Hong Kong Geriatrics Society and Hong Kong Urological Association consensus on personalized management of male lower urinary tract symptoms in the era of multiple co-morbidities and polypharmacy

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ABSTRACT

Lower urinary tract symptoms (LUTS) are common complaints of adult men. Benign prostatic hyperplasia (BPH) represents the most common underlying cause. As the incidence of BPH increases with age, and pharmacological treatment is a major part of the disease's management, the majority of patients with LUTS are managed by primary care practitioners. There are circumstances in which specialist care by urologists or geriatricians is required, such as failure of medical treatment, adverse effects from medical treatment, or complications from BPH. Referral choices can be confusing to patients and even practitioners in different specialties under such circumstances. There is currently no local consensus about the diagnosis, medical management, or referral mechanism of patients with BPH. A workgroup was formed by members of The Hong Kong Geriatrics Society (HKGS) and the Hong Kong Urological Association (HKUA) to review evidence for the diagnosis and medical treatment of LUTS. A consensus was reached by HKGS and HKUA on an algorithm for the flow of male LUTS care and the use of uroselective alpha blockers, antimuscarinics, beta-3 adrenoceptor agonists, and 5α-reductase inhibitors in the primary care setting. This consensus by HKGS and HKUA provides a new management paradigm of male LUTS.

Introduction

In 2019, Hong Kong overtook Japan as the region with the world’s longest life expectancy, with the life expectancy of Hong Kong Chinese men at 82.38 years.1 Benign prostatic hyperplasia (BPH) is the most common prostate problem for men older than 50 years. The occurrence of lower urinary tract symptoms (LUTS) due to BPH increases with age. A 1984 autopsy study showed that the prevalence of BPH rose with each decade after age 40, peaking at 88% in men in their 80s.2 Since the 1980s, medical therapy has been prescribed for patients with bothersome LUTS that negatively affects their quality of life. Moreover, the number of co-morbid diseases also increases with age. Co-morbidity increases from 10% at ages up to 19 years to 80% at ages 80 years and older.3 Co-morbidity also leads to polypharmacy and drug-drug interactions, which may result in serious adverse effects.

There is no established local consensus regarding the management of elderly male patients with LUTS. Thus, the Hong Kong Geriatrics Society (HKGS) and the Hong Kong Urological Association (HKUA) formed a working group with the aim of providing insights to clinicians involved in the medical management of male patients with LUTS through a consensus article.

Diagnostic evaluation

The causes of male LUTS can be multifactorial. Detailed history, appropriate questionnaires, physical examination, and investigation not only help clinicians to reach a diagnosis and identify some alarming conditions (eg, prostate cancer and bladder cancer) but also guide treatment options and give prognostic information for patients’ counselling.

History

It is useful to determine the most predominant and bothersome LUTS to guide their management, eg, voiding symptoms (weak stream, intermittency,
hesitancy, incomplete emptying) and storage symptoms (urgency, frequency, nocturia). The severity of symptoms can be categorised by the International Prostate Symptoms Score as mild (0-7), moderate (8-19), or severe (20-35). It is a validated tool for the assessment of symptoms and quality of life in patients with LUTS (online supplementary Appendix) and allows objective monitoring of treatment response.

Focused histories of the presence of neurological diseases, diabetes mellitus, medication, drinking habits, and prior lower urinary tract procedures are useful to identify causes of LUTS other than BPH (eg, neurogenic bladder, polydipsia, urethral stricture).

Referral to geriatricians should be considered in elderly patients with history of postural hypotension, delirium, dementia, frequent falling, or polypharmacy, as these patients have a higher risk of adverse effects from medical treatment of LUTS, and comprehensive geriatric assessment may be necessary.

Alarming symptoms should raise suspicion of pathologies other than BPH, eg, gross haematuria or unexplained dysuria may imply underlying neoplastic or inflammatory causes, or bedwetting may imply underlying chronic urinary retention with overflow incontinence. Prompt referral to urologists is preferable in the presence of such symptoms.

**Physical examination**

Digital rectal examination is used to assess prostate size, consistency, the presence of prostatic nodules, and anal tone. In addition, focused examination of the abdomen, external genitalia, and lower limbs is important. Palpable bladder, phinosis, penile mass, and abnormal neurological signs are important to notice when considering referral to appropriate specialists.

