

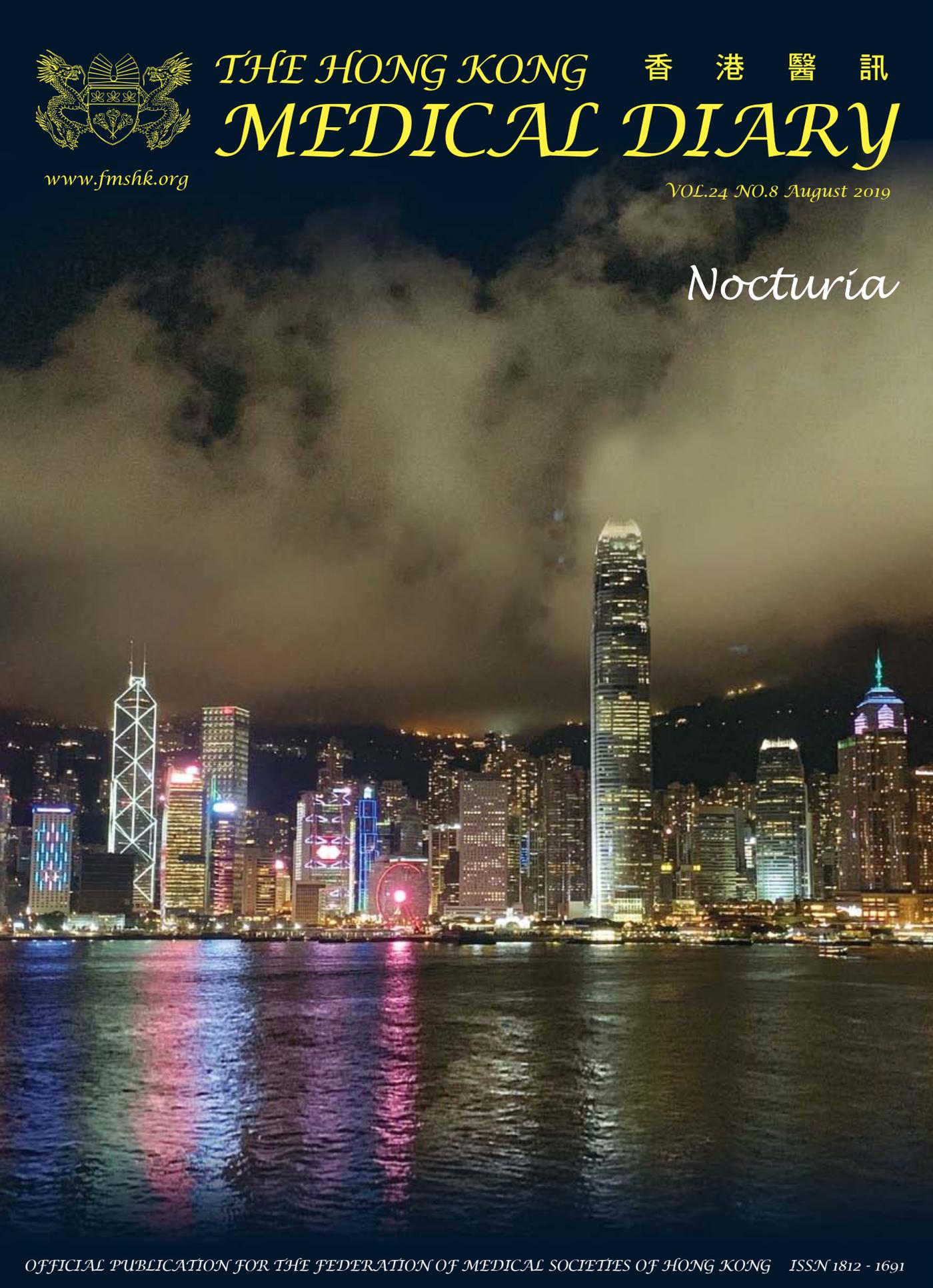


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VOL.24 NO.8 August 2019

Nocturia



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In 7,637 patients with type 2 diabetes at high risk of CV events¹

At baseline: mean age was 65 years, diabetes duration was 16.4 years, HbA_{1c} was 8.4%, and 83.9% were on insulin therapy¹

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Nocturnal severe hypoglycaemia



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Presentation: Tresiba® FlexTouch®. All presentations contain insulin degludec. Tresiba® 100 units/mL – 1 mL of solution contains 100 units insulin degludec (equivalent to 3.66 mg). One pre-filled device contains 300 units of insulin degludec (3 mL solution).
Indications: Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.
Posology and administration: Tresiba® is a basal insulin for once-daily subcutaneous administration any time of the day, preferably at the same time of day. On occasions when administration at the same time of the day is not possible, Tresiba® allows for flexibility in the timing of insulin administration. A minimum of 8 hours between injections should be ensured. In patients with type 2 diabetes mellitus, Tresiba® can be administered alone, or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin. In type 1 diabetes mellitus, Tresiba® must be used with short-acting insulin. Administration by subcutaneous injection only. Tresiba® is available in 100 units/mL. For Tresiba® 100 units/mL, a dose of 1–20 units per injection, in steps of 1 unit, can be administered. When initiating patients with type 2 diabetes mellitus the recommended daily starting dose is 10 units. Transferring from other insulins in type 2 diabetes changing the basal insulin to Tresiba® can be done unit-for-unit, based on the previous basal insulin component; in type 1 diabetes the same applies apart from where transferring from twice-daily basal insulin or patients with an HbA_{1c} <8.0%, the Tresiba® dose needs to be determined on an individual basis with a dose reduction considered. Doses

and timing of concomitant treatment may require adjustment. Using Tresiba® in combination with GLP-1 receptor agonists in patients with type 2 diabetes mellitus; when adding Tresiba® to GLP-1 receptor agonists, the recommended daily starting dose is 10 units; when adding Tresiba® to GLP-1 receptor agonists to Tresiba®, it is recommended to reduce the dose of Tresiba® by 20% to minimize the risk of hypoglycaemia. In all cases, doses should be adjusted based on individual patients' needs; fasting plasma glucose is recommended to be used for optimising basal insulin doses. In elderly patients and patients with renal/hepatic impairment glucose monitoring should be intensified and the dose adjusted on an individual basis. In paediatric population, when changing basal insulin to Tresiba®, dose reduction of basal and bolus insulin needs to be considered on an individual basis in order to minimise the risk of hypoglycaemia. Tresiba® comes in a pre-filled pen, FlexTouch®, designed to be used with NovoPen®. **Contraindications:** hypersensitivity to the active substance or any of the excipients. **Special warnings and precautions:** Too high insulin dose, omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. In children care should be taken to match insulin doses (especially in basal-bolus regimen) with food intake and physical activities in order to minimize the risk of hypoglycaemia. Reduction of warning symptoms of hypoglycaemia may be seen upon lightening control and also in patients with long-standing diabetes. Administration of rapid-acting insulin is recommended in situations with severe hypoglycaemia. Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hypoglycaemia and potentially to diabetic ketoacidosis. Concomitant illness, especially infections, may lead to hypoglycaemia and thereby cause an increased insulin requirement. Transferring to a new type, brand or manufacturer of insulin should be done under medical supervision and may result in a change in dosage. When using insulin in combination with pioglitazone, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. Patients must be instructed to always check the insulin label before each

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Contents

Editorial		Lifestyle	
■ Editorial	2	■ My Life Beyond Medicine	28
<i>Dr Siu-king MAK & Dr Victor Hip-wo YEUNG</i>		<i>Dr Victor Hip-wo YEUNG</i>	
Medical Bulletin		Radiology Quiz	
■ Nursing assessment of Nocturia	4	■ Radiology Quiz	19
<i>Ms Becky Sau-kuen CHAN</i>		<i>Dr Yan-lin LI</i>	
■ Nocturia and Nocturnal Polyuria	9	Federation News 30	
<i>Dr Siu-king MAK</i>		Medical Diary of August 37	
■ MCHK CME Programme Self-assessment Questions	11	Calendar of Events 38	
■ Nocturia and Overactive Bladder Syndrome	13		
<i>Dr Martin Kwok-tin WONG</i>			
■ Nocturia and Benign Prostatic Hyperplasia	17		
<i>Dr Chak-lam CHO</i>			
■ Nocturia and Underactive Bladder	22		
<i>Dr Victor Hip-wo YEUNG</i>			
■ Nocturia and Heart Disease	23		
<i>Dr Kin-ming TAM</i>			
■ Nocturia and Insomnia	24		
<i>Dr Kai-lok MAK</i>			
■ Nocturia and its Impact on the Elderly	26		
<i>Dr Arisina Chung-ye MA</i>			



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The Cover Shot



“Hong Kong is beautiful; Nocturia is stressful.”

This photograph is a frozen moment captured one evening when I wandered along the Tsim Sha Tsui waterfront. As an amateur photographer, I enjoy photography at night after busy daytime clinical work. The Victoria Harbour banked by the skyscrapers is an iconic image of Hong Kong. Not all of my patients are however able to enjoy this moment. Nocturia is a trouble for the elderly but it is often seen as the norm by their family. I hope one day we can live in a world without nocturia, and patients can treasure this night view in the company of their loved ones. Let's chill out and relax by the waterfront to celebrate that nothing is bothering us.



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The term “nocturia” consists of two affixes, “noct-” referring to nighttime, and “-uria” as in urination. As the name suggests, nocturia is the condition of getting out of bed to urinate at night, and more specifically, during sleep. While nocturia is usually believed to happen naturally and inevitably with ageing, it has nonetheless aroused complaints especially in people who are yet to retire, or those who suffer from multiple voids per night.

Before evidence-based investigations came into place, nocturia had been single-mindedly associated with “non-consolidation of kidney Qi” as suggested in Traditional Chinese Medicine (TCM)¹ for centuries. While “non-consolidation of kidney Qi” is considered a root cause accounting for a range of Lower Urinary Tract Symptoms (LUTS), e.g. slow stream, enuresis, and frequent micturition, etc., it is to date still perceived as a basis underlying nocturia among the local population in Hong Kong². For patients diagnosed to have “non-consolidation of kidney Qi”, TCM practitioners would recommend a series of lifestyle changes, dietary therapies, as well as decoction of selected herbal medicines.

Parallel to the TCM approach to resolving nocturia, Western medical doctors have been researching nocturia intensively during the past few decades. While nocturia was most often managed as a LUTS indicative of benign prostatic hyperplasia (BPH) in men or overactive bladder (OAB) in women, it has become clear more recently that waking to void at night is in its own right a manageable clinical entity.³

From the first publication of standardisation of terminology in nocturia by the International Continence Society (ICS) in 2002⁴, the definition of nocturia has evolved from being “the complaint that the individual has to get up one or more times to void”, to “complaint of interruption of sleep one or more times because of the need to micturate. Each void is preceded and followed by sleep” in 2010⁵, to the latest “waking to pass urine during the main sleep period” in 2018, where all episodes must be preceded by sleep, and the last one followed by the intention of getting back to sleep.⁶ In contrary to prior definitions, the updated classification of nocturia is leaving out the element of complaint but simply describing it as incidental, which may or may not do harm to the person’s quality of life, arising from various causes and potentially mixed aetiologies.

Definition of a condition is imperative in aetiological studies. Nonetheless, most authors were calculating nocturia prevalence without an annotation but the presumption of the self-reported occurrences being bothersome for the surveyed. It has been reported that in some scenarios, which are at the same time intuitive, that people may be getting out of bed to pass urine when waking to a crying baby or a snoring partner, rather than woken by the urge to void⁶. However, nocturia episodes with underlying aetiologies or comorbidities are more clinically relevant.



In a multinational study performed in Southeast Asian countries, adult male patients were surveyed during their first visits to urology clinics seeking help for LUTS⁷. The prevalence of nocturia, among other LUTS including urgency, slow stream and post-voiding dribble, in Hong Kong was reported as 93% (95% CI 90-96%) in a secondary care setting, which may lead to an overestimation of the true morbidity in the population. Among the 225 patients from Hong Kong, 71% were aged over 76 years, while the age-stratified prevalence did not show any significant difference among various age groups. "Bothersome" was also asked of the participants, in whom 70% reported nocturia as "bother me some" or "bother me a lot". Notably, 12% of the surveyed reported nocturia as a single symptom, suggesting a gap in nocturia aetiology by urinary tract disorders.

Another local epidemiology study surveying 1,009 people aged 40 years or above using random telephone calls reported a nocturia prevalence of 63% (95% CI 60-66%) (unpublished data)⁸. Upon raising the episode number per night to be 2 or above, which was considered more clinically relevant⁹, the prevalence was 32% (95% CI 29-35%). Parallel to the rise in voids/night, bother/concern significantly rises ($p<0.01$), while quality of life scores (QoL) plummeted ($p<0.01$), and men reported greater impact on their energy level the next day than women ($p<0.01$).

