most common complaints associated with bladder dysfunction or an enlarged prostate. Men with moderate to severe LUTS have an increased risk of developing ED.[12] Treating LUTS can sometimes correct the ED and similarly, treating ED can sometimes improve LUTS.

Physical examination

The physician needs to examine the patient's penis to confirm that there are no abnormal curvatures, plaques, or evidence of trauma, and that the foreskin is not too tight.

Sometimes men will complain about the size of their penis. It is difficult to estimate the erect size of the penis from its size in the flaccid state. However, by stretching the penis, the clinician can estimate the full size based on the length of the corpora cavernosa. In a very obese man with a very deep supra-pubic fat pad, sometimes the penis will retract and appear to be much smaller than it actually is. The clinician should also examine the meatus to ensure sure that it is open and that there is no obstruction to the urinary outflow that may contribute to inflammation of the prostate. Inflammation of the prostate could also cause painful ejaculation which may suppress the desire for sex.

It is important to examine the man's testicles to make sure that there are no abnormal masses. The size, quality, and consistency of the testicles will also help the examiner determine if the patient has any congenital abnormalities. A small, soft testicle may not be producing testosterone efficiently.

Finally, it is very important to examine the prostate by performing a digital rectal examination (DRE). Often one can detect prostate abnormalities such as a significantly enlarged prostate, a disparity in the feel of the two sides of the prostate, or even a discrete, hard, suspicious nodule suggestive of prostate cancer. An enlarged prostate can contribute to LUTS, which can also increase the risk of developing ED.

Laboratory tests

It is important to order laboratory tests that can help identify potential causes of ED. The following basic screening tests can help determine whether the patient has normal hypothalamic-pituitary axis function: thyroid stimulating hormone (TSH), random blood glucose, follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin. Some clinicians suggest doing the latter three tests only if the testosterone level is abnormal. For patients who are about to receive TRT, the following additional laboratory tests should be done: cholesterol, lipid profile, liver enzymes, hemoglobin, and prostate-specific antigen (PSA).

Treatment

First-line treatment for ED includes treating modifiable risk factors (such as hypertension), counseling about making lifestyle changes (such as exercising more, losing weight, and not smoking), and treating the condition with one of the oral phosphodiesterase type-5 (PDE-5) inhibitors, which currently include sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra).[13] The three PDE-5 inhibitors have similar pharmacokinetic profiles and adverse effects, Table 1.

It is important not to create false expectations in patients. I advise patients to take the drug at least 1 hour before anticipated sexual intercourse. PDE-5 inhibitors are most effective when taken on an empty stomach. They can be taken with food and a moderate amount of alcohol, although this will delay drug absorption.

Clinicians need to inform patients about drug differences -- for example, tadalafil is a longer-acting drug than sildenafil or vardenafil. Patients also need

TABLE 1. **Pharmacokinetics and adverse effects of PDE-5 inhibitors**

	Sildenafil	**Tadalafil**	**Vardenafil**
t1/2	4 hrs	17.5 hrs	4-5 hrs
Tmax	1 hr	2 hrs	1 hr
Bioavail	41%	unknown	15%
Food	high fat meal delays onset by 60 min	no effect	no effect but high fat meal delays onset by 60 min
Alcohol	no effect	no effect	no effect
Elimin	feces (80%) urine (13%)	feces (61%) urine (36%)	feces (91%-95%) urine (2%-6%)
Metab	CYP3A4	CYP3A4	CYP3A4
Most frequent adverse effects (seen in 4% or more patients in clinical trials)	headache, flushing dyspepsia, nasal congestion, respiratory tract infection	headache, dyspepsia, back pain, myalgia nasal congestion, flushing	headache, flushing, rhinitis

to know that although the drugs act in a similar way, individuals may have different side effects from each drug. Therefore, if a patient experiences a certain side effect from one of the drugs, he should not be afraid to try one of the other choices. A patient will generally be offered one or two drugs and instructed how to start taking the drug and how to increase the dosage. It is important to encourage a patient to try a drug at least 6 times before he switches to another drug.

None of the PDE-5 inhibitors always works the first time or works every time for every patient. When prescribing these drugs, it is important to provide patients with information about the drugs and how they are used, and to encourage realistic expectations about onset of response, reliability, and performance.

PDE-5 inhibitors are contraindicated in patients who are taking nitrates such as nitroglycerin in pill, spray, or patch form. Administering vardenafil along with non-uroselective alpha blockers (terazosin or doxazosin) may lead to hypotension in some patients. PDE-5 inhibitors can safely be taken with drugs for diabetes, high cholesterol, and low testosterone.[14-16]

If PDE-5 inhibitors alone are not effective in overcoming ED, some men who also have low testosterone levels may benefit from simultaneous TRT.

If this is not effective, men may be offered second-line treatment, such as a noninvasive external vacuum erection device (VED). More invasive alternatives include use of a prostaglandin E1 drug (alprostadil) with vasodilatory properties, and which is available in a type that can be injected into the side of the penis (Caverject) and a type that is inserted into the urethra (Medicated Urethral Suppository for Erection [MUSE]). Another option is injection of a triple therapy of phentolamine, prostaglandin and papaverine. Implantation of a malleable or inflatable penile prosthesis is generally the last alternative.

Recent studies of PDE-5 inhibitors

Sildenafil

A study by Goldstein in 1998 showed that 85% of men who had taken sildenafil for ED were able to achieve an erection hard enough for satisfactory sexual intercourse.[17]

Tadalafil

Until recently, PDE-5 inhibitors were prescribed as needed. About 2 years ago, Health Canada's Health Protection Branch (HPB) approved the use of tadalafil at a dosage of 5 mg/day. Porst and colleagues reported that in a study of men who still had ED after taking 20 mg tadalafil as needed for up to 2 years, after switching to 5 mg daily tadalafil, 40% of the men were salvaged and had less ED.[18] The 5 mg/day dosage did not lead to any serious drug related adverse events. The most common adverse events were dyspepsia, headache, and back pain, each of which occurred in about 5% of the men-- a lower rate than seen in a previous study of tadalafil at a dosage of 20 mg on demand. Peak plasma levels of tadalafil are lower with the lower drug dosage, which might explain the lower incidence of adverse events with the 5 mg daily dosage. After 3 to 5 days

of this daily dose, the drug level is maintained within an effective therapeutic range, meaning that the man is now capable of having intercourse at any time.

In another study by Porst et al, tadalafil was given to men who did not have ED but had LUTS secondary to BPH.[19] The study, which compared escalating dosages of tadalafil versus placebo, found a dramatic improvement in the patients' LUTS with all dosages of tadalafil. Urine flow rate Qmax (peak urinary flow rate) and post-void urine residual, as calculated from patient self-reports of voiding, did not change significantly, but the symptoms of frequency and urgency decreased. One of the cornerstones of managing patients with BPH and LUTS is the use of alpha blockers to reduce smooth muscle tone at the bladder neck and prostate capsule which can lead to improved urine flow rates and decreased frequency and urgency symptoms. For a more detailed discussion, see the article on BPH by Toguri and Barkin in this supplement.[20]

Vardenafil

Management of patients with prostate cancer has become more aggressive over the last few years, mainly because most men are now diagnosed at an early stage of the disease when a potential cure is possible. ED is one of the most common adverse effects following radical prostatectomy. To try to minimize this adverse effect, patients may be given PDE-5 inhibitors before and after surgery.

A recent study by Montorsi found two surprising results in patients who had undergone radical prostatectomy and received vardenafil. First, a dosage of 20 mg of vardenafil as needed appeared to be more effective than a dosage of 10 mg/day. In addition, even if patients delayed starting to take vardenafil for many months after undergoing radical prostatectomy, more than 50% responded to this ED treatment.[21]

Late onset hypogonadism

Testosterone is the male sex hormone that, after stimulating the proper development of secondary sexual characteristics in the prepubertal male, most commonly contributes to the libido in the post-pubertal man. Testosterone, as will be discussed later, has an impact at all stages of a man's life.

Total testosterone includes free testosterone (1% to 2% of the total), testosterone bound to albumin (about 35%), and testosterone bound to sex hormone binding globulin (SHBG; about 65%). Free testosterone and testosterone bound to albumin make up bioavailable testosterone, which is available to tissues.[7]

Phosphodiesterase enzymes hydrolyze both cGMP and cyclic adenosine monophosphate (cAMP). cGMP contributes to smooth muscle relaxation in the corpora cavernosa of the penis, which allows increased blood flow to the penis and an increased ability to attain and maintain an erection. Testosterone may activate the nitric oxide synthase (NOS) enzyme that produces nitric oxide. Low testosterone levels mean that production of nitric oxide is decreased, which will prevent the erection cascade that is activated by cAMP. Castrated rats have a decrease in NOS-containing fibers and a decreased erectile response. If the rats receive exogenous testosterone, these conditions are reversed.[22]

The Massachusetts Male Aging Study found that in men aged 40 to 70 years, free testosterone declined by 2.8% per year, total testosterone declined by 1.6% per year, albumin-bound testosterone declined by 2.5% per year, and SHBG increased by 1.3% per year.[6]

Patient management

History

Overall symptoms of late onset hypogonadism include diminished energy (as well as vitality and sense of well-being), increased fatigue, depression, reduced muscle mass and strength, reduced bone density, anemia, and decreased cognitive ability. Sexual symptoms of late-onset hypogonadism include ED, decreased libido, difficulty achieving orgasm, diminished orgasm intensity, decreased fluid production with orgasm, decreased penile sensation, and decreased body hair. The patient may appear frail.[4]

Conditions that are associated with late onset hypogonadism include HIV-associated weight loss, end-stage renal disease, moderate to severe chronic obstructive lung disease, obesity, and even diabetes.[23]

To assess risk of late onset hypogonadism, John Morley, MD, at Saint Louis University School of Medicine in Saint Louis, Missouri, developed the Androgen Deficiency in Aging Men (ADAM) questionnaire, which consists of 10 questions, Figure 1.[23] Positive answers to two specific questions or to three other questions suggest that the patient has late onset hypogonadism.

Physical examination

The physical examination entails looking for the signs of hypogonadism such as smaller size and abnormal consistency of the patient's testicles, less body hair, central obesity, as well as muscle wasting and other signs of frailty. It is important to perform a DRE to help rule out prostate cancer, before treating a patient with TRT.

St. Louis University ADAM questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased "enjoyment of life"?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

Note: A positive questionnaire result is defined as a "yes" answer to questions 1 or 7 or any 3 other questions.

Figure 1. The androgen deficiency in aging men (ADAM) questionnaire to detect late onset hypoganidism.[23]

Laboratory tests

Testosterone is secreted in a diurnal pattern with a peak secretion in the morning, and often men with low levels of testosterone report that they no longer have morning erections. Late onset hypogonadism is diagnosed based on testosterone levels that are determined in two blood samples drawn before 11 a.m. on different days. Although there are inter-laboratory differences, the commonly accepted lower limit of the normal range for total testosterone is 300 ng/dL.[24]

When a patient has the potential diagnosis of late onset hypogonadism, in addition to measuring testosterone, the following blood tests may be done: FSH, LH, prolactin, glucose, and TSH. High LH and low testosterone levels suggest that the patient has primary testicular failure with an intact cerebral feedback mechanism.