A rough estimation of prostate size by number of finger breaths on digital rectal examination is acceptable and may guide the use of 5α-reductase inhibitors (5ARI). Imaging assessment by ultrasound can be considered if more accurate assessment is preferred.

**Investigations**

Most patients with LUTS have slow deterioration of symptoms, and very few develop complications over a 5-year period.4 In the primary care setting, the aim of initial evaluation is to detect non-BPH causes, and urinalysis should be included. Prostate-specific antigen (PSA) can be measured after proper counselling, and serum creatinine should be checked when renal impairment is suspected. Numerous additional investigations are also possible, such as flow rate measurement, post-void residual urine volume, renal ultrasonography, prostate sizing, or urodynamic study. However, these additional investigations are optional and need not be routinely performed at the initial evaluation, as they are not cost-effective. Selected patients with appropriate indications (eg, LUTS with poor response to medical treatment, presence of alarming symptoms, impaired renal function) benefit the most from these tests, and input from specialists is preferred in these circumstances.

**Urinalysis**

Urinalysis (dipstick or sediment count) should be included in the primary evaluation of any patients presenting with LUTS to search for urinary tract infections, microscopic haematuria, and diabetes mellitus. If abnormal findings are detected, further tests are recommended.5

**Prostate-specific antigen**

One of the differential diagnoses of male LUTS is prostate cancer. Prostate-specific antigen is organ-specific but not cancer-specific. There is substantial overlap in values between men with benign and malignant prostate disease. Hence, elevated PSA levels should be interpreted with caution.

For patients with abnormal DRE, checking PSA can increase the detection rate of prostate cancer. However, for patients with normal DRE, PSA should be checked only when the detection of prostate cancer will cause the disease’s management to be modified. In general, in patients with life expectancy of <10 years or with multiple co-morbidities, checking of PSA to detect prostate cancer might not be beneficial to the patient and should only be performed with special justification after proper counselling.
Serum creatinine
Assessment of renal function should be considered in patients with high risk of renal impairment (eg, those with multiple co-morbidities and polypharmacy).

Treatment
The majority of patients with LUTS have slow progression of symptoms, with fewer than 2% developing urinary retention and fewer than 10% requiring BPH surgery over a 5-year period. Patients not bothered by their symptoms can be safely managed conservatively with education and lifestyle changes. Examples of lifestyle changes include reduction of fluid intake before bedtime to lessen nocturia, avoidance of caffeinated beverages or alcohol to reduce frequency and urgency, urethral milking to prevent post-micturition dribbling, and optimising the timing of medication, especially diuretics.

In addition to education and lifestyle changes, medical treatment can be considered for patients with bothersome symptoms. Voiding symptoms can be regarded as the manifestation of underlying bladder outlet obstruction resulting from BPH, which underpins the rationale of using alpha-1 adrenoceptor antagonists (α1-blockers). Storage symptoms can be attributed to either underlying obstruction-induced change in bladder function or overactive bladder without bladder outlet obstruction. The choice of agent depends on the predominant type of symptoms (ie, voiding vs storage symptoms). For patients with predominant voiding symptoms, the first-line medical treatment is α1-blockers, which have been shown to improve both voiding and storage symptoms. For patients with predominant storage symptoms or residual storage symptoms after a trial of α1-blockers, antimuscarinics and beta-3 adrenoceptor agonist (β3 agonist) can be considered. For patients with large prostate (eg, >40 cc), 5αRIs can be used to reduce the prostate size, improving symptoms and preventing disease progression in terms of acute urinary retention and future need of BPH surgery. It is important to consider adverse effects before starting medical treatment, especially in older patients with multiple co-morbidities and polypharmacy.

Surgical treatment can be considered for patients who develop BPH complications (eg, urinary retention, bladder stones, obstructive uropathy, recurrent urinary tract infection, haematuria) or symptoms refractory to medical treatment. However, surgery is associated with potential morbidities and mortality, especially in frail geriatric patients.

Frailty is a syndrome characterised by reduced physiological reserve and increased vulnerability to adverse outcomes. Even minor stressor events such as surgery can trigger disproportionate worsening of health status in frail elderly people. The most frequently used model to identify frailty is the phenotype described by Fried et al in 2001, which comprises five variables: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength. The definition of polypharmacy has no universally agreed cut-off point with regard to the number of medications. Different researchers have arbitrarily chosen various cut points. In the late 1990’s, the United States Centers for Medicare and Medicaid Services implemented a quality indicator measure that targets patients taking nine or more concurrent medications. An alternative definition of polypharmacy is the use of more medications than are medically necessary.