While nocturia is a highly prevalent condition, it is associated with multiple comorbidities including not only urinary tract disorders but also cardiovascular diseases, anxiety and depression, gastroenterology problems, etc.^{9,10} Nocturia is at the same time a risk factor for falls and fractures, as well as mortality, especially in the elderly^{9,11}. Hong Kong being an ageing society, it is estimated that by 2021, 19.1% of the total population in Hong Kong will be over 65 years old¹². Should this sector of the population not be well taken care of, a significant socio-economical impact is inevitable. It is therefore of paramount importance to evaluate the treatments available, the cost-benefit, as well as the accessibility of care and treatment for nocturia.

The Nocturia Academy was formed in 2018 by a multi-disciplinary team of specialist doctors, nurses and allied health professionals. Our aims are to promote public awareness of nocturia management and to enhance peers' continuous development. We are deeply indebted to our council members especially Dr Martin Kwok-tin Wong, Dr Chak-lam Cho, Dr Gregory Kai-lok Mak, Dr Kin-ming Tam, Dr Arisina Chung-ye Ma and Ms Becky Sau-kuen Chan for their contribution to this issue. We proudly ran our first Nocturia Crash Course in a local medical conference in April 2019. Materials presented in the crash course have been organised to develop this issue of the HK Medical Diary on Nocturia. The QR codes of the audio files of the Nocturia Crash Course can be found at the end of each chapter for easy reference. This is indeed exciting for us to see new advancement in the management of nocturia. Let us come together and build a community free of disturbance from nocturia.

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- Acts rapidly with sustained effect⁵⁻⁹
- Tailored dosages: 50µg for men; 25µg for women¹⁰
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As measured by: *FUSP (First Uninterrupted Sleep Period)^{3,4} and PSQI³, **N-QoL^{5,6} and †WPAI^{5,6}

PSQI, Pittsburgh Sleep Quality Index; N-QOL, Nocturia Quality of Life; WPAI, Work Productivity and Activity Impairment

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Abbreviated Prescribing Information of NOCDURNA

Active Ingredient: Desmopressin acetate. **Indications:** Symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults. **Dosage and Administration:** Women 25 mcg daily, 1 hr before bed time, sublingually w/o water. Men 50 mcg daily, 1 hr before bed time, sublingually w/o water. **Contraindications:** Hypersensitivity. Habitual or psychogenic polydipsia. Known or suspected cardiac insufficiency or other conditions associated w/ fluid overload, sufficient to require treatment w/ diuretics, including history of such conditions. Moderate to severe renal insufficiency (CrCl <50 mL/min). Known history of hyponatremia. Syndrome of inappropriate ADH secretion (SIADH). **Special Warnings and Precautions:** Fluid intake must be limited to a minimum from 1 hr before until 8 hr after administration. Increased risk of hyponatremia in elderly patients w/ serum Na levels in the lower range of normal; females at a 50 mcg dose level. Discontinue if the serum Na level falls below the lower limit of normal range. Caution in patients w/ conditions characterized by fluid &/or electrolyte imbalance. Interrupt & reassess treatment during acute intercurrent illnesses characterised by fluid &/or electrolyte imbalance (eg, systemic infections, fever & gastroenteritis). Concomitant treatment w/ drugs which are known to induce SIADH eg, TCAs, SSRIs, chlorpromazine, diuretics & carbamazepine & some antidiabetics of the sulfonylurea group, particularly chlorpromamide, and concomitant treatment w/ NSAIDs. Patients taking thiazide or loop diuretics for hypertension or other medical conditions not associated w/ fluid overload. Severe bladder dysfunction & outlet obstruction should be considered before starting treatment. Caution is required in cases of cystic fibrosis, CHD, HTN, chronic renal disease & pre-eclampsia. Exercise caution in patients taking lithium in case of masking of early-stage lithium-induced nephrogenic diabetes insipidus. Not recommended in patients suspected of having lithium-induced nephrogenic diabetes insipidus. Pregnancy. **Elderly:** ≥65 yr. **Side Effects:** Dry mouth, Hyponatraemia; headache, dizziness; nausea, diarrhoea. **Interactions:** Increased risk of water retention/hyponatremia w/ substances known to induce SIADH eg, TCAs, SSRIs, chlorpromazine, diuretics & carbamazepine as well as some antidiabetics of the sulfonylurea group particularly chlorpromamide. Potentiated antidiuretic effect w/ NSAIDs & oxytocin. Diminished antidiuretic effect w/ lithium. Increased plasma conc w/ loperamide. Food intake may reduce the intensity & duration of the antidiuretic effect at low oral doses of desmopressin tablet.

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Nursing assessment of Nocturia

Ms Becky Sau-kuen CHAN

Nurse Consultant (Continence)
United Christian Hospital



Ms Becky Sau-kuen CHAN

INTRODUCTION

When one has to “wake to pass urine during the main sleep period”, with at least the intention of getting back to sleep, it is defined that this person has nocturia¹. Nocturia is a highly prevalent condition that brings an impact on the quality of life too great to ignore. It is of paramount importance to perform an assessment of these patients in a multi-disciplinary approach to rule out or treat any underlying diseases that may induce nocturia, e.g. diabetes mellitus, diabetes insipidus, congestive heart failure, etc. In general, the pathophysiology of nocturia can be broadly categorised into (i) reduced bladder capacity, (ii) increased fluid intake and (iii) increased diuresis (Fig. 1).²

THE ASSESSMENT

During the initial assessment of patients presenting with nocturia, the medical history including current medications should be reviewed; in particular, one would look out for diuretics which are taken not long before bedtime, and oedema-causing calcium channel blockers taken for hypertension. The physical examination

should include blood pressure, weight and body mass index (BMI) in addition to a pelvic examination to assess for urogenital atrophy and urogenital prolapse, and to exclude a pelvic mass or chronic urinary residual volume. Signs such as peripheral oedema should also be checked for. Clinical evaluation of such patients should help physicians understand and discriminate lower urinary tract symptoms (LUTS) in general and nocturia in particular.^{2,3}

THE CONTENT OF THE BLADDER DIARY

In all nocturia patients, it is recommended that they complete a frequency volume chart (FVC), or a bladder diary. The chart would contain records of the time of each micturition and the volume voided, while the bladder diary should document fluid intake, pad usage, and incontinence episodes, as well as episodes of urgency if any (Fig. 2).⁵ As defined by the International Continence Society (ICS) in the 2018 Standardisation of Terminology in Nocturia¹, “a 3-day bladder diary is the standard of care for the assessment of patients with lower urinary tract symptoms including nocturia

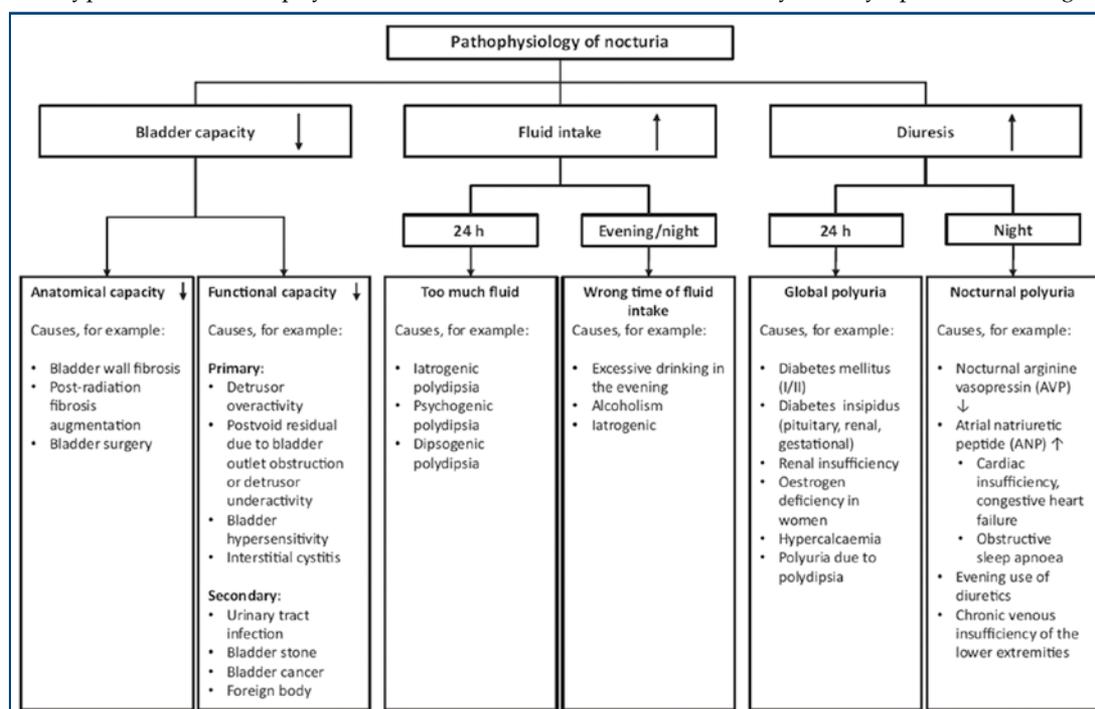


Fig. 1. Pathophysiology of nocturia. Excerpted from Oelke, M. et al.²

and nocturnal polyuria". In fact, the extent of nocturia and nocturnal polyuria can both be quantified using a bladder diary, thus helping physicians make differential diagnoses regarding nocturia.

This simple chart allows you to record the fluid you drink and the urine you pass over 3 days (not necessarily consecutive) in the week prior to your clinic appointment. This can provide valuable information.

• Please fill in approximately when and how much fluid you drink, and the type of liquid.
 • Please fill in the time and the amount (in ml, or ounces) of urine passed, and mark with a star if you have leaked or mark with a "P" if you have needed to change your pad.
 (Please find below an example of how to complete this form.)

DATE/TIME DD.MM.YY	LIQUID INTAKE (ml)	VOLUME OF URINE (ml)	LEAKS	PAD CHANGE
21.02.06			☆	
0215		150		
0715		250		
0800	Mug coffee 250ml			
0820		60	☆	P
0930	Cup orange juice		☆	
1000	Cup orange juice	100		
1200	2 mugs coffee			
1400		300		
1430		20		
1530	Cup of tea 200ml		☆	P
1600		100	☆	
1800	Cup of tea 200ml			
1900		100		
2000	Glass beer 200ml	20		
2030	Glass wine 50ml		☆	
2200				P
2300		150		

SUMMARY
 Frequency = 9; Nocturia = 1; Urine production / 24hr = 1250ml;
 Maximum voided volume = 300ml; Average voided volume = 125ml.

Fig. 2. An example of a bladder diary. Excerpted from Haylen B.T., et al.⁹

In addition to FVC or bladder diary, questionnaires such as the International Prostate Symptom Score (IPSS)⁶ and the ICS Males questionnaire⁷ are also frequently used to assess LUTS, including nocturia. However, when nocturia is not the prominent problem that patients are seeking help for, recall bias is commonly seen and can therefore undermine the accuracy of assessment. On the contrary, when patients are collecting and reporting prospective data in an FVC or bladder diary, the information captured is generally considered precise and essential in the analysis of nocturia⁸.

Completion of a bladder diary is a labour-intensive procedure for both healthcare professionals and patients. It was considered optimal to keep a diary for 7 consecutive days to cover both work and leisure time⁹. Unsurprisingly, it has been proven challenging, with a low patient completion rate of only 50%, comparing to the 90.7% when a 3-day diary is obliged¹⁰. While an undisputed gold standard of measurement and evidence of the optimal duration of bladder diary are yet to be established, literature review indicates that documentation of 3 days, consecutive or not, would be the best compromise between informative necessity and patient compliance^{8,9-13}. The expert opinion even suggests that a one-day diary could be sufficient as individual situation demands¹⁴. To enhance data precision, measuring devices are

recommended when quantifying the voided volume, such as measuring cups for men or urinary hats for women (Fig. 3), either acquired by patients themselves or distributed by healthcare professionals during the patients' first consultation. Physicians are also advised not to treat patients empirically during their first visit but encourage them to keep a bladder diary and at the same time provide sufficient instructions to patients and/or caregivers to record every single void¹⁴. For selected patients who can navigate a smartphone, digital diaries via dedicated mobile apps or tools may be favoured by the patients.



Fig. 3. Urinary hats with measuring scales. Mountainside Medical Equipment © 2018

THE INTERPRETATION OF THE BLADDER DIARY

Upon completion of the diary, the following parameters can be obtained from reading or by calculation^{8,13}:

- 24-hour urine volume
- 24-hour frequency, including daytime and nocturnal frequency
- Nocturnal urine volume, excluding the last void before going to bed but including the first void after rising
- Maximum voided volume (MVV), including daytime and nocturnal MVV
- Nocturnal polyuria index (NPi) = nocturnal urine volume as a fraction of 24-hour voided volume

Should the NPi be >33% in patients over 65 years of age, or >20% in younger individuals, they have met the criteria for nocturnal polyuria¹⁵.

Upon completion of a thorough assessment, differential diagnoses could be made and targeted treatment should be provided accordingly.