If the patient has confirmed low testosterone levels and clinical signs of hypogonadism, the performance of the other confirmatory hormonal tests is not necessary. Treatment for low testosterone is the same regardless of its cause. In addition, prior to prescribing TRT, it is important to determine the patient's PSA level, to help to identify prostate cancer. The patient's hemoglobin level should also be determined, because TRT can sometimes increase the hemoglobin to a polycythemic level. TRT should be curtailed or stopped when the patient's hematocrit is equal to or greater than 52% to 54%.[24]

Treatment

Earlier forms of oral TRT were methylated testosterones, which were metabolized in the liver, potentially leading to liver toxicity and cardiovascular events. All of the TRTs presently available in Canada, listed in Table 2, are esterified and metabolized in the lymphatic system, where they are converted to estrogen and dihydrotestosterone. Therefore, since they are metabolized outside the liver, they do not cause liver toxicity and are much safer than the older forms.

Testosterone therapies are delivered by intramuscular injection or oral ingestion or a transdermal route (patch or gel). Oral testosterone has to be taken several times a day with fatty foods, to maintain target blood levels. Injectable testosterone can cause a peak in the testosterone blood level within 24 hours of injection. Intramuscular injection dosages can be titrated so that they can be given every 3 to 4 weeks. The major disadvantage of the patch form of testosterone is that many users develop moderate to severe skin reactions. The gel form of testosterone is applied once a day and care must be taken so it is not inadvertently transferred to the skin of women and

TABLE 2. **Testosterone replacement therapies for hypogonadism that are available in Canada**

Delivery mode	**Product**
Intramuscular	Testosterone enanthate (Delatestryl) Testosterone cypionate (Depo-testosterone) Testosterone undecanoate (Nebido)*
Oral	Testosterone undecanoate (Andriol)
Transdermal	Skin patch: - Testosterone transdermal system (Androderm) Gel: - Testosterone gel (AndroGel, Testim)

*Currently available in Europe; expected to be available in Canada later in 2010

children. In the future, because of new developments, men with low testosterone may be treated with intranasal TRT, a long-acting intramuscular testosterone therapy, or possibly a sublingual testosterone.

The treatment goal for most men receiving TRT for SLOH is to attain target of the "normal" blood levels of testosterone. In these men, TRT can result in improved sexual satisfaction, increased libido, increased muscle mass and strength, stabilized or increased bone mass, decreased body fat, improved skin appearance, improved mood and feeling of wellbeing, decreased hot flashes, preserved pubic hair, and increased production of red blood cells.[25-27] The men who do not benefit from this therapy may have a condition other than SLOH, or they may have androgen receptors that are refractory to testosterone.

The biggest concern for the family care practitioner when he or she is prescribing TRT is the impact on the prostate. A study by Morgantaler and colleagues showed that patients who received exogenous testosterone in appropriate amounts to achieve target blood levels of testosterone did not have an increased risk of developing prostate cancer.[28] Prostate cancer today is the number one diagnosed noncutaneous cancer in North American men. It is important to do a DRE and determine a patient's PSA level prior to commencing TRT, in order to ensure that the man has no underlying prostate cancer.

Primary care physicians need to carefully and regularly monitor patients who are receiving TRT, in order to detect any undesirable changes in PSA levels, DRE findings, liver-function tests, or hemoglobin levels. If a patient's PSA level increases by more than 20% within 6 months, TRT should be stopped. If the patient's PSA level subsequently returns to the baseline level within 3 months, then a repeat challenge with TRT would be appropriate. If the PSA level rises again, then a prostate biopsy should be performed, since the rising PSA level may indicate an underlying cancer.

Possible prostate cancer suggested by a rise in PSA levels or an abnormal DRE needs to be confirmed by a biopsy. If the biopsy detects cancer, then the patient can be treated effectively because of the likelihood that the cancer has been detected very early in its development.

The treatment goal of TRT is to have the patient's testosterone level in the upper end of the normal range. As long as the patient is within the normal (eugonadal) range, then a benign prostate does not grow significantly, and PSA levels should remain normal.[29] Studies have suggested that among men diagnosed with prostate cancer, those with low-normal or below normal testosterone levels had more aggressive cancers.[30] This suggests that a normal testosterone level may actually protect a man from prostate cancer.

The most notable human models for hypogonadism are the unfortunate men who, years ago, were diagnosed with metastatic prostate cancer and underwent surgical castration, which resulted in abrupt, complete hypogonadism. The commonest signs and symptoms after surgical removal of the testicles were hot flashes, osteoporosis, decreased muscle strength and muscle mass, decreased energy levels, emotional disturbances, ED, decreased libido, depression, decreased feelings of well-being, and very poor quality of life. These are the same signs and symptoms seen in SLOH, although they do not occur as abruptly in that condition.

Some clinicians have questioned whether it is advisable to offer TRT to men who have undergone primary treatment for prostate cancer. My approach is that if a man has undergone surgery that resulted in negative margins and if he has had a PSA of zero for 2 years, then he can be offered hormonal replacement in small amounts with very careful follow up.[31]

Metabolic syndrome

Over the last few years, researchers have identified a combination of risk factors that comprise metabolic syndrome. It is important to identify patients who have metabolic syndrome, because this syndrome is associated with a 2-fold increased risk of cardiovascular events and a 5-fold increased risk of being diagnosed with type 2 diabetes.[32] According to a statement issued in 2005 by the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI), a patient has metabolic syndrome if they meet 3 of 5 criteria, Table 3.[32]

A study by Laughlin and colleagues found that testosterone levels in men with metabolic syndrome were 22% lower than in men without this syndrome.[33] Testosterone insufficiency in older men was associated with a 1.33-fold increased risk of death over a 20 year period, independent of multiple risk factors. In addition, testosterone levels were lower in men with diabetes than in men without diabetes. Another study showed that testosterone levels are lower in men with a high body mass index (BMI) than in men with a lower BMI.[34] Low testosterone levels are also associated with increased depression, and impaired cognitive functions.[35] Testosterone is also important for bone health. A study of men with minimal trauma hip fractures found that these men had significantly lower testosterone levels compared to men without hip fractures.[36]

TABLE 3. **Metabolic syndrome: AHA/NHLBI criteria. Clinical identification (three or more present)**

Risk factor	Defining level
Abdominal obesity	
Male waist	> 102 cm
Female wait	> 88 cm
Triglycerides	> 1.7 mmol/L
HDL-C	
Men	< 1.0 mmol/L
Women	< 1.3 mmol/L
Blood pressure	> 130/> 85 mm Hg c
Fasting glucose	> 5.6 mmol/L

AHA = American Heart Association; NHLBI = National Heart, Lung, and Blood Institute

Men with lower than normal testosterone levels may also have ED and metabolic syndrome. It is important to identify these three criteria.

Clinical implications

If a patient has ED, but a good libido and no other signs of hypogonadism, first-line treatment for his ED consists of modifying lifestyle factors (improving the diet, exercising more, and stopping smoking), followed by PDE-5 inhibitor therapy.

If a patient has signs or symptoms of hypogonadism as well as ED, a TRT can safely be prescribed with a PDE-5 inhibitor, and these can be beneficial. Symptoms of metabolic syndrome, such as hypertension or high cholesterol, would in turn, would require other specific medications.

ED, late onset hypogonadism, or both

The patient's symptoms will determine the appropriate workup, Table 4.

If the patient's primary symptoms are those of ED, and the patient's history and physical examination do not reveal any symptoms or signs of hypogonadism, then the physician's next steps are:

1) Have the following blood tests done: complete blood count (CBC), blood urea nitrogen (BUN), electrolytes, creatinine, FSH, LH, testosterone (free, total, bioavailable), prolactin, blood glucose, C-reactive protein (CRP), and lipid profile.
2) Treat the patient with a PDE-5 inhibitor.

On the other hand, if the patient has symptoms and signs of hypogonadism, after the history and complete physical examination, the physician's next steps are:

1) Have the same blood tests done as for a patient with ED only, as well as blood tests for PSA and liver function.
2) Treat the patient with TRT for 3 months.
3) If patient feels better, continue giving the patient the same dosage of testosterone. Repeat the blood tests including PSA, and perform a DRE--at 6 months and then annually. Expect about a 30% response with TRT if the problem is ED alone.
4) If the patient does not respond, check the blood test results to see if there is a biochemical response. If there is no biochemical response, or if the patient's drug compliance is questionable, then the physician can change the type of testosterone.
5) If the patient does not respond, but his blood levels of testosterone are satisfactory, then the patient could have another problem such as depression.

If the patient presents with both late onset hypogonadism and ED, then simultaneous administration of TRT and a PDE-5 inhibitor is safe and effective.

TABLE 4. **Erectile dysfunction versus late onset hypogonadism**

Erectile dysfunction	Late onset hypogonadism
Ages 40+	Ages 40+
Inadequate erections	Erections may be normal
Sexual desire normal	Sexual desire decreased
Often identifiable risk factors	Often no ED risk factors
Usually gradual onset	Gradual onset
Little response to hormone supplements	Often good response to hormone supplements
Normal testosterone	Erections not usually major focus
Sexual concerns	
May be hesitant to try intercourse	

Conclusion

Increasing age is the most common risk factor for both ED and late onset hypogonadism. Both conditions, however, are potential markers for other significant comorbidities. It is important for primary care practitioners to ask patients about symptoms of ED and late onset hypogonadism. Primary care practitioners also need to understand that metabolic syndrome is much more common in men with low testosterone levels, and metabolic syndrome itself predisposes men to ED and CVD, and more importantly, it carries a higher risk of death. It is no longer acceptable to trivialize either ED or late onset hypogonadism. Clinicians need to take a good patient history and perform a patient work up to be able to diagnose ED and/or late onset hypogonadism. If both conditions are present, the clinician needs to offer sequential or simultaneous treatment depending on the major symptom.

Even today, more than a decade after the release of the first PDE-5 inhibitor, men are still embarrassed to discuss ED. Now that we have identified ED as a significant marker of potential vascular disease, it is critical for the primary care physician to initiate a discussion about ED with their male patients.

The appropriate, successful treatment for ED will not only result in tremendous patient satisfaction, but more importantly, the diagnosis could potentially be a life-saving one.

Disclosure

Dr. Jack Barkin is an active urologist and Chief of Staff at the Humber River Regional Hospital in Toronto. He sits on the medical advisory board for Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Frosst, Paladin, Pfizer, sanofi-aventis and Solvay. He has done the clinical research on AndroGel, Avodart, Casodex, Cialis, Detrol, Flomax, Hytrin, Levitra, Xatral, Proscar and Viagra. He has spoken all over the world for all of the companies outlined. □

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Overactive bladder symptoms in women: current concepts in patient management

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The symptoms of overactive bladder (OAB) -- urinary urgency, frequency, and urge incontinence -- can cause significant lifestyle limitations. Social isolation, depression, employment difficulties, and relationship stress are common findings in patients with this condition. This article focuses on women with OAB who are seen in primary care. Occasionally, OAB (or detrusor overactivity) may be the result of neurological disease, metabolic disease, or urinary tract abnormalities. Primary care practitioners can play a key role in identifying affected individuals by including a focused question in every annual patient physical assessment. Investigation and treatment can then be initiated, beginning with behavioral modification strategies (such as modifying fluid intake) and adding antimuscarinic pharmacotherapy or possibly local estrogen therapy where needed. Only patients with certain concurrent diseases or those who are refractory to conventional management will require referral to a specialist.