After commencement of medical therapy, apart from the monitoring of treatment response and adverse drug reactions, it is also crucial to review medical conditions and identify the new occurrence of geriatric red flags (eg, frailty, polypharmacy) as patients age. The consensus algorithm on male LUTS care flow in the primary care setting by HKGS and HKUA is outlined in Figure 1.

Alpha-1 adrenoceptor antagonists
The use of α1-blockers has been shown to be effective at reducing LUTS associated with BPH. The α1-blockers relax smooth muscle tone at the bladder neck and prostate by blocking the action of endogenously released noradrenaline. They are usually considered as the first-line therapy for male LUTS because of their good efficacy on symptomatic relief but do not alter the natural progression of the disease.

Currently available α1-blockers include prazosin, terazosin, doxazosin, alfuzosin, tamsulosin and silodosin. They have different uroselectivity, pharmacokinetic properties, and formulations (Table 1). Prazosin is a short-acting drug that requires multiple dosing schedules and was the earliest drug to be used for treatment of BPH. However, the 2003 American Urological Association Guidelines concluded that there was insufficient support for recommending prazosin as a treatment option for LUTS secondary to BPH. These and the European Association of Urology Guidelines regard prazosin as a nonstandard treatment.

Although different α1-blockers have similar efficacy in improving symptoms and uroflow at appropriate doses, uroselective agents (α-1A blockers) and long-acting preparations appeared to be better tolerated. The differences between the tolerability of various α1-blockers can be explained by the differences in the expression and distribution of receptor subtypes (alpha 1A and 1B) in the body (Fig 2).
FIG 1. Algorithms of male LUTS care flow

Abbreviations: DRE = digital rectal examination; IPSS = International Prostate Symptoms Score; LUTS = lower urinary tract symptoms; PSA = prostate-specific antigen; USG = ultrasound; UTI = urinary tract infections

- Frequent fall
- Dementia/history of delirium
- Postural hypotension
- Frail
- Polypharmacy

Initial assessment:
- History
- Physical exam including DRE, external genitalia
- Urinalysis
- IPSS

Optional tests:
- PSA after proper counselling
- Serum creatinine if suspected renal impairment
- Uroflowmetry, post-void residual urine, USG, prostate sizing if indicated and tools available

Look for geriatric red flags
- Frequent fall
- Dementia/history of delirium
- Postural hypotension
- Frail
- Polypharmacy

Look for urological red flags
- Suspected urological cancer, eg, gross haematuria, abnormal prostate on DRE, elevated PSA
- LUTS complicated with retention, bedwetting, recurrent UTI, bladder stone, renal impairment caused by lower urinary tract dysfunction confirmed with hydronephrosis on imaging
- Evidence of phimosis

If symptoms are refractory to medical treatment, new occurrence of geriatric or urological red flags, referral to specialists (urologist or geriatrician) should be considered
Major adverse effects of α1-blocker use include dizziness, asthenia, postural hypotension, and syncope, which can result in falling (odds ratio [OR]=1.14) and fractures (OR=1.16), especially in elderly people, the majority of whom cannot tolerate these drugs at the higher adult dose range. Studies have consistently demonstrated that uroselective agents including tamsulosin and silodosin have the least effect on blood pressure and the lowest risk of developing vascular-related events. However, a minor but significant change in blood pressure and heart rate was observed with tamsulosin, whereas no significant change was demonstrated with silodosin compared with placebo in a randomised controlled trial.

There have been reports concerning the association of α1-blockers (especially tamsulosin) with intraoperative floppy iris syndrome, leading to a high rate of complications during cataract surgery, and it is suggested that ophthalmologists be reminded so that they can take precautions. Sexually active patients should be informed of the...
adverse effect of abnormal ejaculation, which was another adverse reaction more commonly related with tamsulosin (OR=8.58) and silodosin (OR=32.5), and patients should be informed of the potential implications.17

Patients who are naïve to α-blockers may develop postural hypotension, known as the “first dose phenomenon,” which is more pronounced with non-selective α1-blockers during the first 8 weeks of treatment. However, it should not be overlooked with uroselective agents, and special precautions should be taken, especially in elderly patients. In addition, swallowing difficulties are not uncommon in elderly patients, in whom modified release preparations are inappropriate.