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18 Sep	Pulmonary Rehabilitation: How is it Different from Other Rehabilitation	Dr. Ida WONG Consultant, Haven of Hope Hospital Ms. LEUNG Siu Yin Physiotherapist, Haven of Hope Hospital Mr. CHAN Tak Ming Occupational Therapist, Haven of Hope Hospital
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Nocturia and Nocturnal Polyuria

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 August 2019.

INTRODUCTION

Nocturia is a condition of high prevalence and with wide-ranging aetiology, therefore requiring a multi-disciplinary approach in both assessment and management. In general, the pathophysiology of nocturia can be broadly categorised into: (i) reduced bladder capacity, (ii) increased fluid intake and (iii) increased diuresis¹. Among the wide-ranging causative disorders, increased diuresis during nighttime, i.e. nocturnal polyuria, is amongst the most common conditions responsible for nocturia. While local data are lacking, it is estimated that up to 88% of nocturia patients suffer an underlying condition which has led to nocturnal polyuria^{2,3}.

DEFINITION OF NOCTURNAL POLYURIA

As clinical experience accumulates, the definition of nocturnal polyuria has been evolving over the years. In 2002, the International Continence Society (ICS) defined nocturnal polyuria as “nocturnal urine volume output greater than 20% of the daily total urine output in the young and 33% in the elderly, with the value for middle age probably falling somewhere in the middle, reflecting an elevated proportion of a 24-hour urine output occurring at night (normally during the 8 hours while the patient is in bed)”⁴. This measurement remains the most well-received definition as well as diagnostic criteria among physicians and researchers worldwide.

Nonetheless, doubts have been raised about the legitimacy of the definition, as it “assumes the subject in concern is 70 kilograms and sleeps eight hours a day, irrespective of gender or age”⁴. Neither have the 20% and 33% numbers been properly validated, nor are they always well-supported in clinical practice. While more robust research on the topic is called for, the ICS recommended in 2018 that nocturnal polyuria should be characterised as “excessive production of urine during the individual’s main sleep period”, while the excessiveness is to be “highlighted in both clinical and research settings and derived from a bladder diary”.

DIAGNOSIS OF NOCTURNAL POLYURIA

A bladder diary (BD), or a frequency volume chart (FVC), is an essential diagnostic tool in clinical assessment for nocturia patients. Proper documentation of voiding episodes and fluid intake would generate parameters including nocturnal polyuria index (NPI, calculated as the nocturnal urine volume as a percentage of 24-hour voided volume), which in turn facilitate differential diagnosis and therefore enables appropriate treatments or interventions for patients. For instance, patients who report drinking a large amount of fluid, or ingest food of a high water content, are likely to have behavioural nocturnal polyuria and can benefit from a change of habit.

Nocturnal polyuria can also be part of global polyuria, induced by drugs, or caused by systemic diseases¹. Patients with global polyuria produce daily urine volume >40 mL/kg body weight, usually have comorbidities such as diabetes insipidus, diabetes mellitus, primary polydipsia, etc. In situations where diuretic drugs are taken just prior to bedtime, excessive nocturnal urine production can be expected. Systemic diseases such as congestive heart failure, venous stasis in the lower extremities and obstructive sleep apnoea (OSA), may also cause nocturnal polyuria.

AETIOLOGY OF NOCTURNAL POLYURIA

A significant association between reduced nocturnal secretion of the antidiuretic hormone, arginine vasopressin (AVP), and the occurrence of nocturia or nocturnal polyuria has been established⁵. When bound to V2 receptors in the kidneys, AVP induces expression of aquaporins in renal tubules, therefore promoting water reabsorption from pre-urine and decreasing urine excretion. While the exact mechanism remains unknown, a circadian rhythm where the plasma AVP level is elevated at night has been observed and is believed to ensure reduced voiding frequency and hence promote better rest and sleep⁵. In elderly patients with severe nocturia, nocturnal AVP deficiency has been observed, suggesting disruption of the diurnal pattern of antidiuretic hormone secretion⁵ (Fig. 1).

While nocturnal polyuria can be due to a wide range of conditions, or at times mixed aetiologies, treatment should be tailored to the underlying cause. Medication review, lifestyle modification, and if required, pharmacological treatment, should be considered by the attending physician. Upon exclusion of systemic diseases and failure of lifestyle modification, supplementary antidiuretics are considered effective and well-tolerated, and recommended as a grade A, level 1 medical intervention by both the International Consultations on Urological Diseases (ICUD) and the European Association of Urology (EAU) committees⁷⁻⁹.

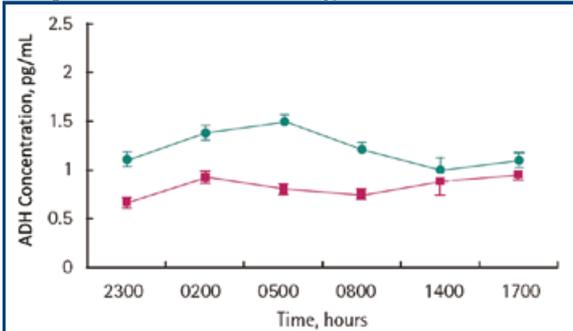


Fig. 1. The circadian variation of ADH in 12 patients with nocturia (red squares) and five age-matched controls (green closed circles), before the administration of desmopressin. Excerpted from Moon et al, 2004⁵.

MEDICAL TREATMENT OF NOCTURNAL POLYURIA

As a synthetic analog of AVP, desmopressin (also known as dDAVP) has been available since 1968. With structural modifications from the natural antidiuretic hormone (Fig. 2), desmopressin has a high affinity for V2 but not V1 receptors, thus enabling a selective and prolonged antidiuretic effect; desmopressin also carries an extended half-life of about 2.8 hours and produces antidiuresis for 6 to 24 hours, making it the drug of choice not only for nocturia or nocturnal polyuria, but also for enuresis as well as central diabetes insipidus¹⁰. To facilitate administration, various formularies of desmopressin have been made, including tablets, oral lyophilisates, and nasal sprays. Desmopressin injections are also available but most commonly used for diagnostic or haematological purposes.

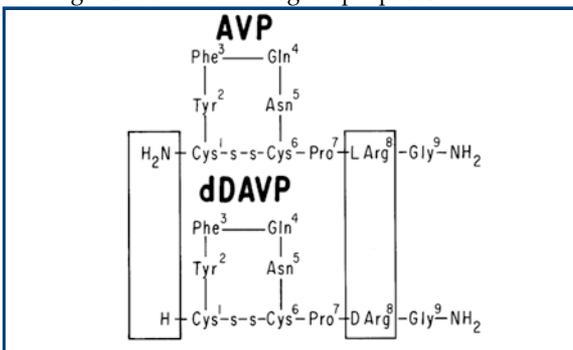


Fig. 2. Comparison of the structure of arginine vasopressin (AVP) with the synthetic analog 1-desamino-8-D-arginine vasopressin (desmopressin, dDAVP). The boxes indicate the differences between the two peptide molecules. Excerpted from Richardson et al, 1985¹⁰.

In patients with nocturia, desmopressin significantly reduces the number of nocturnal voids and increases the time to the first uninterrupted void, as measured by the length of the first uninterrupted sleep period^{11,12}. While hyponatraemia is among the most concerned adverse effects of desmopressin use especially in elderly, a newly available low-dose gender-specific regimen, i.e. 25 µg and 50 µg oral lyophilisates for women and men respectively, is considered safe for adults of all ages¹¹⁻¹³. For patients aged ≥ 65 years, a blood sodium monitoring plan at baseline, week 1 and month 1 of desmopressin use should be put in place. Should the sodium level be < 135 mmol/L at any time, treatment should be discontinued¹³ (Fig. 3).

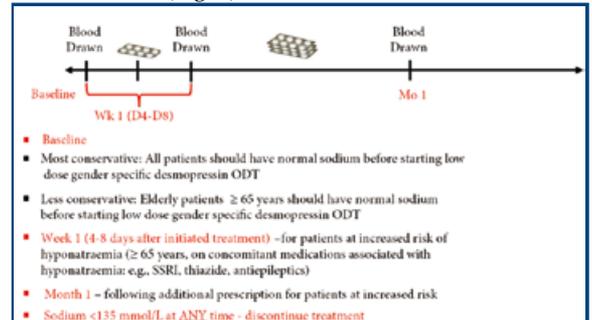


Fig. 3. Sodium monitoring plan to minimise risk of hyponatraemia in patients given desmopressin treatments. Excerpted from Juul et al, 2017¹².

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Nocturia and Nocturnal Polyuria" by Dr Siu-king MAK and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 August 2019. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

- The pathophysiology of nocturia can be broadly categorised into: (i) reduced bladder capacity, (ii) increased fluid intake and (iii) increased diuresis.
- It is estimated that up to 88% of nocturia patients do not have an underlying condition of nocturnal polyuria.
- The International Continence Society (ICS) defined nocturnal polyuria as "nocturnal urine volume output greater than 20% of the daily total urine output in the young and 33% in the elderly."
- Patients who report drinking a large amount of fluid, or ingesting food of a high water content, are likely to have behavioural nocturnal polyuria and can benefit from a change of habit.
- Global polyuria patients produce a daily urine volume > 40 mL/kg body weight.
- Systemic diseases such as congestive heart failure, venous stasis in the lower extremities and obstructive sleep apnoea (OSA) may also cause nocturnal polyuria.
- When bound to V2 receptors in the kidneys, the antidiuretic hormone, arginine vasopressin (AVP) induces expression of aquaporins in renal tubules, therefore reducing water reabsorption from pre-urine and increasing urine excretion.
- In elderly patients with severe nocturia, nocturnal AVP deficiency has been observed, suggesting disruption of the diurnal pattern of antidiuretic hormone secretion.
- In patients with nocturia, desmopressin significantly reduces the number of nocturnal voids and increases the time to first nocturnal void, as measured by the length of the first uninterrupted sleep period.
- For patients aged ≥65 years, a blood sodium monitoring plan at baseline, week 1 and month 1 of desmopressin use should be put into place. Should the sodium level be <135 mmol/L at any time, treatment should be discontinued.

ANSWER SHEET FOR AUGUST 2019

Please return the completed answer sheet to the Federation Secretariat on or before 31 August 2019 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Nocturia and Nocturnal Polyuria

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Answers to July 2019 Issue

Haemostatic Management of Postpartum Haemorrhage

1. T 2. T 3. F 4. F 5. T 6. F 7. T 8. F 9. F 10. T

Briefings on the Private Healthcare Facilities Ordinance (Cap 633)

The Private Healthcare Facilities Ordinance ("the Ordinance"), passed in November 2018, provides for a new regulatory regime for private healthcare facilities.

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Date	Time	Venue
10 Aug (Sat)	2:30pm Registration 3:00-5:00pm Briefing & QA	Hong Kong Academy of Medicine Jockey Club Building, 99 Wong Chuk Hang Road
16 Aug (Fri)	1:30pm Registration 2:00-4:00pm Briefing & QA	Leighton Hill Community Hall 133 Wong Nai Chung Road, Happy Valley
24 Aug (Sat)	1:30pm Registration 2:00-4:00pm Briefing & QA	Princess Alexandra Community Centre 60 Tai Ho Road, Tsuen Wan
5 Sep (Thu)	1:30pm Registration 2:00-4:00pm Briefing & QA	Long Ping Community Hall Long Ping Estate, Yuen Long
16 Sep (Mon)	1:30pm Registration 2:00-4:00pm Briefing & QA	Henry G. Leong Yaumatei Community Centre 60 Public Square Street, Yau Ma Tei
28 Sep (Sat)	2:30pm Registration 3:00-5:00pm Briefing & QA	Yuen Chau Kok Community Hall 35 Ngan Shing Street, Sha Tin

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Nocturia and Overactive Bladder Syndrome

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INTRODUCTION: DEFINITION AND PREVALENCE IN ASIA

The International Continence Society (ICS) defines the overactive bladder (OAB) syndrome by symptoms alone (as reported by patients), as "urinary urgency, usually with urinary frequency and nocturia, with or without urgency urinary incontinence."¹ By conventional urodynamic testing, about half of OAB patients have uncontrolled contractions of the detrusor muscle during bladder filling (i.e. detrusor overactivity or DO). However, about half of the patients with documented DO do not complain of symptoms.¹ OAB is a prevalent condition that affects both genders and increases with age.² It has been associated with lowered health-related quality of life, anxiety and depression, and nocturia, as well as falls and fractures.³⁻⁵ In a recent study of men and women aged ≥ 40 years from China, Taiwan and South Korea (n = 8,284),⁶ the overall prevalence of OAB was 20.8% (women 22.1%; men 19.5%) and increased significantly with age, from 10.8% in the 40–44 years group to 27.9% in the > 60 years group (p = 0.01).