Key Words: overactive bladder, urinary incontinence, antimuscarinic agents, detrusor overactivity

Introduction

Loss of control of excretory functions is a social stigma in all cultures. Although it is difficult to determine the exact incidence of overactive bladder (OAB) syndrome, due to under reporting by individuals with the condition, researchers estimate that OAB affects 14%-18% of adults to some degree.[1] As with many conditions, incidence increases with age. The prevalence of OAB is the same in men and women, although women begin to have OAB symptoms at a younger age. Given the growing population of individuals aged 55 years and older, OAB has the potential to become a major burden on healthcare resources in the future. Fortunately, modern behavioral modification strategies and pharmacologic treatments can significantly modify or even eliminate bothersome symptoms of OAB. This article focuses on women with OAB who are seen in primary care.

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Precipitating factors of OAB

Although the International Continence Society has developed a formal definition of OAB,[2] in practical terms, all patients who report that they are bothered by voiding urgency or frequency (to any degree) should undergo clinical investigations and, if needed, they should receive treatment for OAB. Patients' reluctance to self report abnormalities of voiding function makes it even more important to investigate

further when patients do report these symptoms. Because of patient hesitancy to discuss voiding control problems with anyone, even their family doctor, primary care practitioners are encouraged to routinely include a screening question about voiding control in every patient assessment, regardless of the patient's presenting symptoms.

Factors that can contribute to OAB are summarized in Table 1. Although OAB can be seen in women who have no identifiable contributing factors, careful screening-- even before other necessary investigations are done-- will often uncover contributing behaviors that can be modified.

Many women still believe that drinking at least eight glasses of water a day is essential to maintain good health. In the absence of medical conditions that dictate otherwise, individuals should be advised to drink only when they are thirsty, and then to drink only enough caffeine free fluids to quench their thirst.

Another persistent myth centers on the potential harm from not responding to the first urge to void. Well-meaning but misinformed caregivers in early childhood may be the root of this false assumption, which can lead to unnecessary frequency and limited or absent voiding delay techniques in adulthood. Obesity is a risk factor in most forms of incontinence, and it requires aggressive management.

Pelvic floor evaluation is an essential component of investigating female voiding dysfunction or urinary incontinence. Estrogen deprivation atrophy of the vaginal skin can be considered a proxy for atrophy in the trigone and urethra, since they share a common embryologic origin. Following menopause, the peri-urethral venous plexus diminishes in size, with loss of the so-called "hydraulic sphincter." With local estrogen treatment, this "hydraulic sphincter" again becomes a significant contributor to continence.

Comorbidities

Inability to choose the time and place of bladder emptying-- with or without involuntary urine loss

TABLE 1. **Screening patients for overactive bladder**

Precipitating causes of OAB	Caffeine intake Detrusor hyperactivity with impaired contractility Diabetes – autonomic neuropathy Excessive fluid intake Obesity Outlet obstruction Pelvic organ prolapse Poor voiding habits Urogenital atrophy
Underlying diseases or causes of OAB	Bladder tumor Cardiovascular disease Lower urinary tract infection Metabolic disease – diabetes Neurological disease Outlet obstruction Pharmacologic contributors Spinal cord compression syndromes
Causes and symptoms of OAB in older patients	**DIAPPERS:** **D**ementia **I**nfection **A**trophy **P**harmaceuticals **P**sychological factors **E**xcessive urine production **R**estricted mobility **S**tool impaction

OAB = overactive bladder

on the way to the bathroom-- places significant limits on a normal lifestyle. In addition, urinary urgency, frequency, and nocturia may be causally related to other conditions that threaten health and well-being.

Particularly in an elderly population, nocturnal urgency can lead to incidents where patients trip and fall on the way to the bathroom, which can cause long-bone fractures and significant morbidity.[3] Apart from the suffering of the individual involved, these incidents require surgical and medical management, often with prolonged rehabilitation, which add extra costs to an already overburdened healthcare system. Effective management of OAB can, in some measure, prevent these negative outcomes.

Chronic use of pads and other protective undergarments can result in irritation and excoriation of the vulvar skin. In severe cases, prolonged contact with urine soaked pads can lead to skin breakdown.

Nocturnal frequency of any cause can result in significant sleep disruption. Interruption of sleep by a frequent need to void can interfere with an adequate duration of rapid eye movement (REM) or restorative sleep, resulting in daytime somnolence and irritability.

Women with OAB often limit their social interactions for fear of an embarrassing accident. Travel, even for example, staying overnight at a friend's home, is a frequent casualty of this condition. Not surprisingly, social isolation and clinical depression are seen more frequently in women with all types of urinary incontinence.[4,5] Relationship stress, including avoidance of sexual contact, only adds to the psychological stress associated with deficiencies of bladder control.

Stress in the workplace -- particularly for women in high visibility, group employment situations such as factory work -- can be extreme. When "bio breaks" are rigidly defined by the employer and sanctions are exercised against employees who leave the assembly line at other-than-defined intervals, some women choose to leave their employment rather than subject themselves to repeated criticism and embarrassment.

Investigating OAB

Urge is the defining feature of OAB. This may be present without involuntary urine loss on the way to the bathroom (dry OAB) or with urge incontinence (wet OAB). The perception of urge in OAB patients is difficult to describe, but is different from the gradually increasing awareness of the need to void as the bladder fills, in patients with normal voiding function. If a patient responds affirmatively to a screening question about bladder control, it is worthwhile to direct further questions to the intensity of the urge component.

In most cases of OAB, a focused patient history and a physical examination that emphasizes the anatomic and functional aspects of the lower urinary tract and other pelvic organs are all that is needed to arrive at a correct diagnosis. Questions about the quantity (volume) and quality (for example, caffeine content) of daily fluid intake are often revealing, and they can provide an opportunity to instruct the patient about appropriate fluid management. Patients may have misconceptions about normal voiding, perhaps mistakenly believing that voiding should only occur twice a day. Asking patients to fill in a three day voiding diary can be helpful.

The physical examination of the patient should focus on identifying features likely to initiate or exacerbate urinary incontinence, including obesity, pelvic organ prolapse, and vaginal skin atrophy, Table 1.

Advanced degrees of pelvic organ prolapse may cause mechanical outlet obstruction. Any clinical manifestations of major neurological disease such as multiple sclerosis or Parkinson's disease should be noted as potential contributors to voiding dysfunction. Identification of musculoskeletal disorders with restricted mobility may move the diagnosis away from true OAB to one where measures to enhance the proximity of toilet facilities, including a commode, would solve the problem of urine loss on the way to the bathroom.

While a significant number of patients have OAB of idiopathic origin,[6] it is important to rule out predisposing diagnoses at an early stage of investigation. Table 1 lists potential underlying disease that the physicians should always look for in patients with OAB symptoms.

The incidence of OAB increases with age. In elderly women, the acronym DIAPPERS (which stands for dementia, infection, atrophy, pharmaceuticals, psychological factors, excessive urine production, restricted mobility, and stool impaction) can be a helpful reminder of what to screen for, Table 1.[7]

Women older than 70 years are more likely to be affected by detrusor hyperactivity with impaired contractility (DHIC). If the bladder muscle (detrusor) is constantly or intermittently squeezing, it will give the patient the sensation of the need to void urgently. When the bladder tries to empty, decreased contractility leads to inefficient and incomplete emptying, resulting in increased frequency. Topical vaginal estrogen and a timed-toileting regime can be helpful whereas antimuscarinic agents are of little benefit for these patients.

Treatment

After other contributing factors have been identified and treated, multimodal intervention is the key to success in treatment of OAB. Treatment should begin with strategies to modify behavior (manage fluid intake) and diet (address obesity, restrict caffeine intake). Then pharmacotherapy (such as antimuscarinic agents) can be added where indicated and where necessary. Pharmacologic treatments appear to have a synergistic effect and should be used in combination with behavioral and dietary interventions, wherever possible.

Behavioral interventions and dietary factors

Behavioral therapies include fluid management strategies, Kegel exercises (pelvic floor rehabilitation exercises), and strategies such as timed voiding and urge suppression.

Bladder re-training can be accomplished at any stage of life, and patients should be instructed to increase their voiding interval by 30 minutes per week until a three-hour or longer interval is reliably obtained. An even simpler approach is to instruct patients to tell their bladder to "Call back in 20 minutes – I'm busy."

Patients should be given instructions about the type and amounts of fluids to drink, including advice about not drinking any diet drinks that contain caffeine, and drinking only when they are thirsty (except of course, if they have renal or bowel conditions where they need to drink more fluids).

Kegel exercises are beneficial for patients with either stress or urge incontinence. Patients need to be carefully instructed in the correct technique, as many women instinctively recruit the rectus abdominus, quadriceps, and gluteal muscles in addition to the levators. Those who have difficulty identifying and isolating the correct muscle group may benefit from a course of biofeedback and electrostimulation,[8] after which they may continue with self-initiated exercises. Fifty squeezes per day appears to be the minimum number required to produce an observable benefit, and this level of exercise intensity needs to be continued indefinitely.

Antimuscarinic agents and their side effects

Antimuscarinic pharmacotherapy, in conjunction with behavioral therapies, is the mainstay of OAB management. In Canada, the following antimuscarinic agents are available for treating patients with OAB: darifenacin (Enablex), imipramine (Tofranil), oxybutynin immediate release (generic oxybutynin), oxybutynin extended release (Ditropan XL, Uromax), oxybutynin patch (Oxytrol), solifenacin (Vesicare), tolterodine immediate release (Detrol), tolterodine extended release (Detrol LA), and trospium (Trosec).

Clinicians need to find the drug that results in the fewest side effects and has the greatest efficacy for the patient. In a patient who is refractory to treatment, a combination of different drugs may be beneficial.

All of the antimuscarinic agents act by competing with acetylcholine on the muscarinic receptors in the bladder. M2 and M3 receptors are predominant in the bladder, but all five muscarinic receptors have been identified at this site. In the bladder, close to 80% of the muscarinic receptors are M2 receptors, while close to 20% are M3 receptors, although the M3 receptors are thought to be responsible for detrusor contraction.[9] The function of M2 receptors has not been clarified.

The presence of muscarinic receptors in other organs -- including the brain, salivary glands, eyes, heart and bowel -- explain some of the common side effects from antimuscarinic agents, such as dry mouth, neurologic effects, and cardiovascular effects. Antimuscarinic drugs are commonly contraindicated in patients who have narrow angle glaucoma.

Patients often stop taking antimuscarinic agents due to unpleasant side effects such as dry mouth. However, since the maximum benefit from these drugs does not usually occur until 30 days of treatment, it is important to encourage patients to take these drugs for at least that long, and patients can be given oral moisturizing agents for dry mouth. Researchers are trying to develop a truly M3-specific agent for OAB, but so far, only darifenacin has significant M3 specificity.[1]

The incidence of side effects appears to be somewhat idiosyncratic, so a patient who is unable to tolerate one agent may do well on another agent, even one with a similar molecular structure.