The pitfalls of prescribing α1-blockers are summarised in Table 2.18 Their most troublesome adverse effect is postural hypotension. The situation is even more complicated if the patient has concomitant hypertension or is taking multiple medications with hypotensive effects for various indications. It is estimated that more than 25% of men aged >60 years have concomitant BPH and hypertension,19 which poses a significant challenge in the prescription of α1-blockers. Non-selective α1-blockers have been available as antihypertensive agents for over 40 years. They reduce blood pressure by blocking postsynaptic alpha (mainly alpha-1B) receptors, thereby inhibiting noradrenaline release that induces vasoconstriction, resulting in dilatation of arterioles and venules. Among all α1-blockers, prazosin, terazosin, and doxazosin are approved for the management of hypertension, whereas alfuzosin, tamsulosin, and silodosin have minimal effect on blood pressure.

Because certain α1-blockers are approved treatments for hypertension, they are a reasonable choice for treatment of hypertensive men with LUTS. However, with advances in hypertensive treatment over past decades, the role of α1-blockers in this context has changed, especially after the introduction of uroselective agents. A consensus was reached regarding revision of the use of available safety data on α1-blockers in patients with hypertension (Table 3).20-29

**Patients with hypertension but not yet taking antihypertensive**

For hypertensive LUTS patients who are not taking any antihypertensives, we do not recommend the use of non-selective α1-blockers for treatment of BPH and hypertension together (first-line treatment of hypertension). This recommendation is based on the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Study.20 That study showed that compared with chlorthalidone (diuretics), the use of doxazosin is associated with significantly higher risk of stroke, congestive heart failure, peripheral vascular disease, angina, and cardiovascular disease requiring coronary revascularisation. Multiple guidelines (The Eighth Joint National Committee (JNC8) guideline30, the European Society of Cardiology/the European Society of Hypertension guideline31, the American College of Cardiology/American Heart Association guideline32 and Hypertension Canada’s 2017 guideline for diagnosis33) do not recommend α1-blockers as the first-line therapy for hypertension. Therefore, we recommended treating LUTS with

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**TABLE 2. Pitfalls of prescribing alpha 1 blockers**18

<table>
<thead>
<tr>
<th>Pitfall</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-dose phenomenon</strong></td>
<td>To avoid the potential risk of first-dose phenomenon, patients should be aware of hypotensive symptoms within 8 weeks after initiating treatment of α1-blockers. For drugs with a daily dose, it is advisable to start medication at night time. Reducing the initial dosage is also possible.</td>
</tr>
<tr>
<td><strong>Syncpe</strong></td>
<td>Because of the risk of symptomatic postural hypotension, dizziness, or syncope with any α1-blockers, patients should be instructed to avoid situations where injury may result if syncope occurs upon initiation of therapy. In addition, patients should be asked whether they experienced falls while on treatment.</td>
</tr>
<tr>
<td><strong>Difficulty swallowing</strong></td>
<td>The α1-blockers in modified release form should be used with special precaution.</td>
</tr>
<tr>
<td><strong>Hepatic or renal impairment</strong></td>
<td>Caution and adjustment should be considered for patients with hepatic or renal impairment according to the α1-blockers chosen.</td>
</tr>
<tr>
<td><strong>Ejaculatory disorders</strong></td>
<td>Higher incidence of ejaculatory disorders has been reported with uroselective α1-blockers. Patients should be reminded of the issue if planning to have children.</td>
</tr>
<tr>
<td><strong>Intraoperative floppy iris syndrome</strong></td>
<td>Patient who plan to undergo cataract surgery should inform ophthalmologists about any drug history of α1-blockers.</td>
</tr>
</tbody>
</table>

Abbreviation: α1-blockers = alpha 1 blockers
uroselective agents, and hypertension should be treated with another class of antihypertensives according to existing hypertension guidelines.

Patients with hypertension that is suboptimally controlled with antihypertensive

For hypertensive LUTS patients who have suboptimal blood pressure control but are taking antihypertensive treatment, the addition of non-selective α1-blockers (doxazosin gastrointestinal therapeutic system [GITS] and terazosin) for treatment of hypertension as second- or third-line agents seems to be a reasonable option for achieving optimal blood pressure control.23-26 However, postural hypotension is a significant concern in the treatment group. Therefore, although non-selective α1-blockers are effective at reducing blood pressure as add-on therapy, the risks and benefits of this approach should be balanced and individualised. This is the case especially when other classes of antihypertensives may have additional benefits in certain patients in whom treatment of LUTS with uroselective agents and hypertension separately with another class of antihypertensive agents might be advisable.