AETIOLOGY AND DIAGNOSIS

While the cause of OAB can be neurogenic or arising from neurological conditions (e.g. spinal cord injuries) or non-neurogenic, arising from other detectable diseases (e.g. infections or bladder stones), it can also often be idiopathic, i.e. without apparent underlying causes.⁶ It can co-exist with other common conditions, including benign prostatic hyperplasia (BPH), stress incontinence and nocturnal polyuria. Some pre-existing conditions may increase the risk of OAB. In the above-mentioned Asian study, the prevalence of OAB increased by over two-fold in those with neurological diseases or diabetes, and by almost two-fold in those with cardiac diseases or hypertension.⁶ In younger patients with OAB, the decreased nocturnal bladder capacity has a greater role in the pathogenesis of nocturia symptoms, whereas in older patients the increased nocturnal urine output has a greater role.⁷

To aid diagnosis, patient questionnaires may be used. The International Prostate Symptom Score (IPSS) is composed of 7 questions on storage and voiding symptoms and a quality-of-life index. The Overactive Bladder Symptom Score (OABSS) consists of 4 questions that quantify OAB symptoms into a single score.⁸ Filling cystometry may also be performed, which illustrates the pressure-volume relationship in the bladder during filling.⁹

BEHAVIOURAL MANAGEMENT

Major guidelines recommend beginning OAB treatment with behavioural therapy.¹⁰ The aim is to educate patients about OAB and help them to develop strategies to manage urge and urge incontinence. It is important to communicate to the patient that treatment demands patience and motivation; otherwise, long-term improvements will not be achieved. Lifestyle changes include cessation of smoking, weight reduction, dietary and fluid intake changes (caffeine, acidic foods, and alcohol), bowel regulation, and exercise. Pelvic floor muscle training is aimed at improving reflexes in the pelvic floor that can decrease detrusor contractions, thus reducing urgency episodes and urge incontinence.¹¹ Bladder training employs a habit-training schedule (such as a bladder diary) to suppress urgency, improve bladder emptying and promote healing.⁹

PHARMACOLOGICAL TREATMENT

Antimuscarinic Agents

A successful OAB symptom management often makes use of a combination of behavioural therapy and pharmacotherapy to improve symptoms, reduce morbidity and prevent complications. Traditional anti-muscarinic agents (e.g. oxybutynin, tolterodine, solifenacin) achieve detrusor muscle relaxation by two mechanisms: 1) blocking muscarinic receptors on the muscle cell surface, thus inhibiting parasympathetic stimulation of muscle contraction; and 2) decreasing the afferent activity of urothelial sensory receptors on nerve fibres, thereby reducing urgency sensation and related symptoms.^{11,12} However, anti-muscarinic agents also affect other anti-muscarinic receptors throughout the body, leading to many common side effects, including dry mouth, dry eyes and constipation,¹³ and are contraindicated in patients with certain neuromuscular conditions, such as uncontrolled narrow-angle glaucoma or impaired intestinal motility.¹⁴ Since anti-muscarinic agents belong to the broad family of anti-cholinergic medications, they can impose a side-effect burden on patients. In elderly patients, an anti-cholinergic burden may increase the risk of dementia.¹⁵

The Novel β_3 -Adrenoceptor Agonist

The selective β_3 -adrenoceptor agonist mirabegron was approved for OAB treatment by the US Food and Drug Administration in 2012.¹⁶ β_3 -adrenoceptors, which

can be found in the bladder detrusor and urothelium, downregulate acetylcholine release, resulting in inhibitory control of parasympathetic activity during bladder filling.¹² In a large-scale phase III trial of mirabegron in 26 European countries and Australia (men and women aged ≥ 18 years; $n = 1,978$), mirabegron 50 mg once daily showed significant improvements over placebo at 12 weeks in the number of incontinence episodes per 24 hrs (-1.57; 95% confidence interval [CI]: -1.35 to -1.79) vs. placebo (-1.17; 95% CI: -0.95 to -1.39; Figure 1a) and number of micturitions per 24 hrs (-1.93; 95% CI: -1.72 to -2.15) vs. placebo (-1.34; 95% CI: -1.12 to -1.55; Figure 1b).¹⁷ In a meta-analysis of eight clinical trials, mirabegron demonstrated efficacy vs. placebo in reducing incontinence, urgency and frequency, as well as improving voided volume and nocturia.¹⁶ In a UK retrospective database analysis ($n = 21,996$), the median time-to-discontinuation was significantly longer for mirabegron (169 days; interquartile range [IQR]: 41 – not reached) vs. tolterodine (56 days; IQR: 28 – 254, $p < 0.0001$) or other anti-muscarinics ($p < 0.0001$; Figure 2).¹⁸ This may have been due in part to a lowered observed incidence of dry mouth and constipation in patients treated with mirabegron than with anti-muscarinics.^{18,19} Note that mirabegron should be used with caution in patients with severe uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg, or both).¹³

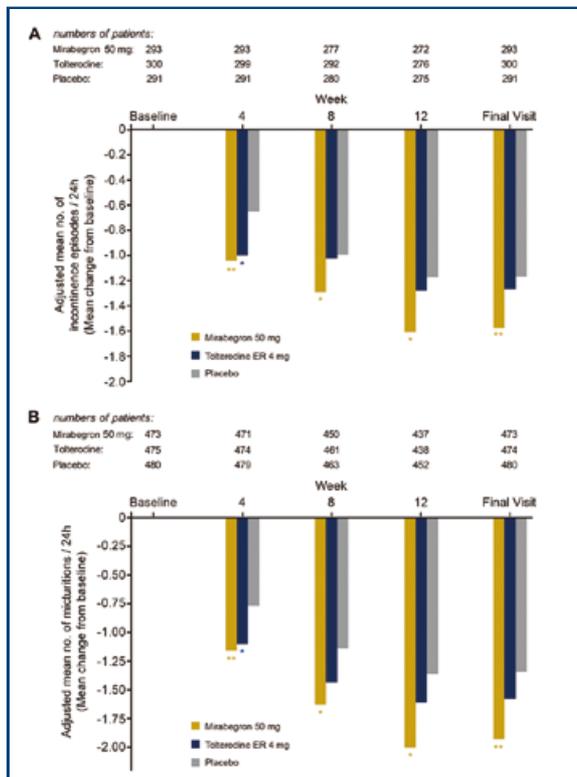


Fig. 1. Co-primary endpoints from the phase III SCORPIO trial of mirabegron: a) mean number of incontinence episodes per 24 hrs; b) mean number of micturitions per 24 hrs. ER, extended release; * $p < 0.05$ for superiority over placebo, without adjusting for multiple comparisons; ** $p < 0.05$ for superiority over placebo, adjusted for multiple comparisons. Tolterodine was an active control in this study.¹⁷ Excerpted from *Eur Urol.* 2013;63(2):283-295, authored by Khullar V, Amarenco G, Angulo JC, et al.

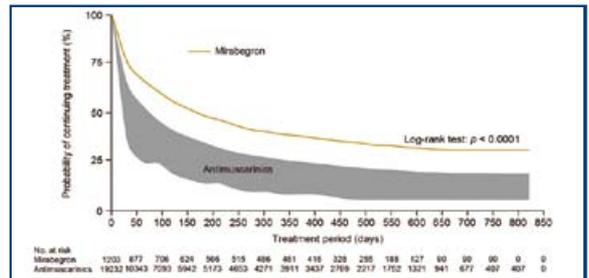


Fig. 2. Time to discontinuation of mirabegron ($n = 1,203$) vs. other anti-muscarinics (darifenacin, fesoterodine, flavoxate, oxybutylin, propiverine, solifenacin, tolterodine and trospium; $n = 19,232$).¹⁸ Excerpted from *Eur Urol.* 2017;72(3):389-399, authored by Chapple CR, Nazir J, Hakimi Z, et al.

For OAB in men with BPH or benign prostatic obstruction (BPO), mirabegron add-on to the $\alpha 1$ -blocker tamsulosin has demonstrated efficacy in improving the mean number of micturitions in 24 hours, mean volume voided per micturition, and OABSS total score, without additional safety concerns.²⁰

TREATMENT FOR REFRACTORY CASES

For patients in whom conservative and pharmacological management are both ineffective, minimally invasive treatment options may include percutaneous tibial nerve stimulation (PTNS), sacral neuromodulation (SNM) and intravesical injection of botulinum toxin A (BTX-A). In PTNS, an electrical current is applied through a needle electrode to the posterior tibial nerve to stimulate afferent fibres travelling to the sacral nerve plexus.²¹ Studies reported an objective success rate of 33–71%, defined as $\geq 50\%$ decrease in urge or urgency urinary incontinence and 25% reduction in daytime and/or nighttime frequency (please refer to the Editorial section in this issue).²² Unlike PTNS, SNM stimulates the sacral nerve plexus more directly from the lower back, and requires a permanent surgical implant of the wire and generator.¹² BTX-A blocks presynaptic release of acetylcholine in the detrusor muscle to decrease contractility; however, repeated administrations may be necessary to sustain effects.¹¹ If these options are ineffective, more invasive surgeries including augmentation cystoplasty or urinary diversion can be considered.²¹

CONCLUSION

OAB syndrome is a prevalent condition that affects both men and women, and its prevalence increases with age. Proper diagnosis and management can help to reduce symptom complaints and improve the quality of life of those affected. Survey instruments such as the OABSS and urodynamic analysis can be helpful for diagnosis. Often, a combination of behavioural and pharmacological management is needed to adequately manage the condition. The novel $\beta 3$ -adrenoceptor agonist has demonstrated efficacy while reducing the anticholinergic burden and side effects associated with traditional anti-muscarinic therapy. It may also be used in combination with $\alpha 1$ -blockers for male patients who have comorbid benign prostatic conditions. For treatment-refractory cases, PTNS and SNM are generally available options.



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IT'S TIME TO THINK OF BETMIGA®

The first β_3 agonist to treat OAB¹

Not contraindicated in patients with glaucoma and acute urinary retention (AUR)²

OAB: overactive bladder

Abbreviated prescribing information of Betmiga® prolonged-release tablets

Version: 003 Pl version: Apr 2016. **Composition:** Mirabegron **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adult including elderly 50 mg once daily with or without food. **Administration:** Swallow whole with liquids. Do not chew/divide/crush. **Contraindications:** Mirabegron is contraindicated in patients with - Hypersensitivity to the active substance or to any of the excipients - Severe uncontrolled hypertension defined as systolic blood pressure \geq 180 mm Hg and/or diastolic blood pressure \geq 110 mm Hg. **Special warnings and precautions for use:** Renal impairment: Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m² or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²) concomitantly receiving strong CYP3A inhibitors. Hepatic impairment: Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors. Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure \geq 160 mm Hg or diastolic blood pressure \geq 100 mm Hg). Patients with congenital or acquired QT prolongation: Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medications for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga, however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB. **Undesirable effects:** Summary of the safety profile: The safety of Betmiga was evaluated in 8,433 patients with OAB, of which 5,648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with Betmiga, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. List of adverse reactions: The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (\geq 1/10); common (\geq 1/100 to <1/10); uncommon (\geq 1/1,000 to <1/100); rare (\geq 1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Infections and infestations: Common: Urinary tract infection; Uncommon: Vaginal infection, Cystitis. Psychiatric disorders: Not known (cannot be estimated from the available data); Insomnia*. Eye disorders: Rare: Eyelid oedema. Cardiac disorders: Common: Tachycardia. Uncommon: Palpitation, Atrial fibrillation. Vascular disorders: Very rare: Hypertensive crisis*. Gastrointestinal disorders: Common: Nausea, Constipation*, Diarrhoea*. Uncommon: Dyspepsia, Gastritis, Rare: Lip oedema, Skin and subcutaneous tissue disorders: Uncommon: Urticaria, Rash, Rash macular, Rash papular, Pruritus, Rare: Leukoerythrocytic vasculitis, Purpura, Angioedema*. Musculoskeletal and connective tissue disorders: Uncommon: Joint swelling. Reproductive system and breast disorders: Uncommon: Vulvovaginal pruritus. Investigations: Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased, Renal and urinary disorders: Rare: Urinary retention*. Immune system disorders: Common: Headache*, Dizziness*, observed during post-marketing experience. **Full prescribing information is available upon request.**

Reference: 1. Chapple CR, et al. *Neurourol Urodyn* 2014 Jan 33 (1):17-30 2. Hong Kong package insert of Betmiga® Apr 2016

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DUAL ACTION:

- Superior symptoms improvement¹ (adjusted mean change in IPSS from baseline to year 4 was **-6.3** points for combination therapy versus **-3.8** points for tamsulosin)
- Reduce prostate size up to **27%**[#]

DUAL PROTECTION:

- Reduce relative risk of
- AUR by **68%**
 - BPH related surgery by **71%** vs tamsulosin monotherapy¹