Dry mouth

Dry mouth and constipation are the most common side effects from antimuscarinic agents. The VEsicare in Comparison To Oxybutynin for oveRactive bladder patients (VECTOR) study was designed to compare dry mouth in patients with OAB who were treated with solifenacin versus immediate-release oxybutynin, and trial results presented at the 2009 AUA meeting showed that patients receiving solifencin had fewer and milder episodes of dry mouth.[10] In a sub-analysis of this trial presented at another recent meeting, researchers reported better tolerability with solifencin

TABLE 2. **Properties of antimuscarinic agents that affect their ability to cross the blood brain barrier[13]**

	Tolterodine	Darifenacin	Trospium	Oxybutynin	Solifenacin
Solubility	slight	low	low	soluble	soluble
Size	475.6	507.6	427.9	357	480.6
Charge	+	+	+	neutral	unknown

than with oxybutynin, in younger patients as well as patients over age 65.[11]

Neurological effects

Muscarinic receptors are critical in cognitive function, especially memory.[12] Antimuscarinic drugs--particularly agents that are lipophilic and have relatively low molecular weight-- can have a significant harmful effect on the brain. Agents with a neutral charge are also more likely to cross the blood-brain barrier, Table 2.[13]

Increased permeability of the blood-brain barrier begins after the age of 45 years, and can be exacerbated by the presence of diseases or conditions such as diabetes, multiple sclerosis and hypoxia.

A 2006 study by Kay and colleagues[14] compared the cognitive effects in geriatric patients who received oxybutynin, darifenacin or placebo for 3 weeks. The study subjects had a mean age of 67 years and, based on pretreatment tests, had age appropriate memory. After treatment, patients who received oxybutynin had a decrease in memory consistent with aging 10 years, whereas darifenacin had no significant effects on memory compared to placebo.

A study by Anderson and colleagues showed that compared to oxybutynin, long-acting tolterodine (tolterodine LA) had no negative impact on memory.[15]

According to FDA 2009 prescribing guidelines for oxybutynin chloride tablets (Ditropan), "a variety of CNS anticholinergic effects have been reported, including hallucinations, agitation, confusion and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly in the first few months after beginning treatment or increasing the dose. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered. Ditropan should be used with caution in patients with preexisting dementia treated with cholinesterase inhibitors due to the risk of aggravation of symptoms."[16]

TABLE 3. **Cardiovascular effects of antimuscarinic agents**

Drug	QT prolongation
Darifenacin	No
Oxybutynin	No
Solifenacin	Yes
Tolterodine	Yes
Trospium	No

Cardiovascular effects

Some OAB drugs can prolong the QT interval, leading to potentially fatal tachyarrhythmias including torsades de pointes, Table 3.

In practical terms, the use of these drugs in conventional doses in patients without major cardiac risk factors confers little additional risk. It is essential for the clinician to take a careful drug history, as many other drugs are also associated with QT prolongation, and the effect may be additive.

Local estrogen therapies

In postmenopausal women, irritative voiding symptoms and nocturia become more troublesome, and stress urinary incontinence may become more severe. These issues can be effectively addressed through the use of local vaginal estrogen preparations, which are more effective than systemic estrogen.

Various local estrogen preparations are available, including a conjugated equine estrogen cream (Premarin vaginal cream), an estradiol vaginal suppository (Vagifem), and a sustained release (depot preparation) in the form of an estradiol vaginal ring (Estring) that requires removal and reinsertion every 3 months. All are effective. Systemic absorption of estrogen is significantly lower with Vagifem and Estring than with Premarin vaginal cream.

Until fairly recently, the only option available was conjugated estrogen vaginal cream which has a systemic absorption rate of approximately 15%. Newer agents such as Estring and Vagifem contain slow-release preparations of 17-beta estradiol with a systemic absorption rate of between 2% and 3%. In

fact, these new local estrogen delivery systems can even be used in patients with breast cancer who experience vaginal dryness and dyspareunia associated with vaginal mucosal atrophy.[17]

Surgery

Obesity is a significant contributor to both stress and urge incontinence. However, surgical procedures to reconstruct the pelvic floor are more prone to fail in patients who are significantly overweight. For this reason, the author believes that anti-incontinence surgery should not normally be offered to patients who have a body mass index (BMI) that is higher than 30.

Other treatments

If the patient has idiopathic OAB and does not respond to conventional pharmacologic or behavioral interventions, new methods of treatment such as neuromodulation and intravesical injection of botulinum toxin A show promise for managing refractory cases. A discussion of these treatment modalities is beyond the scope of this paper.

Conclusion

OAB affects approximately 15% of Canadian women, often with a profoundly negative impact on their health, social, and personal well-being. Many women are reluctant to seek help either due to embarrassment or the mistaken belief that diminished bladder control is a normal part of aging, and nothing can be done.

Primary care practitioners can play a key role in identifying affected individuals by including a focused question such as "Do you ever have any trouble controlling your bladder?" in every annual patient assessment. Investigation and treatment can then be initiated, beginning with behavioral modification strategies (such as modifying fluid intake) and adding antimuscarinic pharmacotherapy where needed. Only patients with concurrent neurological disease or symptomatic pelvic organ prolapse, or patients who are refractory to conventional management will require referral to a specialist.

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Prostate-specific antigen tests and prostate cancer screening: an update for primary care physicians

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Prostate cancer is a highly prevalent malignancy. Using serum prostatic-specific antigen (PSA) levels to screen for prostate cancer has led to a greater detection of this cancer, at earlier stages. However, screening for prostate cancer by determining PSA levels remains controversial. Concerns include the risk of overdiagnosis and conversely, the failure to detect all prostate cancers. This article, aimed at primary care practitioners, reviews the characteristics of an ideal screening test, in relation to the characteristics of the PSA test. It then discusses the implications of recent findings from two large, randomized, prospective screening trials: the American Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) screening trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial. The latter trial demonstrated a modest survival benefit from PSA screening. Lastly, the article summarizes recommendations from recently updated guidelines about PSA testing from the American Urological Association (AUA), and it discusses when a primary care practitioner might refer a patient to a urologist.

Key Words: prostate adenocarcinoma, prostate-specific antigen, review, early cancer detection

Introduction

Of all the aspects of prostate cancer, none is more relevant to the primary care physician than screening for this cancer. Treatment of prostate cancer is typically directed by specialists, but the primary care physician is generally the gatekeeper and expert in screening patients for prostate cancer and detecting cancer cases.

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For a complete review of the "diagnosis and management of prostate cancer" the primary care physician should refer to the *Urology Update for Primary Care Physicians 2008*, The Canadian Journal of Urology supplement.[1,2] This article discusses two large trials of prostate cancer screening[3,4] and new American Urological Association (AUA) guidelines for prostate cancer screening[5] that have been published since then. The need for widespread prostate cancer screening by measuring prostate-specific antigen (PSA) levels remains controversial.[6]

PSA is a protein produced by the prostate. It is a normal secretary product of the prostate that is present in seminal fluid in mg/mL levels but only present in

serum in ng/mL levels -- a million-fold difference in concentration.[7] Its physiologic role and its function in reproduction is to liquefy semen.[8]

PSA was originally a forensic laboratory test to confirm the presence of semen.[7,8] Subsequently, researchers recognized that patients with a diagnosis of prostate cancer often had relatively high levels of serum PSA, particularly when they had more advanced stages of the disease.[9] PSA testing in patients not known to have prostate cancer began, which revealed a substantial increased ability to detect prostate cancer compared to existing methods.[10] PSA screening essentially began without fully evaluating it as a screening test, and measurement of PSA levels has become widespread.

Characteristics of an ideal screening test

An ideal screening test exists when certain disease, test, and population features are present.[11,12] The disease should have a significant effect on quality or length of life. It should have an asymptomatic period during which detection and treatment can result in better outcomes. It should also have available, acceptable, potentially curative treatments. The test should have sufficient sensitivity (few false negatives) and specificity (few false positives) and be acceptable to patients. The population should have sufficiently high disease prevalence and be compliant with and accepting of subsequent testing and treatment.[11,12]

Disease features

Prostate cancer is the most commonly diagnosed cancer in men in North America, and it is the most commonly diagnosed noncutaneous cancer in men and women combined.[5,13] It has a significant health impact. Prostate cancer ranks as the third most prevalent "cancer killer" in men. In 2009, in Canada, an estimated 4400 men died from prostate cancer, which is comparable to the number of men who died from colon cancer (about 4900) and the number of women who died from breast cancer (about 5400).[13] A man's lifetime risk of being diagnosed with prostate cancer is 1 in 7, and his lifetime risk of dying from prostate cancer is 1 in 27.[13]

Prostate cancer does not typically have any symptoms in its early stages, and it is often incurable once symptoms become apparent. Therefore, the critical point for diagnosing prostate cancer is prior to development of symptoms. The potential benefit of a screening test for prostate cancer seems self evident.

Whereas an estimated 4400 men in Canada died from prostate cancer in 2009, an estimated 25 500 new cases were diagnosed.[13] Thus, there is an almost 6:1 ratio of diagnosis of prostate cancer to death from prostate cancer, supporting the belief that many prostate cancers are indolent and not life threatening. This creates concerns about overtreating these prostate cancers, resulting in unnecessary cost, morbidity, and side effects that diminish quality of life.

In fact, the presence of histological prostate cancer is very high. Autopsy studies of men who had died from other causes did not detect any prostate cancer in men who died at age 10 to 19, but it detected small foci of prostate cancer in 0%-2% of men who died at age 20 to 29, in 27%-29% of men who died at age 30 to 39, in 32%-34% of men in who died at age 40 to 49, in 55% of men who died at age 50 to 59, and in 64% of men who died at age 60 to 69.[14,15] Thus a man's risk of harboring some prostate cancer appears to be approximately equal to his age in years, at least after age 30. Several important points can be extrapolated from this study. The presence of some histological cancer potentially predates a clinical diagnosis by decades. Prostate cancer can be extremely slow to progress. A great many prostate cancers will never be clinically important. Prostate cancer screening, unlike screening for most diseases, is potentially limited by the disease being too common (too many clinically "insignificant" cancers). Ideally screening for prostate cancer would involve identifying "clinically significant" cancers, not necessarily all cancers.

Test features

Table 1 summarizes how parameters of screening tests -- specificity, sensitivity, and negative and positive predictive values--are defined. Most studies report that using a traditional upper-normal cutoff of 4.0 ng/mL, current PSA tests have a sensitivity of 70% to 80% and a specificity of 60% to 70%.[16] The positive predictive value of a PSA > 4.0 ng/mL is about 30%,[17] which means that among men who have a PSA level higher than 4 ng/mL, biopsies would confirm (detect) prostate cancer in only 30% of the men.

Whether it is possible to determine absolute values (presence or absence of prostate cancer) from PSA test results is debatable. In determining the binary possibilities of "cancer" or "no cancer," "true cancer" is generally defined as cancer detected with a transrectal ultrasound (TRUS)-guided biopsy. However, as discussed above, the presence of small amounts of histological prostate cancer at autopsy is very high: some prostate cancer is present in close to 30% of men in their fourth decade,[14,15] an age when clinical diagnosis of this disease is very rare.

TABLE 2. **A 4 x 4 chart comparing cancer presence or absence to screening test results**

	Cancer is present	**Cancer is absent**
Screening test is positive	True positive (TP)	False positive (FP)
Screening test is negative	False negative (FN)	True negative (TN)

Test characteristics are defined as follows:

$$\text{Positive predictive value} = \frac{TP}{TP+FP}$$

$$\text{Negative predictive value} = \frac{TN}{TN+FN}$$

$$\text{Sensitivity} = \frac{TP}{TP+FN}$$

$$\text{Specificity} = \frac{TN}{TN+FP}$$

Like the PSA test, analysis of biopsy samples is subject to concerns about sensitivity and negative predictive value (that is, is cancer being missed?). Historically, six core samples were taken at the time of a TRUS-guided biopsy. Researchers subsequently determined that the six-core technique had 30% more false negatives than the 12-core technique.[18,19] Guidelines now recommend performing an extended biopsy in most cases, and six sample cores are no longer considered sufficient.