Patients with hypertension that is optimally controlled with antihypertensive

The safety data on non-selective α1-blockers in normotensive LUTS patients who are taking antihypertensives with optimal blood pressure control are largely based on post-hoc analysis of randomised controlled trials assessing standard versus intensive blood pressure control, which involves non-selective α1-blockers as third- or fourth-line antihypertensives. In the Action to Control Cardiovascular Risk in Diabetes trial, which involved 10 251 high-risk participants with type 2 diabetes mellitus at 77 centres, non-selective α1-blockers were significantly associated with postural hypotension, which was associated with higher mortality and rates of heart failure and hospitalisation.27 Another European study, the Systolic Blood Pressure Intervention trial, which involved 9 361 patients with increased cardiovascular risk but without diabetes, found that non-selective α1-blockers were associated with higher risk of syncope and falling, although no significant hypotensive events were demonstrated.28 Therefore, we recommend the use of uroselective agents for management of LUTS in this group of patients.

Apart from the risk of postural hypotension,

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**TABLE 3. Recommendations on concomitant use of alpha 1 blockers with antihypertensive agents (panel’s expert opinion)**20-29

<table>
<thead>
<tr>
<th>Hypertensive</th>
<th>Normotensive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not taking antihypertensive agents</strong></td>
<td><strong>Patients with hypertension but not yet taking antihypertensive:</strong></td>
</tr>
<tr>
<td></td>
<td>Antihypertensive should be initiated to treat hypertension, whereas uroselective α1-blockers should be used to treat BPH.</td>
</tr>
<tr>
<td></td>
<td>Non-selective α1-blockers should NOT be used as the first-line medication for hypertension and BPH.</td>
</tr>
<tr>
<td><strong>Taking antihypertensive agents</strong></td>
<td><strong>Patients with hypertension but suboptimally controlled with antihypertensive:</strong></td>
</tr>
<tr>
<td></td>
<td>Adjust antihypertensive agent(s) for blood pressure control and start uroselective α1-blockers for treatment of BPH, or continue current antihypertensive agent(s) and add non-selective α1-blockers.23-26</td>
</tr>
<tr>
<td></td>
<td>Patients with hypertension and optimally controlled with antihypertensive:</td>
</tr>
<tr>
<td></td>
<td>Uroselective α1-blockers are preferable over non-selective α1-blockers.27-29</td>
</tr>
</tbody>
</table>

Abbreviations: α1-blockers = alpha 1 blockers; BPH = benign prostatic hyperplasia
the selection between non-selective and uroselective agents should also be based on other factors, including the risk of falling, polypharmacy, co-morbidities, and specific situations where the use of uroselective agents is advisable (Table 4).

Nevertheless, α1-blockers are effective in relieving LUTS and improving quality of life for patients with BPH. However, treatment decisions should be individualised and based on comprehensive assessment of patients with different needs, especially in frail elderly patients, as they tend to have accumulated co-morbidities, disabilities, and polypharmacy that often interact with each other.

**Antimuscarinics**

Antimuscarinics are commonly used as pharmacological treatments for overactive bladder. This class of drug can also be used in predominant or mixed storage LUTS. These drugs increase bladder capacity and reduce urgency by blockading the muscarinic receptor during bladder storage.34 Antimuscarinics have shown a modest benefit over placebo in reducing urgency incontinence in women.35,36 The efficacy of all the antimuscarinics is similar.37 However, there is lack of head-to-head comparison, and not all antimuscarinics have been tested in elderly men. These drugs often require higher doses to achieve the optimal effects, and we recommend starting with the lowest dose and titrating up as needed if the patient has insufficient response and minimal adverse effects. Antimuscarinics should be avoided if the patient has clinically palpable bladder. These drugs can be associated with increased post-void residual urine volume after therapy, but acute retention is rare.5 Follow-up is recommended at 4 to 6 weeks to assess therapeutic response and determine whether a change in medication is necessary. Men should be advised to discontinue medication if they develop voiding difficulty, urinary infection, or worsening LUTS after initiation of therapy.