BPH: Benign Prostatic Hyperplasia
AUR: Acute Urinary Retention

DUODART (Dutasteride-tamsulosin) abbreviated prescribing information²

Indications Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH). Reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH. Limitations of use: Dutasteride-containing products, including DUODART, are not approved for the prevention of prostate cancer. **Dosage and Administration** The recommended dose of DUODART (Dutasteride-tamsulosin) is one capsule (0.5 mg/0.4 mg) taken once daily. The capsules should be swallowed whole and not chewed or opened. Contact with the contents of the dutasteride capsule contained within the hard-shell capsule may result in irritation of the oropharyngeal mucosa. **Contraindications** Patients with known hypersensitivity to dutasteride, other 5 α -reductase inhibitors, tamsulosin (including tamsulosin-induced angioedema), soya, peanut or any of the excipients; history of orthostatic hypotension, with severe hepatic impairment; women and children and adolescents. **Warnings and Precautions** Cardiac Failure In two 4-year clinical study, the incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was higher among subjects taking the combination of dutasteride and an α 1A-adrenoceptor antagonist, primarily tamsulosin, than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was low ($\leq 1\%$) and variable between the studies. **Effect on prostate-specific antigen (PSA) and prostate cancer detection** Serum prostate-specific antigen (PSA) concentration is an important component in the detection of prostate cancer. DUODART causes a decrease in mean serum PSA levels by approximately 50%, after 6 months of treatment. Patients receiving DUODART should have a new PSA baseline established after 6 months of treatment with DUODART. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on DUODART may signal the presence of prostate cancer or non-compliance to therapy with DUODART and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5 α -reductase inhibitor. In the interpretation of a PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison. Treatment with DUODART does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established. Total serum PSA levels return to baseline within 6 months of discontinuing treatment. The ratio of free to total PSA remains constant even under the influence of DUODART. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing DUODART therapy, no adjustment to its value appears necessary. Digital rectal examination, as well as other evaluations for prostate cancer or other conditions which can cause the same symptoms as BPH, must be performed on patients prior to initiating therapy with DUODART and periodically thereafter. Prostate cancer and high grade tumours The REDUCE study, a 4-year, multicentre, randomised, double-blind, placebo controlled study investigated the effect of dutasteride 0.5 mg daily on patients with a high risk for prostate cancer (including men 50 to 75 years of age with PSA levels of 2.5 to 10 ng/ml and a negative prostate biopsy 6 months before study enrollment) compared to placebo. Results of this study revealed a higher incidence of Gleason 8 – 10 prostate cancers in dutasteride treated men (n=29, 0.9%) compared to placebo (n=19, 0.6%). The relationship between dutasteride and Gleason 6 - 10 prostate cancers is not clear. Thus, men taking Avodart should be regularly evaluated for prostate cancer. **Renal impairment** The treatment of patients with severe renal impairment (creatinine clearance of less than 10 ml/min) should be approached with caution as these patients have not been studied. **Hypotension/Orthostatic:** As with other α 1A-adrenoceptor antagonists, a reduction in blood pressure can occur during treatment with tamsulosin, as a result of which, rarely, syncope can occur. Patients beginning treatment with DUODART should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness, weakness) until the symptoms have resolved. **Symptomatic:** Caution is advised when α 1A-adrenoceptor blocking agents including tamsulosin are co-administered with PDE5 inhibitors. α 1A-adrenoceptor antagonists and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension. **Intraoperative Floppy Iris Syndrome (IFIS),** a variant of small pupil syndrome has been observed during cataract surgery in some patients on or previously treated with tamsulosin. IFIS may increase the risk of eye complications during and after the operation. The initiation of therapy with DUODART in patients for whom cataract surgery is scheduled is therefore not recommended. During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with DUODART in order to ensure that appropriate measures will be in place to manage the IFIS during surgery. Discontinuing tamsulosin 1 – 2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of stopping therapy prior to cataract surgery has not yet been established. **Leaking Capsule** Dutasteride is absorbed through the skin, therefore women and children and adolescents must avoid contact with leaking capsules. The contact area should be washed immediately with soap and water. **Inhibitors of CYP3A4 and CYP2D6** Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4, or to a lesser extent, with strong inhibitors of CYP2D6 can increase tamsulosin exposure. Tamsulosin hydrochloride is therefore not recommended in patients taking a strong CYP3A4 inhibitor and should be used with caution in patients taking a moderate CYP3A4 inhibitor, a strong or moderate CYP2D6 inhibitor, a combination of both CYP3A4 and CYP2D6 inhibitors, or in patients known to be poor metabolisers of CYP2D6. **Hepatic Impairment** DUODART has not been studied in patients with liver disease. Caution should be used in the administration of DUODART to patients with mild to moderate hepatic impairment. **Excipients** This medicinal product contains the colouring agent Sunset Yellow (E110), which may cause allergic reactions. **Breast neoplasia** There have been rare reports of male breast cancer reported in men taking dutasteride in clinical trials and during the post-marketing period. However, epidemiological studies showed no increase in the risk of developing male breast cancer with the use of 5 α -reductase inhibitors. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge. **Interactions** Tamsulosin Concomitant administration of tamsulosin hydrochloride with drugs which can reduce blood pressure, including anaesthetic agents, PDE5 inhibitors and other α 1A-adrenoceptor antagonists could lead to enhanced hypotensive effects. Dutasteride-tamsulosin should not be used in combination with other α 1A-adrenoceptor antagonists. Concomitant administration of tamsulosin hydrochloride and ketorolac (a strong CYP2A4 inhibitor) resulted in an increase of the Cmax and AUC of tamsulosin hydrochloride by a factor of 2.2 and 2.8, respectively. Concomitant administration of tamsulosin hydrochloride and paroxetine (a strong CYP2D6 inhibitor) resulted in an increase of the Cmax and AUC of tamsulosin hydrochloride by a factor of 1.3 and 1.6, respectively. A similar increase in exposure is expected in CYP2D6 poor metabolisers as compared to extensive metabolisers when co-administered with a strong CYP3A4 inhibitor. The effects of co-administration of both CYP3A4 and CYP2D6 inhibitors with tamsulosin hydrochloride have not been evaluated clinically, however there is a potential for significant increase in tamsulosin exposure. Concomitant administration of tamsulosin hydrochloride (0.4 mg) and cimetidine (400 mg) every six hours for six days resulted in a decrease in the clearance (26%) and an increase in the AUC (44%) of tamsulosin hydrochloride. Caution should be used when dutasteride-tamsulosin is used in combination with cimetidine. A definitive drug-drug interaction study between tamsulosin hydrochloride and warfarin has not been conducted. Results from limited in vitro and in vivo studies are inconclusive. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin. Caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride. **Fertility, pregnancy and lactation** DUODART is contraindicated for use by women. There have been no studies to investigate the effect of DUODART on pregnancy, lactation and fertility. As with all 5 α -reductase inhibitors, when the patient's partner is or may potentially be pregnant it is recommended that the patient avoids exposure of his partner to semen by use of a condom. As with other 5 α -reductase inhibitors, dutasteride inhibits the conversion of testosterone to dihydrotestosterone and may, if administered to a woman carrying a male foetus, inhibit the development of the external genitalia of the foetus. Dutasteride has been reported to affect semen characteristics (reduction in sperm count, semen volume, and sperm motility) in healthy men. The possibility of reduced male fertility cannot be excluded. Effects of tamsulosin hydrochloride on sperm count or sperm function have not been evaluated. The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in healthy volunteers aged 18 to 52 (n=27) (dutasteride, n=22; placebo) throughout 52 weeks of treatment and 24 weeks of post-treatment follow-up. At 52 weeks, the mean percent reduction from baseline in total sperm count, semen volume and sperm motility were 23%, 26% and 18%, respectively, in the dutasteride group when adjusted for changes from baseline in the placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride group remained 23% lower than baseline. While mean values for all parameters at all time points remained within the normal ranges and did not meet the predefined criteria for a clinically significant change (30%), two subjects in the dutasteride group had decreases in sperm count of greater than 90% from baseline at 52 weeks, with partial recovery at the 24 week follow-up. The possibility of reduced male fertility cannot be excluded. It is not known whether dutasteride or tamsulosin are excreted in human milk. **Adverse Reactions** Clinical Trial Data (Dutasteride and tamsulosin co-administration): Impotence, altered (decreased) libido, ejaculation disorders, breast disorders (includes breast tenderness and breast enlargement), alopecia (primarily body hair loss), hypercholesterolemia (Tamsulosin Monotherapy), Dizziness, abnormal ejaculation, palpitations, constipation, diarrhoea, vomiting, asthenia, rhinitis, rash, pruritis, urticaria, orthostatic hypotension, syncope, headache, nausea, angioedema, tachycardia, pruritus, Stevens-Johnson syndrome, During postmarketing surveillance, reports of Intraoperative Floppy Iris Syndrome (IFIS), a variant of small pupil syndrome, during cataract surgery have been associated with α 1A-adrenoceptor antagonists, including tamsulosin. In addition atrial fibrillation, arrhythmia, tachycardia, dyspnoea, epistaxis, vision blurred, visual impairment, erythema multiforme, dermatitis exfoliative, ejaculation disorder, retrograde ejaculation, and eye dry mouth have been reported in association with tamsulosin use. The frequency of events and the rate of tamsulosin in their causation cannot be reliably determined. **Combination P** based on HK072017(GDS151v1/EMC20170628). Please refer to the full prescribing information before prescribing. Full prescribing information is available upon request.

At month 48, the adjusted mean percentage change from baseline in total prostate volume was -27.3% for combination therapy, +4.6% (p<0.001) for tamsulosin, and -26.0% (p=0.42) for dutasteride.

References: 1. Roehrborn CG, et al. *Eur Urol* 2010;57(1):123-31. 2. DUODART Hong Kong Full Prescribing Information. Version number: HK072017(GDS151v1/EMC20170628).

For adverse events report, please call GlaxoSmithKline Limited at (HK) 852 9046 2498. Full prescribing information is available on request from GlaxoSmithKline Ltd, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong.

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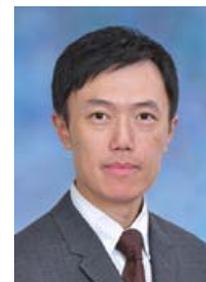
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Nocturia and Benign Prostatic Hyperplasia

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INTRODUCTION

Nocturia is an often neglected and poorly understood symptom complex despite the fact that it is a significant problem affecting a large proportion of the population¹. The International Continence Society defines nocturia as “the complaint that an individual has to wake up at night one or more times to void, with each void preceded and followed by sleep”². However, the definition is still not without debate. Nonetheless, the profound detrimental impact of nocturia on quality of life and sleep pattern is increasingly being recognised³.

Lower urinary tract symptoms (LUTS) attributed to benign prostatic hyperplasia (BPH) is common in ageing males¹. At the same time, the incidence of nocturia shares the same increasing trend with age⁴. In patients with BPH, nocturia may be the result of increased outflow resistance and impaired bladder contractility. The resultant increase in residual urine, in turn, leads to a reduction in functional bladder capacity. Nocturnal voiding is inevitable when urine production at nighttime exceeds the functional capacity of the urinary bladder⁵. Despite the hypothesis that may explain the correlation between nocturia and BPH, the causal relationship remains to be clarified. The absence of prostate in elderly women but with a similar prevalence of nocturia in both genders suggests that nocturia and BPH in elderly men may be merely coincidental in the majority of patients.

All elderly men presented with LUTS suggestive of BPH are generally evaluated with a bladder diary, the International Prostate Symptom Score (IPSS) (Fig. 1) and uroflowmetry including post-void residual urine assessment in addition to the clinical history and physical examination. While urinalysis is recommended as a standard test, assessment of the renal function, prostate-specific antigen and prostate volume are considered optional⁶. This set of workup is also considered adequate for elderly men who report nocturia as the chief complaint. The bladder diary is an important diagnostic tool for nocturia and objective recording of the nocturia episodes and voided volume. The finding on the bladder diary may be more specific for certain underlying aetiologies which will guide further investigation and management. On the other hand, the IPSS nocturia question (“During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?”) reflects patients’ subjective assessment of nocturnal voids.

In the following sections, the efficacy of common treatment modalities for LUTS/BPH in elderly men — namely alpha adrenergic receptor blockers (AARB), 5-alpha reductase inhibitors (5ARI) and transurethral resection of the prostate (TURP) — on nocturia is discussed. The discussion will help clinicians to formulate a rational treatment algorithm for patients with nocturia and BPH.

國際前列腺狀評分表 International Prostate Symptom Score (IPSS)							
姓名:	日期:						
	無	少於五份一時間	少於一半時間	大約一半時間	多於一半時間	幾乎每次	
						你的分數	
1. 排尿不清 在過去一個月中，你是否經常有未能把尿排盡的感覺？	0	1	2	3	4	5	
2. 尿頻 在過去一個月中，你是否經常在排尿後兩個小時內又要小便？	0	1	2	3	4	5	
3. 排尿斷續 在過去一個月中，你是否經常在排尿時尿流斷斷續續？	0	1	2	3	4	5	
4. 尿急 在過去一個月中，你是否經常感到“忍尿”有困難？	0	1	2	3	4	5	
5. 尿流無力 在過去一個月中，你是否經常有尿流細弱的症狀？	0	1	2	3	4	5	
6. 排尿費力 在過去一個月中，你是否經常需要用力才能開始排尿？	0	1	2	3	4	5	
IPSS 總評分							
總評分結果：0-7 分為輕度徵狀；8-19 分為中度徵狀；20-35 分為重度徵狀。							
就排尿徵狀作生活質素評分	非常好	好	滿意	尚可	不滿意	不愉快	很痛苦
假如按現在排尿情況，你覺得今後的生活質素如何？	0	1	2	3	4	5	6

Fig.1. Question 7 on International Prostate Symptom Score (IPSS) is specific to assessment of nocturia.