If the primary care physician is referring patients directly for biopsies, he or she should ensure that the procedure is done using an up-to-date technique with sampling of ten or more cores, as reviewed by Laspina and Haas.[1] On the other hand, biopsies with sampling of more than 12 cores have been associated with increased risk of adverse events without increased cancer detection.[18] Care should be taken not to interpret a negative biopsy finding as an absolute confirmation of the absence of cancer, as there is a continued risk of a false negative result. Where appropriate, patients should have ongoing monitoring and undergo repeat biopsies, as needed.

Efforts to diagnose prostate cancer have typically focused on patients with elevated PSA levels and a perceived increased risk of cancer. However, the placebo arm of the Prostate Cancer Prevention Trial (PCPT) provides data from men with "normal" PSA and digital rectal exam (DRE) findings. In this trial, 2950 men in the placebo arm who had a PSA of 4.0 ng/mL or lower and a normal DRE underwent an end-of-study biopsy. Prostate cancer was diagnosed in 15.2% of the men.[20] Since 90% of men over age 50 have a PSA of 4 ng/mL or lower,[21] this suggests that most men over age 50 with prostate cancer detected by means of a needle biopsy have "normal" serum PSA levels. This is consistent with autopsy findings discussed earlier, although the detection of cancer in a needle biopsy sample from a living tissue sample suggests the presence of greater disease than the detection of small, histologic foci of cancer in an autopsy sample.

Table 2 illustrates a hypothetical group of 1000 men undergoing biopsy with the assumption of 10% with PSA > 4.0 ng/mL, a positive predictive value of 30% for PSA > 4.0 ng/mL, and 15% cancer rate when the PSA is 4.0 ng/mL or less. The specificity is 92%, but the sensitivity is only 18%.

A subanalysis of PCPT trial results showed that even very low serum PSA levels did not predict the complete absence of cancer. The prevalence of prostate cancer was 6.6% among men with a PSA level up to 0.5 ng/mL, 10.1% among men with a PSA of 0.6-1.0 ng/mL, 17% among men with a PSA of 1.1-2.0 ng/mL, 23.9% among men with a PSA of 2.1-3.0 ng/mL, and 26.9% among men with a PSA of 3.1-4.0 ng/mL.[20] Nevertheless, PSA levels do clearly correlate with the likelihood of cancer. Furthermore, PSA also correlates with higher-grade cancer and tumor volume.[20,22,23]

TABLE 2. **A hypothetical comparison of 1000 men undergoing prostate biopsy**

	Cancer present	**Cancer absent**
PSA > 4.0 ng/mL	30	70
PSA 4.0 ng/mL or less	135	765

Population features

Prostate cancer is common in Canadian men. The risk of prostate cancer increases with age, but the potential benefit from treatment decreases with age, since the potential number of years of life lost to disease decreases and morbidities and mortalities from other diseases increase. Guidelines typically recommend screening men aged 50 to 70 years old, to be able to detect cancer early in younger men and to avoid overdiagnosing and treating older men who would most likely die from other diseases. Men with a family history of prostate cancer and men of African ancestry have a greater chance of being diagnosed with prostate cancer, compared to men without these risk factors.[1]

PSA determination is an attractive screening test, as it requires simply drawing a blood sample, and high patient compliance with testing is expected. Similarly, a DRE is an inexpensive test with a low morbidity. Patients should, however, be aware that screening with PSA and DRE is only an initial step, which may then lead to TRUS-guided biopsy. Patients need to be informed of the consequences of screening and the risks and benefits of treatment, even though this is a complex topic.

Screening should be performed during a "well visit," for example, during an annual physical examination. Table 3 summarizes the characteristics of patients who should not be screened for prostate cancer. In addition, screening should not be performed when the patient has had an acute event such as urinary infection or urinary retention which can lead to falsely elevated PSA levels.[24] Other factors such as ejaculation and DRE have not consistently been shown to effect the PSA levels.[5]

The prevalence and characteristics of prostate cancer in the population being screened will influence the effectiveness of screening. In fact, if screening is effective, it will alter the population by removing cases of prostate cancer. With PSA screening this would leave a progressively higher proportion of patients in the population with PSA elevations from benign conditions, thus reducing the effectiveness of PSA screening.

Since the introduction of PSA testing there has been a trend towards diagnosis of prostate cancer at earlier stages. Beginning in 1991, the incidence of advanced-stage or metastatic prostate cancer decreased at an annual rate of 17.9%, which has been interpreted as being the result of PSA screening.[25] Stamey reported in1989 that cancer volume was the primary determinant of serum PSA levels in men undergoing radical prostatectomy.[26] The same author concluded in 2002 that serum PSA had a "clinically useless" relationship with cancer volume, and that BPH is a strong contender for the cause of PSA elevation.[27]

The screening "no man's land"

Many of the previously mentioned issues -- particularly the potentially high rate of cancer in patients with low PSA levels-- raise serious questions about the utility of PSA determinations in screening for prostate cancer. Lowering the PSA cutoff or simply performing biopsies on all men of a certain age will increase the detection of cancer, but it will also increase the number of patients who will unnecessarily undergo investigations. Furthermore, the increased cancer detection will lead to diagnosis and treatment of more patients with potentially indolent or insignificant disease.

A PSA threshold above which biopsies need to be performed may, however, still be useful in that it defines the lower limit of a "no man's land" or a grey zone of PSA levels where cancer is detectable at reasonable rates, at an early enough stage to be curable, but which spares many men from unnecessary and potentially harmful investigation. It is believed that biologically active prostate cancer will typically result in an increasing PSA level at some point in its natural history. Even in men with cancer and initially low serum PSA levels (e.g. < 4 ng/mL), PSA levels are expected to rise above the cutoff at some point if the disease progresses. The cancer is "picked up" when the PSA goes above the threshold into the "no man's land" (e.g. > 4 ng/mL). If the threshold is too high, then the cancer will be detected at too advanced a stage. With a PSA between 4 and 10 ng/mL, 75% of prostate

TABLE 3. **Characteristics of patients who should not undergo prostate cancer screening with PSA and DRE**

- Patient does not want screening
- Patient would not wish to undergo biopsy or further pursue management and treatment for prostate cancer
- Patient is too old and/or ill to potentially benefit from prostate cancer management
- Patient is too young, or otherwise in too low a risk group for prostate cancer to potentially benefit from screening
- Patient has an acute event that is likely to confound screening results (e.g. infection, urinary retention)

cancers are confined to the prostate, but this drops below 50% when the PSA is higher than 10 ng/mL.[28] A review of 875 men who underwent radical prostatectomy concluded that cure rates appeared constant in men with preoperative PSA levels up to 9 ng/mL, suggesting that earlier diagnosis does not lead to added benefit.[29]

Extensive attempts have been made to argue "for" or "against" screening, but only recently, with the publication of two very large trials, have substantial randomized control data become available.

The PLCO trial[3]

The prostate, lung, colorectal and ovarian cancer (PLCO) screening trial is an American study that was designed to evaluate the value of screening for these four cancers.

In this study, 76 693 men aged 55 to 74 years were randomized to a "screened group" or to a "usual care" (control) group. Patients in the screened group were offered annual PSA testing for 6 years and an annual DRE for 4 years. In the screened group 85% of the patients were compliant with PSA testing and 86% were compliant with DRE. Patients in the usual care group could receive some form of screening, but this was not necessarily regular or annual screening. By the sixth year 52% of the patients in the usual care group had undergone PSA testing at least once.

At 7 years, the incidence of prostate cancer in the screened population was 116 per 10 000 and it was 95 per 10 000 in the control group. The incidence of death was 2.0 per 10 000 in the screened group and 1.7 per 10 000 in the control group, which was not a statistically significant difference.[3]

This study looked at a very large number of patients, and failed to show a benefit from screening for prostate cancer. The study raises several important points.

First, compliance with screening is imperfect, yet as many as 52% of men in the control group in the PLCO study received some type of screening. Approximately 44% of the men in both groups had undergone previous PSA testing, and the population was thus to an extent prescreened prior to the trial. This would have removed some cancers that would have been detected in one of the randomized groups. The cancer incidence was only slightly higher in the screened group (rate ratio 1.22). One would expect the incidence to be much higher in a screened population; in fact a concern of screening is overdiagnosis.

Historically the introduction of PSA testing has resulted in a marked increase in the incidence of prostate cancer. From 1986 in the pre-PSA testing era to 2005 after many years of PSA testing the relative incidence of prostate cancer increased 1.91 times for men aged 60 to 69 years and 3.64 for men aged 50 to 59 years.[30] Since PSA and DRE are the prime methods of developing suspicion of cancer, the comparable rates of diagnosis in the screened group and in the usual care group in the PLCO study suggest that these tests are being carried out sufficiently often in both groups and yield a similar detection of cancer.

The mortality incidence was also low in both groups in the PLCO study. The overall rate of prostate cancer mortality in Canada is 2.3 per 10 000 across the male population of all ages.[11] This suggests the population studied in the PLCO study is at low risk for prostate cancer mortality, or both groups are undergoing effective treatment. Although 10-year analysis was included (which was consistent with analysis of 7-year data), the follow up may be somewhat short. Patients with early localized prostate cancer demonstrate a significant increase in cancer mortality 15 years after diagnosis.[31]

Overall, the PLCO study demonstrated no benefit from the study's screening program compared to usual care, probably because the men in the study had already undergone some form of screening. What this really means is that the "usual care population" was not an unscreened population.

Researchers used a different approach in the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial.

The ERSPC trial[4]

The ERSPC trial identified 182 000 men aged 50 to 74 years who were randomized to a screened group that was offered screening with PSA at an average of once per 4 years or a control group that was not offered screening. In the screened group, 82% of men were screened at least once. The median follow up was 9 years. The cumulative incidence of prostate cancer was 4.8% in the control group and 8.2% in the screened group. The rate of prostate cancer death was 20% lower in the screened group. To prevent one death, 1410 men would need to be screened and 48 would need to be treated.[4]

This study demonstrates an expected increased incidence in prostate cancer in a screened group. It is likely that the control group in this study was less "contaminated" by screening tests such as PSA tests than the control group in the PLCO study. Therefore, this study may be a purer comparison of screening versus no screening. The frequency of PSA testing was relatively low, at an average of once every 4 years. The traditional

annual PSA test is perhaps more frequent than necessary. In the ERSPC trial, the mortality benefit was small, but statistically significant. As screening generally detects cancer early in its natural history and because prostate cancer is often slow to progress, the benefits of screening, if they exist, only become apparent over time. In the ERSPC trial, the mortality curves of screened men versus men who were not offered screening only separated around the 7-year point. It may be that longer-term follow up will show a greater benefit from screening. Nevertheless this study as well as the PLCO trial illustrates a high rate of overdiagnosis.