All antimuscarinics exert peripheral anticholinergic effects that may limit drug tolerability and dose escalation.35 Common adverse events include dry mouth (up to 16%), constipation (up to 4%), dizziness (up to 5%), micturition difficulty (up to 2%), blurred vision for near objects, tachycardia, drowsiness, and worsened cognitive function.5 Up to two-thirds of patients discontinue these medications beyond 1 year.38 Constipation and compensatory fluid intake for dry mouth may exacerbate urinary incontinence. Patients with dementia are more vulnerable to adverse effects of antimuscarinics.39,40 Antimuscarinics should be avoided in patients with uncontrolled tachyarrhythmia, myasthenia gravis, and narrow angle-closure glaucoma. The adverse effects of antimuscarinics can be explained by the distribution of muscarinic acetylcholine receptor subtypes throughout the body (Fig 3). The differences in tolerability between antimuscarinics can be explained by their differences in selectivity for receptor subtypes and tissue penetration.

Antimuscarinics may have additive adverse effects when combined with other medications that have strong anticholinergic effects. They should be used with caution or preferably avoided if elderly patients are concomitantly taking other medications with high anticholinergic potency, eg, first-generation H1 antihistamines (chlorpheniramine, hydroxyzine, diphenhydramine), anti-Parkinson’s drugs (benztrapine, trihexyphenidyl), spasmyotics (atropine, hyoscine), anti-emetics (promethazine), muscle relaxants, antipsychotics (chlorpromazine, fluphenazine, trifluoperazine, clozapine), and tricyclic antidepressants (amitriptyline, clomipramine, doxepin, imipramine, nortriptyline).41-43

The antimuscarinics registered in Hong Kong include oxybutynin, solifenacin, tolterodine, trospium, darifenacin, and fesoterodine. Solifenacin, darifenacin, and trospium may have less impact on the central nervous system (Table 5).

### Table 4. Consensus for prescribing uroselective agents (panel’s expert opinion)

<table>
<thead>
<tr>
<th>Factors to be considered</th>
<th>Situations where uroselective agents should be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of postural hypotension</td>
<td>Symptomatic hypotension, postural hypotension, or syncope/near syncope prior to or while on a non-selective α1-blocker</td>
</tr>
<tr>
<td>High fall risk</td>
<td>Patients with benign prostatic hyperplasia who develop symptomatic hypotension while taking concomitant treatment of antihypertensive agent and a non-selective α1-blocker</td>
</tr>
<tr>
<td>Multiple co-morbidities</td>
<td>Patients with polypharmacy (multiple co-morbidities)</td>
</tr>
<tr>
<td>Concomitant use of antihypertensive agents/PDE5i on demand</td>
<td>Patients with conditions that do not allow adequate time for titration with a non-selective α1-blocker</td>
</tr>
<tr>
<td></td>
<td>Patients who are taking PDE5i on demand (be aware of the potential risk of hypotension)</td>
</tr>
</tbody>
</table>

**Abbreviation:** PDE5i = phosphodiesterase type 5 inhibitor
TABLE 5. Dosage, formulation, metabolism, and administration of antimuscarinics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting dose</th>
<th>Maximum dose</th>
<th>Metabolism</th>
<th>Administration information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin (5 mg tablet)</td>
<td>5 mg, 2 or 3 times daily</td>
<td>5 mg, 4 times daily</td>
<td>Dizziness and somnolence can occur Often not tolerated by elderly patients because of anticholinergic adverse effects (including the central nervous system) Reduced dose in older adults Short duration of effects may be useful when continence is desired at specific times</td>
<td>Can be crushed Suitable for tube feeding</td>
</tr>
<tr>
<td>Tolterodine (1 and 2 mg tablets)</td>
<td>1 mg, twice daily</td>
<td>2 mg, twice daily</td>
<td>Reduced dose for renal and/or hepatic impairment, not recommended for severe renal or hepatic impairment Modestly prolongs QTc interval, caution with other QTc-prolonging drugs and in patients with congenital prolonged QT</td>
<td>Can be crushed Suitable for tube feeding</td>
</tr>
<tr>
<td>Tropium (20 mg coated tablet)</td>
<td>20 mg, once daily</td>
<td>20 mg, twice daily</td>
<td>Needs to be taken on an empty stomach or 1 hour before a meal Reduced dose for renal impairment, not recommended for severe renal impairment Low risk of drug-drug interactions Avoid alcohol consumption within 2 hours</td>
<td>Can be crushed</td>
</tr>
<tr>
<td>Solifenacin (5 and 10 mg tablets)</td>
<td>5 mg, once daily</td>
<td>10 mg, once daily</td>
<td>Reduced dose for severe renal impairment or moderate hepatic impairment, not recommended for severe hepatic impairment Modestly prolongs QTc interval; caution with other QTc-prolonging drugs and in patients with congenital prolonged QT</td>
<td>Do not crush</td>
</tr>
<tr>
<td>Darifenacin prolonged-release (7.5 and 15 mg tablets)</td>
<td>7.5 mg, once daily</td>
<td>15 mg, once daily</td>
<td>Metabolised in liver; reduced dose for moderate hepatic impairment, not recommended for severe hepatic impairment</td>
<td>Do not crush or chew Not suitable for tube feeding</td>
</tr>
<tr>
<td>Fesoterodine prolonged-release (4 and 8 mg tablets)</td>
<td>4 mg, once daily</td>
<td>8 mg, once daily</td>
<td>Metabolised in liver; reduced dose for severe renal impairment, not recommended for severe hepatic impairment</td>
<td>Not suitable for tube feeding</td>
</tr>
</tbody>
</table>