SURGICAL TREATMENT

TURP remains the gold standard in BPH-related surgery. The long-term efficacy of TURP in relieving symptoms and urodynamic obstruction has been widely reported⁷. In contrast, the impact of surgical intervention on nocturia is substantially less clear. The majority of the studies were not dedicated to the treatment effect of TURP on nocturia and the IPSS nocturia question was the only assessment tool of treatment outcome. In general, TURP for patients with



LUTS/BPH was associated with 0.8 to 1.6 reduction in nocturia episodes per night. However, only around 30% of patients perceived significant improvement of ≥ 1 episode per night⁸ and predictors of response of nocturia to TURP remained unclear⁹. More recently, the potential benefit of TURP on quality of life in nocturia patients has been suggested by the application of a validated 13-item Nocturia Quality-of-Life (N-QoL) questionnaire¹⁰. Improvement in sleep quality with an increase in hours of undisturbed sleep (HUS) after TURP in patients with nocturia has also been reported⁸. While the reported efficacy of surgical treatment on nocturia has been inconsistent, the majority of studies concurred that the nocturia score in IPSS is the least specific symptom associated with BPH and the least sensitive to therapeutic effects¹¹. This also implies that nocturia and BPH may not have a direct correlation in pathophysiology in most patients.

MEDICAL TREATMENT

Alpha adrenergic receptor blockers (AARB) and 5-alpha reductase inhibitors (5ARI) are the most widely used medications in patients with LUTS/BPH. Their treatment effects on nocturia have been reported by a number of studies which yielded contrasting results. In the literature, the largest studies were initially designed to investigate the efficacy of a combination therapy with AARB and 5ARI in patients with LUTS/BPH. Response of nocturia to these medications has been reported during secondary data analysis.

In the Veterans Affairs Cooperative Study Trial, 1,078 men who had completed 12 months of trial were included and the majority of them had two or more nocturia episodes. Overall, nocturia decreased from a baseline mean of 2.5 to 1.8 in terazosin, 2.1 in finasteride, 2.1 in combination, and 2.0 in placebo groups. The study defined a 50% reduction in nocturia as being significant in patients with two or more episodes of nocturia. It was observed in 39%, 25%, 32% and 22% in terazosin, finasteride, combination and placebo groups respectively. The study showed that only the result of the terazosin arm was statistically significant compared to other arms¹². Data from the Medical Therapy of Prostate Symptoms (MTOPS) trial involving 3,047 patients revealed similar findings. The mean nocturia episode was reduced at 1 year by 0.35, 0.40, 0.54 and 0.58 in the placebo, finasteride, doxazosin and combination groups, respectively. A similar result was obtained after 4 years of treatment. Significant reduction in nocturia was noted in the doxazosin and combination groups compared to the placebo and finasteride groups¹³. Both studies included patients with similar characteristics with a mean age of around 65, the prostate volume of approximately 35 mL, and nocturia episodes of 2.5. The results support the value of AARB in the reduction of nocturia in patients with BPH. It also showed that the addition of 5ARI may not provide further benefit in terms of nocturia. However, the net reductions in the mean nocturia among treatment groups were modest in view of the robust placebo effect because of the placebo-controlled double-blind study design. The clinical significance of a 0.1 to 0.3 mean nightly reduction is elusive and less impressive. Further studies using novel assessment tools on quality of life and quality of sleep are eagerly needed.

More recently, the improved pharmacokinetics of prolonged-release tablet formula of AARB may provide a better relief for patients with nocturia. Most classic AARB formulations rely on the presence of water for drug release. As a result, drug release is essentially limited to the upper gastrointestinal tract since the colon is relatively devoid of water. Consequently, the plasma concentration is less consistent over a 24-hour period and the absorption is food-dependent. The oral controlled absorption system (OCAS) technology of tamsulosin tablets was designed to overcome the limitation by incorporating a gel-forming and a gel-enhancing component. The gel layer of the tablet rapidly absorbs water during its transit through the stomach and small intestine. The water is then continuously released to allow stable drug release in the colon resulting in more favourable pharmacokinetics¹⁴. The more consistent drug level is believed to result in a lower risk of peak-associated adverse events and a good control of day- and nighttime symptoms. A pilot study evaluating tamsulosin OCAS 0.4 mg in men with LUTS/BPH and two or more nocturnal voids showed a slight superiority of tamsulosin OCAS in reducing nocturia as captured by the IPSS. The study included 117 patients in a 8-week randomised, double-blind, placebo-controlled trial. After a run-in period of 2 weeks, the patients were randomised to either placebo or tamsulosin OCAS for 8 weeks. In addition to the reduction of nocturnal voids, an increase in hours of undisturbed sleep (HUS) was observed in the treatment group compared to the placebo group suggestive of better sleep quality in the treatment group¹⁵. With better understanding of the pathophysiology of LUTS, the use of a combination of medical therapy is more widely adopted nowadays. The better safety profile of extended-release formula of AARB is preferable when used in combination with antimuscarinics, beta-3 agonists and desmopressin which are often prescribed for patients with overactive bladder syndrome and nocturnal polyuria. Concomitant use of AARB with phosphodiesterase type 5 inhibitors in the treatment of erectile dysfunction remains a precaution and should be avoided.

SUMMARY

Nocturia and BPH often coexist in ageing men. Impaired bladder emptying due to BPH may reduce the functional capacity of the urinary bladder which leads to nocturia. However, the causal relationship still remains unclear since nocturia is the least specific symptom associated with BPH and the least responsive to BPH treatment. BPH-related surgery, particularly TURP, has been reported to reduce nocturia episodes but significant reduction was only observed in a minority of patients. On the other hand, randomised placebo-controlled studies has consistently reported efficacy of AARB in the reduction of nocturia episodes compared to placebo. The combination of AARB with 5ARI offered no additional benefit in terms of nocturia. The improved pharmacokinetics of extended-release formula of AARB provides a more favourable side effect profile and may be preferable particularly when used in combination with other medications.



CONCLUSION

Patients with bothersome LUTS suggestive of BPH and nocturia should undergo evaluation including a bladder diary. The use of AARB represents a rational first step in the management in view of its proven efficacy in the reduction of nocturia episodes and improvement in other aspects of LUTS. The quick onset of action and favourable side effect profile of AARB also support its use as a trial of medication in patients with nocturia and BPH. Current literature on the management of nocturia and BPH remains limited. Further well-designed studies are required in delineating the best management approach in patients with nocturia and BPH.

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Radiology Quiz



Radiology Quiz

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Dr Yan-lin LI



A 7 mm solid lung nodule is incidentally discovered on a CT abdomen scan performed for a patient with acute appendicitis. The patient no respiratory complaint and does not smoke.

Questions

1. What does the density of the nodule tell about its nature?
2. Is follow-up required?
3. Is PET scan helpful?
4. One year later, the nodule grows to 22 mm and biopsy is considered. What were the options?
5. Pathology shows adenocarcinoma and the lesion is resected. The patient's brother is a chronic smoker and is worried about lung cancer. Should he undergo a screening low dose CT scan (LDCT)?

(See P.40 for answers)

This Casebook provides an open-access online resource for doctors, nurses, social workers and allied health professionals who face ethical issues when caring for older adults at the end of life.

The Casebook covers the following topics:

- Conflict between team members
- Feeding tube decision in a dying demented patient
- ICU triage for patient with advanced cancer
- Family requests to withhold the truth from patient
- Disagreements over timing for advance care planning
- Withholding antibiotics at the end of life
- Opting for Chinese over Western medicine
- Challenges in careful hand feeding
- Filial piety in end-of-life care decisions



An expert commentary for each case provides a perspective on the ethical challenges and a practical clinical approach. Background readings on key topics in end-of-life care of older adults and additional resources are also provided. The Casebook will continue to be updated with additional cases and background readings over time.

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FEEDING TUBE DECISION IN A DYING DEMENTED PATIENT

Case Description:

Mr. Chan was an 84-year-old male, with a history of hypertension, diabetes and recurrent ischaemic stroke. His wife died a few years ago. He had two sons and one daughter living in Hong Kong. He was diagnosed to have vascular dementia five years ago and became chair-bound. For two years, he lived with his second son's family, cared for primarily by his daughter-in-law Mary. However, Mr. Chan had gotten progressively weaker in the last few months and Mary no longer could transfer him out of bed alone. Mr. Chan was then brought to live at a private old aged home.

In the last year, he became bed bound and double incontinent and required assisted feeding. He also had recurrent hospital admissions due to chest infections and the speech therapist recommended puree diet and thickener

in fluid. After an episode of aspiration pneumonia, the speech therapist suggested non-oral feeding due severe oropharyngeal dysphagia.

The doctor asked to meet with the family and the second son and the daughter came. His son said, "Father would not want to have a feeding tube placed. He had seen many tube-fed elderly people at the old age home. They just lied in bed all day and it was not a life that he wanted. He told us that he would rather die than have one put into him."

The daughter had also heard her father express that and they both made the decision for careful hand feeding rather than tube feeding. They understood the risk of aspiration, pneumonia and death.

The patient tolerated careful hand feeding for several months. However, he then developed fever and became unarousable. He was transferred to the hospital and was found to have a severe pneumonia. He was kept nil by mouth and given parenteral antibiotics. His second son and daughter were informed of deteriorating clinical condition and imminent death. They understood and agreed to continue conservative management.

The next day, however, the oldest son turned up and insisted on starting tube feeding. He accepted that his father was dying and agreed to continue comfort care and continue DNACPR order. However, he said "It's important that my father would die with a full stomach. I do not want him to become a hungry ghost." The clinician was not sure whether he should simply reject the son's request or not.

Read the case
and commentary :



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Please visit <http://www.ioa.cuhk.edu.hk/en-gb/casebook> for more details on the Casebook

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Nocturia and Underactive Bladder

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INTRODUCTION

The urinary bladder is a special organ with complex physiology. There are two functional states of the urinary bladder, namely the storage phase and the voiding phase¹.

The storage phase occurs during the filling of the bladder, and it is enabled by the inhibition of detrusor activity as well as contraction of the smooth muscle sphincter (Sympathetic Innervation via the hypogastric nerve – T10-L2), and contraction of the striated sphincter (somatic innervation via the pudendal nerve – S2-4)².

The voiding phase occurs when the bladder filling has passed a certain set-point, and it will activate the pontine micturition centre (PMC) located in the brainstem². Once the PMC is activated, several processes will occur simultaneously. First, the detrusor muscles will contract (parasympathetic innervation via the branches of pelvic splanchnic nerves – S2-S4). Second, there will be a relaxation of the striated sphincter (somatic innervation via the pudendal nerve). Third, there will be a relaxation of the smooth muscle sphincter and opening of the bladder neck (sympathetic innervation via the hypogastric nerve).

AETIOLOGY OF UNDERACTIVE BLADDER

After going through the basic physiology of the urinary bladder, I will focus more on the pathophysiology of underactive (hypocontractile) bladder and how it is related to nocturia. The urinary bladder is like a pump, and underactive bladder means that the bladder is not able to contract properly thus resulting in incomplete emptying of urine. It is usually caused by damage to the nerves supplying the detrusor muscles³. Clinically, it may present as incomplete bladder emptying, urinary frequency or nocturia³.

There are many possible causes of underactive bladder including diabetes mellitus, bladder outlet obstruction (such as benign prostatic hypertrophy or prostate cancer), ageing, cerebrovascular accidents, Parkinson's Disease, injury to spinal cord or cauda equina, and many more such as AIDS / multiple sclerosis / pelvic surgery / neurosyphilis / Guillain-Barre Syndrome⁴.

MANAGEMENT OF UNDERACTIVE BLADDER

When a patient is suspected to have an underactive bladder, we need to take a very detailed history and ask him to do a voiding diary. Further investigation includes a urodynamic study, which will be useful to confirm the diagnosis⁴.

For the treatment of underactive bladder, we can start off with lifestyle modification, which includes fluid restriction and bladder training⁵. If these methods do not work, then we can try medications including Distigmine Bromide (an anti-cholinesterase that inhibits the breakdown of acetylcholine) or Bethanechol (a parasympathomimetic choline carbamate that selectively stimulates muscarinic receptors without any effect on nicotinic receptors)⁵.

Other treatment modalities for underactive bladder include clean intermittent self-catheterisation (CISC), neuromodulation of the sacral nerve and stem cell therapy⁵. The aim of CISC is to help complete emptying of the bladder periodically. Usually, it is performed 4 to 6 times per day, aiming at catheterisation of less than 400 ml of urine each time. Amendment of the regimen might be necessary based on a patient's condition, and it will be best to have a daily catheterisation record for monitoring.