The American Urological Association (AUA) PSA best practice statement[5]

The AUA updated its statement on PSA tests in 2009. The recommendations include[5]:

- The decision to use PSA should be individualized and patients should be informed of the known risks and benefits.
- Early detection and assessment should be offered to asymptomatic men 40 years or older who wish to be screened and have an estimated life expectancy of more than 10 years. Testing at this age may help to identify men at a curable stage who would otherwise die from prostate cancer between age 55 to 64 years.
- Men younger than 50 years old are more likely to have curable cancer.
- PSA is a more specific test for cancer in younger men because increased PSA from benign prostate enlargement is less common at that age. Compared to annual testing beginning at age 50, infrequent testing of men in their 40s and men age 50 and older might reduce prostate cancer mortality and the cost of screening.
- Establishing a baseline PSA level for use in evaluating PSA velocity (the rate of annual increase in PSA) could help identify men with life-threatening prostate cancer when a cure is still possible.
- Screening intervals should be based on the patient's PSA level. For men with PSA levels of 2 ng/mL or lower, screening every 2 years is unlikely to miss curable cancer.
- No specific upper age limit for PSA testing is advised.
- A physician should assess a patient's individual health status to determine the appropriateness of PSA testing at any age. A distinction should be made between screening and treatment. It may be helpful for an older man to know that he has a diagnosis of prostate cancer, but he may not require treatment. Older men with aggressive prostate cancer, however, should not be denied the opportunity for diagnosis and treatment.
- Screening should include both a PSA test and a DRE.
- TRUS adds no additional diagnostic information, but it is useful to guide biopsies.
- A single threshold PSA value is not recommended. The decision to biopsy should be based primarily on a patient's total PSA level and DRE findings, but it should also take into account multiple factors including values for free PSA, PSA velocity, and PSA density (serum PSA level/prostate volume), as well as the patient's age, ethnicity, family history, prior biopsy history, and comorbidities.

Indications for urology referral

The AUA recommendations are relevant for the primary care physicians, but present challenges as

TABLE 4. **Possible indications for urology referral**

Abnormal DRE: nodule, asymmetry, induration, irregularity
Elevated PSA > 4.0 ng/mL
Elevated age-specific PSA[31]
40-49 yrs > 2.5 ng/mL
50-59 yrs > 3.5 ng/mL
60-69 yrs > 4.5 ng/mL
70-79 yrs > 6.5 ng/mL
Low free/total PSA ratio < 0.10
PSA velocity: increase of 0.75 ng/mL or greater per year (at least 3 PSA levels over 18 months)
Sufficient concern raised by family history, African ancestry, or patient anxiety to warrant referral

there is no distinct, recommended PSA cutoff, and multiple risk factors need to be balanced in decisions about who to screen and biopsy. Depending on the primary care physician's comfort level about making treatment decisions, any of the patient findings listed in Table 4 might warrant a referral of the patient to a urologist.

Conclusions

Prostate cancer screening remains controversial. It is important for the primary care practitioner to note that if a patient presents with BPH symptoms, this patient deserves a PSA test to help rule out prostate cancer as the cause of their symptoms. In this setting the PSA test is not considered to be a 'screening test. As further randomized controlled study data with longer follow up to better demonstrate survival benefits become available, the possible benefit or lack of benefit of PSA testing may become clearer. It is reasonable to offer the PSA test to a motivated, informed patient who believes in the potential long term benefit of early prostate cancer detection.

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Management of benign prostatic hyperplasia by family physicians

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The past decade has profoundly changed how physicians manage patients with benign prostatic hyperplasia (BPH). The concepts of symptom indices, symptom complexes, flow rates, prostate-specific antigen (PSA), prostate size and new medical approaches supported by new clinical studies, have provided family practitioners as well as specialists with evidence-based management algorithms to treat BPH. Men with BPH most often visit a physician due to their partner's urging because of the many symptoms, with the most bothersome being nocturia. Today, primary care physicians are the gatekeepers for diagnosing and managing lower urinary tract symptoms (LUTS) in men. They need to be aware of long term negative consequences if these major symptoms are not treated early.

Key Words: symptom complex, BPH, PSA, LUTS, symptom index, flow rate

Introduction

This article is an update of an earlier article concerning diagnosis and management of patients with benign prostatic hyperplasia (BPH) by primary care physicians.[1] It aims to reinforce the importance of early identification of patients with BPH and lower urinary tract symptoms (LUTS) and to provide recent study data that support treatment algorithms.

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LUTS are a constellation of symptoms related to voiding problems, which can be experienced by men or women. These symptoms may be caused by urinary tract infections (UTIs), bladder stones, bladder cancer, prostate cancer, urethral strictures, BPH, or overactive bladder (OAB). The International Continence Society (ICS) defines OAB as a condition characterized by urgency with or without urge incontinence, generally in the presence of frequency and nocturia.[2] It is important to note that a man who has been medically treated for BPH and is voiding better and stronger but still has symptoms of frequency and urgency may require additional pharmacotherapy to manage OAB.[3]

Approximately 60% of men have LUTS. In 50% of men over age 50 who have LUTS, the cause is clinically significant BPH, but it is important for the primary care physician to be able to rule out other causes. Prevalence of LUTS and BPH increases with age.[4]

Diagnosis

The diagnostic algorithm from the Canadian guidelines for the diagnosis and management of clinically significant BPH provides a useful approach, Figure 1.[1,5]

Patient history

BPH symptom score questionnaires

The American Urological Association (AUA) symptom index for BPH[6] -- or the very similar International Prostate Symptom Score (IPSS) sheet for BPH--- consist of a score sheet with seven questions about BPH symptoms plus an eighth question about quality of life (QOL). These questions have been validated and used for over a decade to provide quantified information about symptom severity in BPH and LUTS before and after any treatment.

The symptom indices were designed to detect and quantify the most common symptoms of patients presenting with LUTS. Each of seven questions about symptom frequency in the past month can have a score from 0 (not at all) to 5 (almost always). Based on the total score, LUTS is classed as mild (total score 1 to 7), moderate (8 to 19), or severe (20 to 35). The question about quality of life is scored from 0-6, with 6 being "terrible." The questionnaire is later repeated to determine if symptoms have improved (lower score) or worsened (higher score). The patient becomes his own "control".

The eighth question, about quality of life, probes how "bothered" the patient is by his symptoms. For patients with "moderate symptoms" (greater than equal to 3 out of 6), it can give an indication about whether a patient should be observed or given treatment. This question can be seen as a "motivational index," because a high score for this question can mean that the patient will be more motivated to accept treatment suggestions.

By filling out a BPH symptom score sheet, patients increase their awareness of which voiding symptoms they have and how severe the symptoms are. The symptom score can also serve as an objective parameter for comparing symptoms before and after treatment.

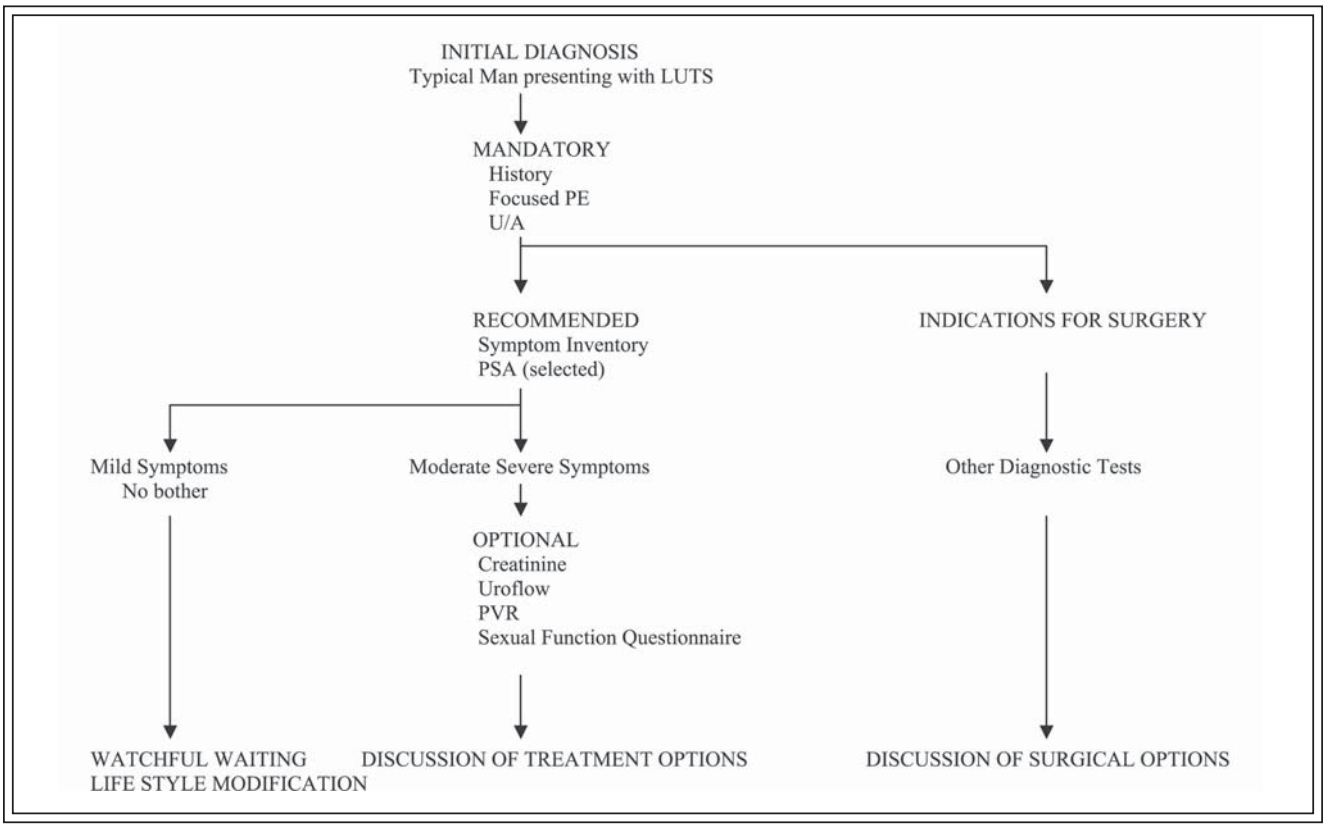

Figure 1. Diagnostic algorithm.[1,5]

These symptoms can be matched to the voiding cycle –storage, voiding, and post micturition, as per the International Continence Society's analysis of symptoms.[7]

The development of symptom score questionnaires for BPH has helped patients and physicians focus on the nature and severity of obstructive and irritating voiding symptoms. These symptoms scores have been used in all recent clinical trials of drugs and interventional therapies for the management of BPH, to demonstrate treatment efficacy.

A key aspect of these questionnaires is that the patient fills them out and then acts as his own control to assess the impact of the treatment. Over time, the symptom score will either improve or deteriorate. A study by Barry and colleagues published in 2000 determined the required change in symptom score for a patient to perceive a clinical difference in his condition.[8]

Having a patient fill out this symptom sheet as part of his clinical history can help the physician define and quantify the patient's symptoms, which can then guide the physical examination. Replies to the seven questions can direct attention to specific voiding symptoms.

PSA test

The prostate-specific antigen (PSA) blood test is another useful parameter to evaluate prostatism or LUTS. Roehrborn et al demonstrated that there is a direct relationship between of a patient's age, prostate size, and serum PSA levels.[9]

As Roehrborn and others have suggested, PSA level is an excellent and reliable surrogate marker for prostate volume.