FIG 3. Connection between the expression and distribution of muscarinic acetylcholine receptors and the tolerability of antimuscarinics

Relaxation of bladder muscle Bladder: M2 and M3 receptors
Constipation Gastrointestinal tract: M2 and M3 receptors
Dry mouth Salivary glands: M1 and M3 receptors
Cognitive impairment Brain: M1-M5 receptors
Beta-3 adrenoceptor agonist

Beta-3 agonist is a new class of pharmacological treatment used to relieve storage symptoms (urgency, urinary frequency, and urge urinary incontinence) associated with overactive bladder. It acts by binding to the β3 adrenergic receptors on the bladder smooth muscle causing bladder relaxation during the storage phase. Mirabegron is currently the only approved β3 agonist for treatment of overactive bladder.

In a phase III clinical trial, mirabegron 50 mg daily resulted in a 50% reduction in the number of urgency episodes per 24 hours and a 128% increase in the mean volume voided per micturition compared with placebo.44 Unlike antimuscarinics, it has better tolerability with less dry mouth. In the study, mirabegron’s incidence of dry mouth was similar to that of placebo.45

Mirabegron has no influence on bladder contraction during the voiding phase. In the clinical trial, the incidence rate of acute urinary retention was the lowest in mirabegron-treated patients compared with the tolterodine and placebo groups (0.1%, 0.6%, and 0.2%, respectively).44 The same trial showed that mirabegron did not increase intraocular pressure, and it is therefore not contra-indicated in patients with glaucoma.

Regarding cardiovascular safety, the review and real-world data on mirabegron did not show any increased risk compared with conventional antimuscarinics or in those with coexisting cardiovascular disease.46,47 The European Association of Urology guideline recommends β3 agonist as a first-line medication for men with moderate-to-severe LUTS who have predominantly bladder storage symptoms.48

Beta-3 agonist can be considered when antimuscarinic adverse effects and high anticholinergic burden are concerns, especially in elderly adults with multiple co-morbidities and cognitive impairment. Several studies have shown that mirabegron is safe and effective in patients with glaucoma.

5α-reductase inhibitors

5α-reductase is responsible for conversion of testosterone to dihydrotestosterone, which has an important role in prostate growth and the development of BPH.53 There are two isoforms of 5α-reductase: type 1—the predominant enzyme in extraprostatic tissue such as skin and liver; and type 2—the predominant enzyme in prostate (>90%), which is critical to development of BPH.

The 5ARI drugs inhibit conversion of testosterone to dihydrotestosterone, inducing apoptosis and atrophy of prostatic epithelial cells.54 It results in reduction of prostate volume and hence relief of bladder outflow obstruction. There are two types of 5ARI: finasteride, which acts only on type 2 5α-reductase, and dutasteride, which acts on both types. Meta-analysis has shown no differences in efficacy or safety among these two drugs.55,56 There are a few registered 5ARI drugs: Proscar (finasteride 5 mg), Avodart (dutasteride 0.5 mg), and Duodart (combination of dutasteride 0.5 mg and tamsulosin 0.4 mg).