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Nocturia and Heart Disease

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INTRODUCTION

Nocturia is a term for waking up at night to void urine. It is usually preceded and followed by sleep. By definition, a single episode of awakening to urinate is already termed nocturia, and it is of clinical relevance if a patient voids two or three times each night. Risk factors of nocturia include the following:

- Obesity
- Hypertension
- Diuretic usage
- Snoring
- Restless leg syndrome
- Benign prostatic hyperplasia (BPH)
- Coronary artery disease
- Prostatic cancer
- Congestive heart failure
- Diabetes
- Antidepressant usage

For a normal pattern of urination, there will be a decrease in nighttime urination relative to daytime. Overproduction of urine at nighttime, with a normal 24-hour urine output, is termed nocturnal polyuria. In adults greater than 65 years, nocturnal polyuria means nocturnal urine output > 33% of the 24 hours urine volume¹. The principal cause of nocturia in the elderly is related to a loss of the diurnal variation of solute excretion or a loss of the ability to raise the urine osmolality above plasma resulting in increased nocturnal urine flow without an obvious increase in the daytime urine volume.

NOCTURIA IN HEART FAILURE PATIENTS

Any clinical condition associated with loss of the normal diurnal variation in solute excretion or the loss of renal concentrating ability will result in nocturia. Patients with congestive heart failure have decreased renal plasma flow and increased filtration fraction during ambulation which is associated with sodium retention. Nighttime recumbency improves renal haemodynamics and sodium excretion and will result in nocturia (recumbency reduces the deficit in cardiac output in relation to O₂ demand.) Renal vasoconstriction will diminish the promotion of urine formation.

Atrial natriuretic peptide, a peptide hormone of cardiac origin, is released in response to atrial distension and serves to maintain sodium homeostasis and inhibits activation of the renin-angiotensin-aldosterone system. Congestive heart failure is a clinical syndrome characterised by increased cardiac volume and pressure overload with an inability to excrete a sodium load, which is associated with increased activity of systemic neurohumoral and local autocrine and paracrine mechanisms. Circulating atrial natriuretic peptide is greatly increased in congestive heart failure as a result of increased synthesis and release of this hormone. Atrial

natriuretic peptide has emerged as an important diagnostic and prognostic serum marker in congestive heart failure. In early heart failure, it may play a key role in preserving the compensated state of asymptomatic left ventricular dysfunction. However, in overt heart failure, the kidney retains sodium and is hyporesponsive to exogenous and endogenous atrial natriuretic peptides despite increased circulating atrial natriuretic peptides².

Nocturia may be an early manifestation of heart failure occurring in the pre-oedematous stage³. It affects the quality of life of heart failure patients and may prevent them from obtaining much-needed rest^{4,5}.

However, in the late course of heart failure, oliguria will occur due to markedly reduced cardiac output from severely reduced left ventricular function.

In situations where diuretic drugs are taken just prior to bed-time, excessive nocturnal urine production can be expected. Studies had shown that a diuretic administered in mid-afternoon e.g. 6 hours before sleep was able to decrease nocturia frequency without decreasing the nocturnal voided volume. The aim of this treatment was to induce diuresis well before sleep so as to decrease the frequency of urination during sleep⁶.

CONCLUSION

In conclusion, nocturia in patients with stable heart failure is not uncommon. It may be severe and closely associated with decrements in sleep and daytime functional performance. It will lead to daytime increases in fatigue and sleepiness, resulting in a detrimental effect on physical function and quality of life. Manipulation of the diuretic dosage and timing to reduce the nocturia severity may improve sleep and fluid overload among heart failure patients.

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Nocturia and Insomnia

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INTRODUCTION

Understanding the role of sleep in general physical and mental function is always the prerequisite to investigate the correlation between nocturia and insomnia.

Poor sleep quality is highly prevalent among the elderly¹, with nocturia being one of the causes². Nocturia-related insomnia has been shown to cause impairment of quality of life, health and productivity³. Patients reporting two or more voids every night will feel disturbed and bothered by the nocturia, which in turn leads to mental disturbances.⁴ For many years, lay people have been ignoring the importance of a good sleep at night. They are under the impression that older people seem to need fewer hours of sleep, while doctors have always emphasized that an average of 7 to 8 hours of sleep is needed for both adults and the elderly.

Studies have shown that because of insufficient sleep, there is increased risk of poor physical functioning, decreased cognitive function, and even mortality¹. Although there are many other reasons giving rise to disturbed sleep, the sensation of a full bladder is a common reason for being awakened at night, and nocturia at multiple times per night defines the medical entity of nocturia.

TYPES OF INSOMNIA

Insomnia is defined clinically as persistent difficulties in both initiating or maintaining a good and enough duration of sleep or having a non-refreshing sleep throughout the night⁵. It will cause significant daytime distress and impaired social and occupational functioning. At least 15% of adults have suffered from Insomnia and it is especially common among people suffering from chronic disorders.⁵ A Hong Kong study conducted in 2011 even showed that nearly 40% of the Chinese population suffered from insomnia⁶.

There are 3 main types of insomnia, namely sleep onset insomnia, sleep maintenance insomnia and early morning insomnia⁷. They are classified according to a typical sleep-wake cycle. Among the three, sleep maintenance insomnia is the one frequently reported in older adults. One-third of elderly experienced nocturnal awakening at least 3 times per week, and 23% of them reported awakening every night. Ninety percent of these nocturnal awakenings has been running a chronic course for at least six months. This is therefore specifically defined as nocturia-related insomnia.

There are different reasons which may give rise to insomnia. It can occur independently as functional insomnia or it can be in conjunction with other medical or psychiatric conditions. The most frequent co-morbidity associated with nocturia-related insomnia, especially among the elderly, is fall. In many studies, nocturia is a significant and independent risk factor of elderly falls. It is also a significant and independent predictor of insomnia. Using a sleep diary can help to define how the nocturia is related to the different types of insomnia.

IMPACT OF NOCTURIA ON SLEEP

Real-life burden from nocturia-associated insomnia includes not only impaired quality of life, but also the Impairment of the cognitive and physical functions, hospitalisations, and even work absence.³ Studies showed that the quality of life has been much affected among patients who reported two or more voids at night. One's work performance is severely affected because of sick leave days taken. In the West, road traffic accidents and workplace accidents are common as a result of fatigue and a lack of refreshing sleep. Falls and fractures are also commonly seen. The frequency of voiding per night is positively associated with the prevalence of bone fractures. There is at least a two-fold increase in fracture risk among those patients with nocturia. The risk of hip fractures from nocturia in men and women are no different, and is age-independent.⁸

Nocturia has also been associated with sleep apnoea: sleep apnoea has been shown to be related to decrease in nocturnal plasma renin and aldosterone secretion.⁹ Use of continuous positive airway pressure (CPAP) for obstructive sleep apnoea (OSA) reverses these effects. Hence in OSA, good compliance with nocturnal CPAP use will decrease the nocturnal diuresis and normalise the sodium output.

CONCLUSION

In summary, nocturia is a multi-factorial problem. It can be associated with serious medical conditions, such as diabetes mellitus, diabetes insipidus and congestive heart failure; these medical conditions need to be excluded². Furthermore, it is important to rule out OSA in patients with nocturia.

Given the various medical conditions associated with nocturia, and given the resultant insomnia and functional impairment, it is understandable that nocturia poses an increased risk of depression in both men and women. It is therefore important to look out



for comorbid anxiety and depression symptoms among patients with nocturia.¹ Combination treatment with transient use of hypnotics as well as completing a course of anti-depressant treatment will help to alleviate anxiety or depression related to nocturia. This will, in turn, have a positive effect on the frequency of nocturia.

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Date	Topics	Speakers
17 Oct	New algorithms in prenatal diagnosis	Dr. Wing-cheung LEUNG Consultant Obstetrician & Chief-of-service, Department of O&G, Kwong Wah Hospital
24 Oct	Ultrasonography of early pregnancy complications including scar pregnancy	Dr. Vincent Yuk-tong CHEUNG Clinical Associate Professor in Obstetrics & Gynaecology The University of Hong Kong
31 Oct	Ultrasonography of placenta, liquor, membranes and cervix	Dr. Tak-yuen FUNG Chief of Service, Obstetrics & Gynaecology Hong Kong Baptist Hospital
7 Nov	Commonly missed abnormalities in routine scan	Dr. Meliza Choi-wah KONG Consultant, Obstetrics & Gynaecology United Christian Hospital
14 Nov	Tips in performing fetal echocardiography	Dr. Wan-pang CHAN Honorary Consultant in Obstetrics & Gynaecology Hong Kong Sanatorium and Hospital
28 Nov	Ultrasonography of craniofacial abnormalities	Dr. Kwok-yin LEUNG President, Hong Kong Society for Ultrasound in Medicine

Date : 17, 24, 31 October and 7, 14, 28 November 2019 (Thursday, skip 21 Nov)

Time : 7:00 p.m. – 8:30 p.m.

Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong

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Nocturia and its Impact on the Elderly

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Dr Arisina Chung-yee MA

INTRODUCTION

Nocturia and urinary disorder is an essential topic in geriatric medicine. Nocturia is highly prevalent in older adults, and the prevalence increases with age. For the younger old, it is more common among women, but more men are affected in the older old.¹

AGEING OF THE URINARY SYSTEM

The physiology of the human urinary system changes with ageing. The compliance, the storage capacity, and the contractility of the urinary bladder decrease while the overactive symptoms increase with age. (Table 1)

Table 1: Physiological changes of urinary bladder

Physiological changes of the Urinary bladder due to Ageing	Clinical symptoms
Higher deposition of collagen	Decreased Compliance & Storage Capacity
Decreased vascular supply to the bladder wall	Decreased Contractility
Increased adrenergic innervation, decreased cholinergic innervation to detrusor	More Overactive Bladder symptoms

The urine concentrating ability of the kidneys declines with age. The ability of the kidneys to conserve solute, and the maximum urinary osmolality decrease by 50% and 20% respectively. Atrial natriuretic peptide [ANP] is a hormone that is released from myocardial cells in the atria in response to volume expansion; it has a diuretic effect. Arginine-vasopressin [AVP], a peptide hormone secreted by the neurohypophyseal system, is released when the plasma osmolality is increased; it controls urine concentration at the kidney level, and it has an antidiuretic effect. In many older adults, there is a higher basal level of ANP, lower level and absence of diurnal variation in AVP release. Nocturnal urine production becomes more a more prominent issue in older adults, being as high as 35% of the whole-day urine production, compared with 15% in the young.

THE IMPACT OF NOCTURIA ON OLDER ADULTS

The impact of nocturia on older adults is profound. Nocturia disrupts their sleep, mood and cognitive function. It worsens the control of cardiovascular disease and diabetes. Cohort studies show that nocturia is associated with adverse survival outcome.²

Some older adults fall when they go to the toilet at night unattended. Falls and fractures are more common in the nocturia group in various studies.³

Similar to frailty and cognitive impairment, nocturia and urinary disorder is one of the geriatric syndromes.(Fig.1) Those syndromes interact with each other, and with other comorbidities. When we manage nocturia, we must consider our patients as a whole, and offer them patient-centred care.

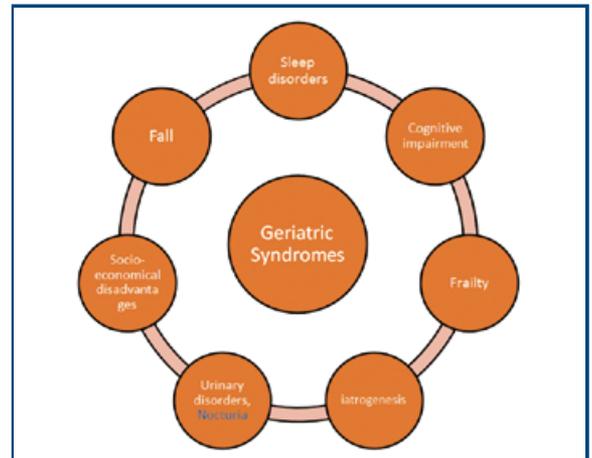


Fig.1. Geriatric Syndromes

Older adults share some common causes of nocturia as the younger adults, but nocturia in this age group is more likely related to medical conditions, such as congestive heart failure, diabetes mellitus, chronic kidney disease, and neurodegenerative diseases. (Table 2)

EVALUATION OF NOCTURIA IN OLDER ADULTS

Besides a routine assessment, we should pay attention to medication use and medical history when we evaluate nocturia in older adults. A complete geriatric assessment and cognitive screening should be considered for individual patients. Nocturia is sometimes under-reported. We should actively screen for it in certain at-risk groups, e.g., in patients with sleep & mood problems, patients presented with falls, or patients with the history of neurodegenerative diseases, diabetes mellitus or congestive heart failure.