All prostate cells make PSA. As the benign prostate increases in volume, serum PSA levels will increase. PSA is specific to the prostate, but it is not necessarily specific for prostate cancer. Serum PSA levels increase with inflammation of the prostate--which could be due to prostatitis or a UTI-- obstruction, cancer, sexual intercourse, and trauma--which could be caused by riding a bicycle or a motorcycle to the doctor's office, or by a vigorous digital rectal examination (DRE).

Different laboratories measure serum PSA levels in different ways. To best compare PSA test results from different times for the same patient, the test should ideally be done in the same laboratory using the same technique.

In addition to total PSA, other measures of PSA can include free-to-total PSA ratio, PSA density, PSA doubling time, age-specific PSA, and PSA velocity (change in the level of PSA over a specific period of time). Sometimes, changes in PSA levels can be used as a measure of the effectiveness of pharmacotherapy.

If a patient's baseline total PSA is in the "grey zone," (higher than expected for age or prostate volume), the physician can request another (repeat) total PSA test or a different type of PSA test, to determine what patient management is warranted: observation or referral for a biopsy.

The total PSA value and all its variations help in diagnosis and treatment decisions, as explained in more detail in the article by Kell, in this supplement.[10]

Physical examination

The assessment of a patient's flanks and abdomen will provide clues about possible hydronephrosis (dilation of the kidney due to obstructed urine flow), bladder obstruction as indicated by a supra-pubic mass, epididymo-orchitis (inflammation of the epididymis and testes caused by a bacterial infection, recurrent UTIs, or bladder stones), or the detection of a meatal stenosis.

A DRE will provide a measure of the prostate's size (for example, the number of finger widths), detect tenderness, induration, irregularities, or nodules, and detect differences between the two sides of the prostate. It is rare to find the classical, discrete, hard, pea-sized nodule that suggests prostate cancer. Rather, subtle differences comparing one side to the other or changes over time are more likely to suggest cancer.

Some anaplastic (poorly differentiated) prostate cancers will NOT produce PSA and thereby not cause an increase in serum PSA levels, so a DRE must be done every time to rule out the "silent PSA " prostate cancer as well as any other DRE abnormalities. Often today, the patient may have a disproportionately high serum PSA value that does not correspond to the size of the prostate found by DRE. This higher-than-expected PSA level suggests the need to look for underlying prostate cancer.

If the prostate feels benign, the patient's PSA levels will accurately predict prostate volume, without the need for doing a transrectal ultrasound. Unfortunately, not all the benign feeling prostates are benign - that is another reason to do the PSA. A PSA value greater than 1.4 ng/mL guarantees a prostate volume of greater than 30 cc, which is the critical cut-off volume that defines an "enlarged" prostate.[1] As we will see, it is this 30 cc volume that is the "watershed" for the different types of medical therapy for BPH.

Patient management

Treatment options for BPH, depending on the patient's symptoms, signs and bother, include watchful waiting, surgery, or pharmacotherapy, as explained in the treatment algorithm from the Canadian guidelines, Figure 2.[1,5]

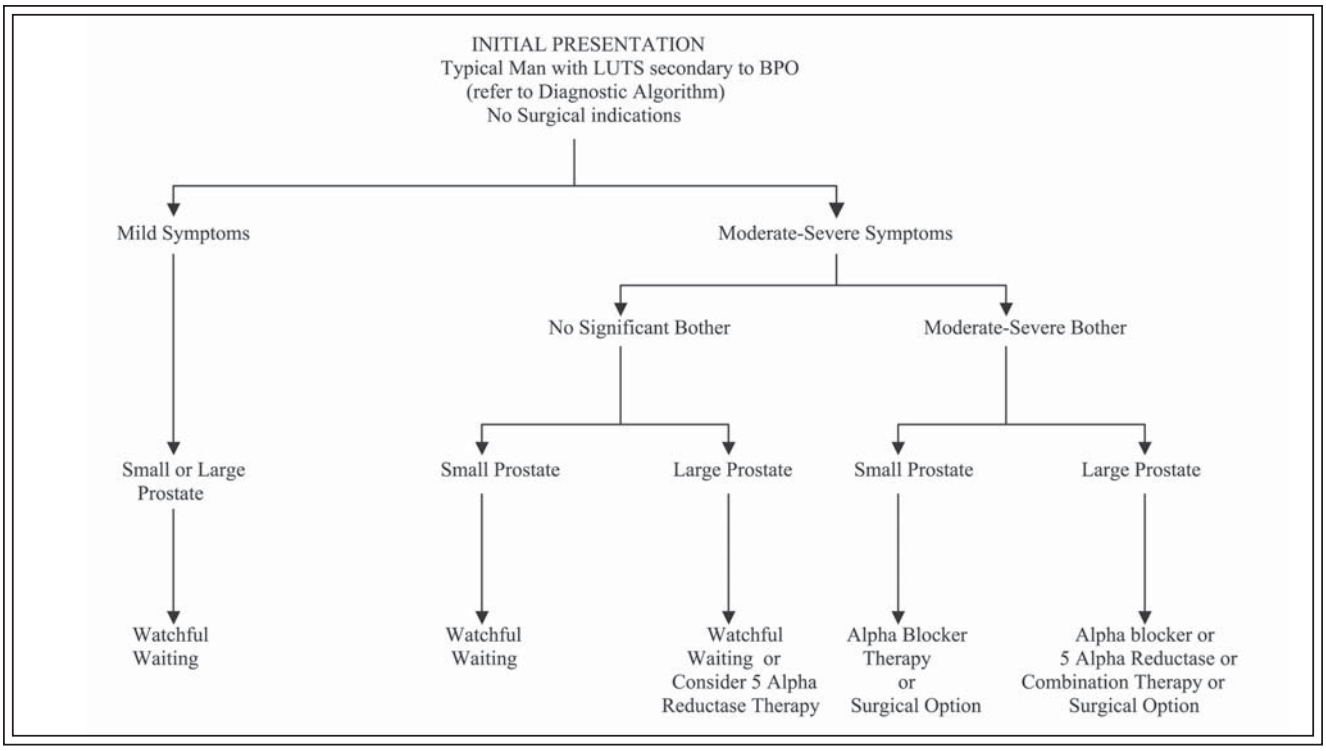

Figure 2. Treatment algorithm.[1,5]

Whereas previously the only option for treating BPH was surgery, drugs from two different classes are now available to treat BPH, and pharmacotherapy can be either monotherapy or combination therapy.

Therapeutic choices

Alpha blockers

The four long-acting alpha blockers that are commonly used to treat BPH are terazosin and doxazosin (older agents) and alfuzosin and tamsulosin (newer agents). With respect to efficacy, the different alpha blockers appear similar. They act by blocking alpha-1a receptors in the smooth muscle of the bladder neck and prostate, which causes the smooth muscle in the bladder neck and prostate to relax or "open." This allows for fuller, stronger, and more complete urination resulting in diminished frequency and nocturia (dynamic obstruction).

Since non-selective alpha blockers can also block alpha 1 receptors found in places other than the prostate -- such as alpha-1d receptors found primarily in the spinal cord, or alpha-1b receptors found primarily in the smooth muscle of peripheral vasculature -- this leads to different potential side effects.[11]

Side effects from alpha blockers include postural hypotension and dizziness (5%-10%), nasal congestion (5%), headache (5%-10%), asthenia (5%-10%), and retrograde ejaculation (3%-10%).[12]

Alfuzosin and tamsulosin are more "uroselective" and have fewer cardiovascular side effects than terazosin and doxazosin.[12,13]

With time, most patients taking alpha blockers for BPH will experience tachyphylaxis, and lose their "BPH symptom control" that was previously produced by the alpha blocker. One reason is that the prostate will continue to grow while the patient takes the alpha blocker. Patients taking alpha blockers should be closely followed to determine if the doses or agents should be altered, as needed.

Alpha blockers "rapidly" (usually within 1 week) improve urine flow and symptoms initially, but they do not reduce prostate size, prevent prostate growth, reduce the long-term risk of symptom progression, or urinary retention, or the need for surgery.[14,15]

Alpha blockers may not be effective due to hypotonic bladder, an irreversible outlet obstruction secondary to scarring, or due to continued bulky growth of the prostate (static obstruction).

Silodosin (Rapaflo) is a new alpha blocker that is available in the United States. This drug predominantly blocks alpha-1a receptors and blocks alpha-1d receptors to a lesser extent. In a double-blind placebo-controlled study of sildosin versus tamsulosin, patients taking

silodosin achieved uroflow response in 4-6 hours and symptom response in 3-4 days, which was better than early-treatment results with tamsulosin. The study also suggested that because of the sildosin's uroselectivity, vascular side effects were minimized.[16]

5-alpha reductase inhibitors

In the prostate, the enzyme 5-alpha reductase reduces testosterone to dihydrotestosterone (DHT), which is the principal androgen responsible for stimulating prostate growth. The 5-alpha reductase inhibitors (5-ARIs) prevent the conversion of testosterone to DHT in the serum and the prostate, which causes the prostate to shrink or to dramatically slow its continued growth.[17,18]

Two 5-ARIs --finasteride (Proscar) and dutasteride (Avodart) -- are currently available.

The 5-alpha reductase enzyme has two isoenzymes: type 1 and type 2. Finasteride acts on type 2 receptors, and dutasteride acts on type 1 and type 2 receptors. Tests have been done to determine if there is an impact of the different types of isoenzyme blockade. Because of the dual blockade, it has been shown that dutasteride lowers DHT production in the prostate by over 90%, whereas finasteride only lowers it by 70%.[19]

Side effects of 5-ARIs are loss of libido (in 3%-8% of patients), ejaculatory dysfunction (1%-5%), reduction in ejaculate volume and some erectile dysfunction (5%-10%), and some breast tenderness (1%).[20,21] The side effects of breast tenderness and decreased libido might appear to be surprising, given that 5-ARIs prevent the breakdown of testosterone, so the effective serum level of testosterone should be higher. However, testosterone is metabolized to DHT and estrogen in the liver. This increased estrogen or change in the estrogen-to-testosterone ratio as a result of 5-ARI therapy may be a cause of the decreased libido and breast tenderness in a small number of men.

The benefits of 5-ARIs are reduced BPH symptoms, reduced prostate size, improved voiding, long-term prevention of disease progression, reduced risk of urinary retention, and reduced risk of the need for surgery.[20,21]

Deciding on optimal therapy

The use of the symptom score sheet will identify and quantify-- for the patient and the physician-- symptoms that are most frequent and bothersome and will indicate the extent to which symptoms are causing a poorer quality of life.

By using objective parameters such as patient age, clinical physical examination findings, DRE findings, serum PSA levels, and urine flow rates, clinicians can identify men who are at risk of progression of LUTS/BPH and who would consequently benefit from medical therapy to prevent complications of BPH. These assessments can also identify men in need of immediate surgery for irreversible, significant, benign disease as well as men who should have further investigation to rule out possible malignant disease.

Several key papers provide evidence that supports the treatment guidelines.

MTOPS study

The Medical Therapy of Prostate Symptoms (MTOPS) was designed to determine if medical therapy (monotherapy or combination) would prevent or delay the progression of BPH, and/or prevent acute urinary retention, the need for surgery, renal insufficiency, recurrent UTI or urosepsis, incontinence, or a deterioration in quality of life.[15]

Patients were randomized into four treatment groups and received an alpha blocker (doxazosin) alone, a 5-ARI (finasteride) alone, combination therapy, or placebo.