Long-term 5ARI treatment in patients with moderate to severe LUTS and prostate volume >40 cc has been shown to reduce the symptoms score, risk of urinary retention, and risk of BPH-related surgery. In a landmark study, patients taking finasteride had improvement in symptoms and uroflow, their prostate size reduced by 20%, their risk of acute urinary retention reduced by 57%, and their risk of BPH-related surgery reduced by 55% compared with placebo after 4 years of treatment.56

There are some practical tips for prescribing 5ARI. First, the patient should have an enlarged prostate >40 cc on ultrasound imaging. If ultrasound is not readily available, it is acceptable to start 5ARI treatment when the prostate size is greater than two finger breadths on DRE. Second, it is important to inform the patient that 5ARI have a slow onset of action (3-6 months), as time is required for prostate volume reduction. Continuous long-term treatment should be expected. Third, the effects of 5ARIs on PSA levels should be explained to patients. The PSA level is expected to be reduced by 50% after 6 to 12 months of treatment,56 and therefore, good drug compliance is required for proper interpretation of the PSA level in prostate cancer screening. A persistent PSA rise from the nadir in a patient on long-term 5ARI treatment is an indicator for prostate biopsy, and urological referral should be considered.57 Finally, although some studies have suggested a higher incidence of high-grade prostate cancer in patients taking long-term 5ARI, no causal relationship has been proven, and there is no difference in long-term survival.58 The common adverse effects are sexual dysfunction, such as decreased libido, erectile dysfunction, and ejaculatory problems in around 4%
to 8% and breast enlargement in 1% of patients.56

Conclusion

Male LUTS is a common presentation to primary care practitioners. Focused history and physical examination are essential to differentiate BPH from other causes of male LUTS and to guide its management. Patients with minimal symptoms can be managed conservatively, and pharmacological treatments can be considered if symptoms are bothersome. For patients with symptoms refractory to pharmacological treatments or who have complications (eg. urinary retention, obstructive uropathy), surgical intervention can be performed after assessment by urologists. With an ageing population, geriatricians are adopting an increasing role in the management of male patients with LUTS in the era of multiple co-morbidities and polypharmacy, as these patients are at higher risk of adverse effects from pharmacological treatments and are not optimal for surgical intervention. A consensus has been reached by the HKGS and HKUA regarding the diagnosis, evaluation, management, and referral mechanism for LUTS in the primary care setting. With collaboration between primary care practitioners, geriatricians and urologists, we hope that more holistic care can be provided to male patients with LUTS in Hong Kong.

Author contributions

All authors contributed to the concept or design of the study, acquisition of the data, analysis or interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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APPENDIX. International Prostate Symptoms Score (Hong Kong Chinese Version 2)

International Prostate Symptoms Score (Hong Kong Chinese Version 2)

<table>
<thead>
<tr>
<th>姓名：</th>
<th>日期：</th>
<th>無</th>
<th>五次內不到一次</th>
<th>少於一半時間</th>
<th>大約一半時間</th>
<th>多於一半時間</th>
<th>幾乎每一次</th>
<th>你的分數</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 排尿不清 在過去一個月中，你多常有未能把尿排盡的感覺？</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2. 尿頻 在過去一個月中，你多常在排尿後兩個小時內又要小便？</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3. 排尿斷續 在過去一個月中，你多常在排尿時尿流斷斷續續？</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>4. 尿急 在過去一個月中，你多常感到“忍尿”有困難？</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>5. 尿流無力 在過去一個月中，你多常有尿流細弱的症狀？</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6. 排尿費力 在過去一個月中，你多常需要用力才能開始排尿？</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>無</td>
<td>一</td>
<td>二</td>
<td>三</td>
<td>四</td>
<td>五或以上</td>
<td>你的分數</td>
</tr>
<tr>
<td>7. 夜尿次數 在過去一個月中，你晚上醒來小便的次數是：</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPSS 總評分 (1+7) =</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>總評分: 0-7分為輕度症狀 8-19分為中度症狀 20-35分為重度症狀</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

8. 就排尿症狀作生活質素評分

假如你現在的排尿情況一直持續不變，你會覺得怎樣？

<table>
<thead>
<tr>
<th>興奮</th>
<th>滿意</th>
<th>大致滿意</th>
<th>滿意及不滿意</th>
<th>不滿意</th>
<th>不滿意</th>
<th>大致不滿意</th>
<th>不滿意</th>
<th>很痛苦</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>