Prostate volume decreased most in the patients treated with finasteride alone to the same extent as the patients treated with finasteride plus an alpha blocker. Prostate volume increased in size in patients treated with placebo or the alpha blocker alone. Patients who received combination therapy had the highest maximum flow rate, most improved symptom scores, a 67% reduced risk of BPH progression (compared to patients taking placebo), and a 69% lower risk of needing surgery (compared to patients taking placebo).

TABLE 1. **Patient characteristics at baseline: CombAT versus MTOPS**

Mean +	**CombAT (n = 4844)**	**MTOPS (n = 3047)**
Age (yrs)	66.1 + 7.01	62.6 + 7.3
Caucasian	4259 (88%)	2509 (82%)
Total IPSS	16.4 + 6.16	16.9 + 5.9
Prostate volume (cc)		
Total	55.0 + 23.58	36.3 + 20.1
Transition zone	29.5 + 21.97*	16.4
Serum PSA (ng/mL)	4.0 + 2.08	2.4 + 2.1
Qmax (mL/sec)	10.7 + 3.62	10.5 + 2.6
Post void residual volume (mL)	67.7 + 64.87	68.1 + 82.9

*Subgroup of 656 men
CombAT = Combination of Avodart and Tamsulosin;
MTOPS = Medical Therapy of Prostate Symptoms

CombAT study

The 4-year results from the Combination of Avodart and Tamsulosin (CombAT) study: were recently published.[22] CombAT differed from MTOPS in a number of ways, Table 1. It included only patients with proven, enlarged prostates (over 30 cc), that is, patients who, because of their larger prostate volumes alone, were at "higher risk" of BPH progression. The study was designed to determine whether dutasteride and tamsulosin in combination were more effective than either monotherapy alone for improving BPH symptoms, preventing progression, and improving long-term outcomes compared to untreated BPH.[23]

Combination therapy with an alpha blocker (tamsulosin) and a 5-ARI (dutasteride) resulted in significant improvement in symptoms and long term outcomes and was much better than monotherapy for all measures of BPH progression, Table 2.[23]

This is believed to be the first time that a 5-ARI outperformed an alpha blocker in "symptom control" alone as early as 15 months. Previously, as in MTOPS, the alpha blocker was always shown to be more effective for symptom control when compared to the 5-ARI.

The 4 year study results, like the 2 year results,[24] demonstrated an improvement (in quality of life question). The improvement is demonstrated by a symptom score reduction out of 6 as compared to the baseline score. The scores improved most with combination therapy (2.2-point reduction) versus dutasteride alone (1.8-point reduction) versus tamsulosin alone (1.2-point reduction).

The 4 year primary endpoint of the CombAT trial was different from the 2 year endpoints. The primary endpoint at 4 years was the risk reduction of developing acute urinary retention or the need for surgery. Patients who received combination therapy had a 66 % lower risk. It must be remembered that in MTOPS, the 67% risk reduction in developing urinary retention and the need for surgery was compared to placebo, whereas in CombAT, the 66% risk reduction was compared to a well-accepted active treatment: tamsulosin. This supports the previous statement that alpha blockers in the long term do not prevent progression of BPH.

The incidence of ejaculatory side effects in the combination arm was surprisingly greater than this incidence in the two monotherapy arms combined (10% versus 6%). The side effects experienced by the individuals on combination therapy represented a combination of side effects seen from each of the individual monotherapies.

Concern about the increased incidence of different types of side effects raised the question about the possibility of "withdrawal" of one of the medications after a period of time. Because the alpha blocker usually does not provide a long term effect in all patients, further studies were performed looking at alpha blocker withdrawal. The results of these studies, one using finasteride and the other using dutasteride, were similar.

In most cases, men with improvement on combination therapy may, after 6-9 months, stop taking the alpha blocker and still maintain good symptom response. However, about 20% of men with severe symptoms may require continued use of the alpha blocker.[5,25-27]

TABLE 2. **CombAT: BPH clinical progression at 4 years[23]**

	Combination (n = 1610)		**Dutasteride (n = 1623)**		**Tamsulosin (n = 1611)**	
At year 4	**n**	**%**	**n**	**%**	**n**	**%**
Clinical progression	203	12.6%	289	17.8%*	347	21.5%*
Risk reduction versus combination (95% CI)			31.2% (17.7%-42.5%)		44.1% (33.6%-53.0%)	
IPSS incr. > 4 points	139	8.6%	212	13.1%*	229	14.2%*
AUR	26	1.6%	37	2.3%	82	5.1%*
Incontinence	49	3.0%	60	3.7%	65	4.0%
UTI	3	0.2%	5	0.3%	5	0.3%
Renal insufficiency	1	< 0.1%	2	0.1%	7	0.4%

Crude rate based on ITT population
*$p < 0.001$ versus combination

PSA and medical therapy

The 5-ARIs lead to an "expected" reduction in serum PSA levels of about 50% within 6-9 months of starting therapy.[15,22] Failure to see a reduction in serum PSA levels, or seeing a rise in PSA levels following a drop in PSA to its lowest levels after treatment, might indicate treatment non compliance or the suspicion of prostate cancer.[28]

The prostate should be examined carefully, as it should shrink with 5-ARI therapy, which may allow prostate nodules to become more readily palpable and more easily biopsied.

A pretreatment PSA level is critical for comparison with post-treatment levels. Tracking PSA levels is important, since a rise in PSA levels (or an absence of the expected drop in PSA levels) in a patient receiving 5-ARIs requires referral for a biopsy, to rule out a now-suspected underlying prostate cancer.

Prostate cancer and 5-ARIs

The Prostate Cancer Prevention Trial (PCPT) revealed that compared to patients given placebo, patients given finasteride had 24% lower risk of detection of prostate cancer.[29] Patients enrolled in this trial had PSA levels lower than 4 ng/mL and no clinical indications of underlying prostate cancer (normal DRE). All patients had a prostate biopsy at the end of the study (at 5.5 years on average). The pathological biopsy results raised some questions concerning the increased risk of detecting a more aggressive cancer (higher Gleason score) in the treatment arm of the study compared to the placebo arm of the study. Most people do believe that this was a volume reduction artifact.[30]

Results from the Reduction by Dutasteride of Prostate Cancer Events or REDUCE trial were also recently reported. This trial only enrolled patients who had already undergone a prostate biopsy "for cause," which was shown to be negative. Because of that enrollment criterion, some people believe that these patients were at higher risk of subsequently having prostate cancer detected. Study subjects were randomized to dutasteride or placebo for 4 years. They each had a biopsy at 2 years and at 4 years (end of study).

REDUCE also showed a 23% lower risk of detecting prostate cancer in patients who were treated with dutasteride versus patients who received placebo. The recently reported end-of-study biopsy results from the REDUCE trial found that patients receiving dutasteride did not show a statistically significant increased risk of developing high-grade cancer.[28]

Medical management and sexual health

Erectile dysfunction (ED) was a side effect in some men taking tamsulosin (0.8%-2%) and the 5-ARI inhibitors (5%-9%).[12,20,21] This can be assessed and managed with drugs for ED.

Canadian guidelines

The Canadian Urological Association developed guidelines for the management of BPH that are clearly represented in the algorithms mentioned earlier, Figures 1 and 2. The decisions are made based on the size of the prostate in combination with the severity of symptoms and the degree of symptom bother. The importance of taking a patient history and doing a DRE is pivotal in deciding whether to immediately start the symptomatic patient on an alpha blocker alone, a 5-ARI alone, or combination therapy of an alpha blocker with a 5-ARI.[5]

Recently, Nashlund et al reported results from a trial that was designed to determine the consequences from delay in adding a 5-ARI to an alpha blocker at the outset versus initiating combination therapy at the time of the initial diagnosis of the patient with significant BPH symptoms. They found that for every 30 day delay in adding the 5-ARI dutasteride, the patient had a 2%-3% increased chance of developing urinary retention or needing surgery within 1 year of commencmeny of the medical therapy. [31]

Indications for referral to a urologist

Any of the following symptoms or signs reported by the patient or detected by the primary care physician warrant a referral to a urologist for investigation or management:

1. Acute or chronic urinary retention.
2. Significant microscopic or any gross hematuria.
3. Recurrent UTIs.
4. Renal insufficiency.
5. Failure of response to medical therapy.
6. Suspicion of prostatic cancer at baseline (elevated PSA or abnormal DRE).
7. Insufficient expected lowering or unexpected rise in PSA after 5-ARI treatment.
8. Patient concerns.

Summary

For a patient presenting with BPH symptoms, the primary care physician can use the AUA or IPSS symptom score sheets to determine the severity of

prostatic obstruction. Severity of symptoms, degree of bother, size of the prostate, and PSA levels are part of the Canadian guidelines algorithm, and when combined with the patient's age if over 50, these can help the physician identify and diagnose patients with clinically significant BPH and predict which patients are at risk for progression of BPH disease.

The guidelines also suggest which medical management strategy --an alpha blocker alone, a 5-ARI alone, or combination therapy— will provide the most rapid response and is the best treatment choice to prevent long term disease progression, urinary retention, or the need for surgery in a patient with symptomatic BPH.

Disclosure

Dr. Jack Barkin is an active urologist and Chief of Staff at the Humber River Regional Hospital in Toronto. He sits on the medical advisory board for Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Frosst, Paladin, Pfizer, sanofi-aventis and Solvay. He has done the clinical research on AndroGel, Avodart, Casodex, Cialis, Detrol, Flomax, Hytrin, Levitra, Xatral, Proscar and Viagra. He has spoken all over the world for all of the companies outlined.

Dr. Allan Toguri is an active senior urologist at The Scarborough Hospital. He has participated at the advisory board meetings of Astra Zeneca, Merck Frosst, and GlaxoSmithKline. He has been involved in clinical trials involving the 5-alpha reductase inhibitors and alpha blockers. □

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Uropharmacology in primary care: 2010 update

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

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

Introduction

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

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Symptomatic benign prostatic hyperplasia

Pathophysiology and pharmacology

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

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

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

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

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

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

Alpha blockers

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

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

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

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

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

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

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

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

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

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

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

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

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

*Dose titrated weekly to desired response

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

5-alpha reductase inhibitors

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

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

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

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

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

5-AR = 5-alpha reductase

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

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

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

Combination sBPH therapy

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

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

Erectile dysfunction

Pathophysiology and pharmacology

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

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

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

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

Oral therapy for erectile dysfunction

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

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

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

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

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

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

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

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

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

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

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

Intraurethral therapy for erectile dysfunction

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

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

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

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

Intracavernosal therapy for erectile dysfunction

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

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

Hypogonadism

Pathophysiology and pharmacology

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

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

Testosterone replacement therapy

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

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

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

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

TABLE 6. **Medications for male hypogonadism**

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

*Monitor serum testosterone levels for all agents.

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

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

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

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

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

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

Overactive bladder

Pathophysiology and pharmacology

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

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

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

Antimuscarinics

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

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

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

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

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

BBB = Blood brain barrier; M = muscarinic receptor type

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

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

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

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

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

Hormonal therapy for prostate cancer

Pathophysiology and pharmacology

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

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

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

LHRH manipulation

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

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

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

LHRH agonists and antagonists

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

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

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

LFTs: liver function tests

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

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

Antiandrogens

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

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

Conclusions

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

Disclosure

Dr. Leonard Gomella is a consultant or investigator for GlaxoSmithKline, Watson, Ferring and Astra Zeneca Pharmaceuticals.
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