Table 2: Common causes of nocturia in old adults (excerpted from D Kujubu, Chapter 19: Nocturia in Elderly Persons and Nocturnal Polyuria, Geriatric Nephrology Curriculum, American Geriatric Society, 2009)

Common causes of nocturia in old adults
Bladder dysfunction <ul style="list-style-type: none"> Bladder outlet obstruction (e.g. benign prostatic hyperplasia) Severe detrusor dysfunction/sizeable residual urine volume Detrusor overactivity Urinary tract infection Decreased functional bladder capacity Bladder tumour or bladder stones Pelvic floor laxity (caused by, e.g., cystocele, uterine prolapse)
Excessive nocturnal urine production <ul style="list-style-type: none"> Oedema-forming states (e.g., congestive heart failure, nephrosis) Obstructive sleep apnoea Neurodegenerative conditions (e.g., Parkinson's disease, Alzheimer's disease) Hypokalaemia and hypercalcaemia (causing nephrogenic diabetes insipidus) Diabetes mellitus and diabetes insipidus Drugs (diuretics, calcium channel blockers, caffeine, alcohol, SSRI) Chronic kidney disease Autonomic neuropathy and venous stasis Excessive fluid intake Idiopathic nocturnal polyuria

A tip for managing any medical problem in older adults is balancing the impact of the issue as well as the interventions. (Fig. 2) On the one hand, we should analyse the severity, the distress, and the adverse outcome related to the problems. On the other hand, we should also consider if the interventions we offer are applicable, and well accepted by our patients.

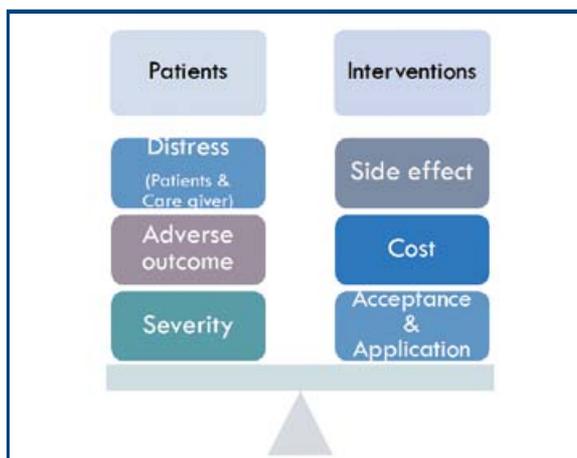


Fig.2. Management of medical problems in geriatric patients

TREATMENT

For the treatment of nocturia, we should first try the non-pharmacological ones. Pharmacological therapies should be tailored according to the underlying causes. We should always remember that older adults are more sensitive to the side effects of certain drugs, e.g., postural hypotension from alpha blockers, and

anticholinergic effects of antimuscarinics. The newer generation of drugs, β_3 -adrenoreceptor agonists⁴ and low dose desmopressin, cast the light of safe and effective treatment for older adults. (Table 3)

Table 3: Treatment of nocturia in older adults

Non-pharmacological	Pharmacological
<ul style="list-style-type: none"> Reducing fluid intake 6 hr before sleep Reduce caffeine and alcohol intake Compression stockings Biofeedback, bladder/pelvic floor exercises Phototherapy Continuous positive airway pressure (for obstructive sleep apnoea) 	<ul style="list-style-type: none"> Alpha-adrenergic blockers, 5-α-reductase inhibitors Oestrogen creams, hormone replacement Melatonin Antimuscarinics, β_3-Adrenoreceptor agonist (Mirabegron) diuretics 6 hr before sleep Desmopressin

In the past, desmopressin was seldom used in older adults with nocturia because they are more prone to develop hyponatraemia. The risk is dose-related, and it is much smaller in low dose like 50 micrograms per day, even in older adults.⁵ Hyponatraemia can be prevented if we use the minimum effective dose, only give it to someone with a baseline sodium level greater than 135 mmol/L, and monitor the sodium level regularly. Desmopressin should be discontinued if sodium level drops below 135 mmol/L.

CONCLUSION

In conclusion, nocturia is frequent in older adults. Nocturia and urinary disorder is a geriatric syndrome. Multidisciplinary and patient-centred care is the essence of management.

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Audio presentation available at:



My Life Beyond Medicine

Dr Victor Hip-wo YEUNG

MBBS(HK), FRCSEd(Urol), FCSHK, FHKAM(Surgery)

*Specialist in Urology
Honorary Clinical Assistant Professor, Department of Surgery,
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Dr Victor Hip-wo YEUNG

Training to be an urologist is challenging yet rewarding, and I am delighted that my knowledge and skills can be applied to patient care in the clinic as well as in the operating theatre. Despite a demanding life as a doctor, I feel very fortunate to have managed to keep up with my two main hobbies, namely, table tennis and singing. These hobbies have made my medical life more well-balanced.

I started to learn table tennis when I was ten years old. I was trained by the legendary Hong Kong table tennis team representatives: Ms Po-wah Chai (齊寶華) and Ms Tan-lui Chan (陳丹蕾). Thanks to their careful guidance, my skills improved by leaps and bounds, and I became the captain of my high school's table tennis team. I went on to empower my college (Johns Hopkins University in the United States) to win the national team championship in 1998 and 1999. My passion for table tennis did not stop after I returned home to study medicine at the University of Hong Kong (HKU). I won the HKU freshman table tennis tournament in 2001 and became a member of the Ricci Hall table tennis team. After graduation, I participated in the Hospital Authority's competition and helped my cluster to win the overall championship. In 2017, I became the co-captain of the Hong Kong Medical Association (HKMA) table tennis team along with Dr Hilton Hok-tin Koo, and our team won the joint professional competition from 2006 to 2016 consecutively. I also helped to organise the first Federation of Medical Societies of Hong Kong (FMSHK) Table-Tennis Competition in 2019 and I look forward to more teams to compete with in the coming years.



Apart from helping my teams to win trophies, I also cherish passing on my skills and experience to the younger generation. Since 2003, I have been the head coach of the Lady Ho Tung Hall Table Tennis Team (LHTTTT) at HKU. 2019 marked my 16th year as a coach, and I enjoyed sharing my techniques as well as

tactics with my fellow teammates. Under my guidance, the LHTTTT has won multiple intra-hall championships throughout these years. During my coaching career, I have found many similarities between being a player or coach in the competition and being a surgeon in the operating theatre.

First, pre-operative preparation is very similar to the preparation ahead of a competition. Before surgery, I will carefully review the indications of the operation, and choose the best option to deal with the pathology such as cancer or stone. Prior to a competition, I will study the skills of my opponents, and select the most appropriate players in my team to play against them. A well-prepared plan will usually result in a favourable outcome.



While preparation is essential, the ability to deal with sudden changes is also important. During an operation or a competition, occasionally I will encounter some unexpected events. I always remind myself to stay calm during these situations, and to keep a clear mind in making a prompt as well as appropriate decision. Timeout (a 1-minute break from the competition) is one of the good methods to let me stop and rethink what I should do next, and this could be utilised in surgery as well. Regular training at the competitions allows me to apply this adaptation skill to difficult operations when necessary.

Debriefing after each match is an important part of the training process, allowing me to revisit the good and bad things the players have done throughout the competition. As a result, I can help correct their weaknesses, and improve their skills in the next match. This is just the same as performing an operation, after which I regularly review my post-operative outcome and reflect on what I can do better next time, targeting at better and better operative outcome.



Apart from coaching table tennis, I enjoyed singing and was lucky enough to be the champion of the singing competitions held by the Hong Kong Medical Association (HKMA) in 2016 and the Hong Kong Doctors' Union (HKDU) in 2018. Personally, I have performed singing in various charity organisations such as the St. James' Settlement.



I have also joined a medical doctors' A Cappella group called Medipella. Medipella is formed by a group of enthusiastic doctors (including Alan, Kenny, Jeffrey, Tomoko, Flora, Irene, Sherby and myself) who are interested in singing, and we aim at raising money for various charity organisations by performing in concerts. In the previous years, we have been performing in various venues including the Queen Elizabeth Stadium, City Hall and Fringe Club, and raised over HK\$300,000 for different charity groups including the Médecins Sans Frontières (MSF), Mother's Choice, etc.

Medipella also hopes to raise public awareness on health promotion as well as disease prevention. We have participated in various shows including psoriasis awareness, organ donation campaign, deaf awareness,

Healthy Hong Kong 2025 and anti-smoking concert (World No Tobacco Day) hosted by the Radio Television of Hong Kong (RTHK). Our new song named (無煙生活) reminds the public of the harms caused by different types of cigarettes and advises smokers to quit as soon as possible in order to achieve better health.



In July 2018, Medipella went to compete in the Singapore AcaChamps (an international A Cappella competition), and we won the silver award as well as the judge's favourite award. We have since then been invited to perform on different occasions by the Hong Kong Medical Association (HKMA), the University of Hong Kong Medical Alumni Association (HKUMAA) and Hong Kong College of Obstetricians and Gynaecologists. We have also been interviewed by various media including the Metro Broadcast Corporation Limited (百分百張瑪莉), Television Broadcasts Limited (Today VIP) and Hong Kong Open TV (Fit 開有條路).

I am thankful to be able to continue my interest in singing and table tennis despite having a hectic work schedule. I sincerely hope that all my medical colleagues can also find their lives beyond medicine.



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Dream Cruises Presents: Federation Annual Dinner 2018

The Annual Dinner of the Federation, held on New Year's Eve each year, is one of the flagship events of the Federation, at which friends and families gather to enjoy themselves and welcome the arrival of a new year. This year we are grateful to have Dream Cruises as our Title Sponsor. Apart from representing Dream Cruises, the keyword "Dream" also represented Federation's dream to unite the medical organizations in Hong Kong and to exchange advanced medical knowledge with the world. The glittering evening was ushered in by Dr Ludwig TSOI, Honorary Secretary of the Federation, and Ms Sally POON, Chairman of Hong Kong Practising Dietitians Union, who served as Masters of Ceremony for the evening. It was attended by over 250 guests from our member societies and partners from the medical and healthcare communities.

We were privileged to have many distinguished guests joining us, including the following guests at our head table:

Prof the Hon Sophia CHAN, Secretary for Food and Health;
Prof the Hon Joseph LEE, Member of Legislative Council (Health Services);
Prof Diana LEE, Professor of Nursing, The Nethersole School of Nursing, Faculty of Medicine, The Chinese University of Hong Kong;
Dr the Hon Pierre CHAN, Member of Legislative Council (Medical);
Dr & Mrs. Che-Hung & Lilian LEONG;
Prof Gabriel LEUNG, Dean of The Li Ka Shing Faculty of Medicine, The University of Hong Kong;
Dr York CHOW, former Secretary for Food and Health; and Mrs. Shelley CHOW;
Prof Chak-sing LAU, President of Hong Kong Academy of Medicine, and Mrs Kim LAU; Dr Chor-chiu LAU, Vice-President (General Affairs) of the Hong Kong Academy of Medicine, and Mrs Anita LAU; and
Dr Cissy YU, Founding President of Hong Kong Women Doctors Association.

At other tables were our distinguished guests and representatives of member societies.

Dr Wai-sum LUK, Vice President of the Association of Licentiates of Medical Council of Hong Kong;
Dr Samuel KWOK, President of the Association of Private Medical Specialists of Hong Kong;
Dr Pak-chin CHOW, Immediate Past President of the College of Ophthalmologists of HK;
Dr Lobo LOUIE, President of the Hong Kong Association of Sports Medicine & Sports Science;
Dr Kai-sing TONG, Council Member of the Hong Kong Medical Association;
Dr Henry YEUNG, President of the Hong Kong Doctors Union;
Dr Laurence HOU,
Dr Wilson YEE, President of the Hong Kong Thoracic Society;
Dr Petrus Shek SZETO, President of The Hong Kong Society of Practising Urologists;
Dr Shao-haei LIU, President of the Hong Kong College of Health Service Executives; &
Dr Nancy YUEN, Past President of The Hong Kong Ophthalmological Society.

The presence of these honourable guests brightened up the evening and we owe them our heartfelt thanks.



Throughout the evening, many superb and talented performers from the medical community gave a variety of performances, including funky jazz dance performances by EC Swag; band performances by HKOTA Band and St. John's Band; ballroom dance performances by Dr Wei-lee HUI and Mr Johnny LIU, and by Dr Dui WU and Mr Jianyu ZOU; singing by Dr York CHOW, Dr Nancy YUEN and Dr Samuel KWOK, Dr Henry YUENG, Dr Mario CHAK, Ms Sally POON, Dr Johnny Leo CHAN and Dr Kenneth LIU and Dr Victor YEUNG. The dinner was indeed a star-studded event. The highlight was undoubtedly the rendition of the Cantopop classics, 'Star' (星) and 'Below the Lion Rock' (獅子山下), by Prof the Hon Sophia CHAN, Prof the Hon Joseph LEE and Prof Diana LEE, Dr Che-Hung LEONG, Prof Gabriel LEUNG, Dr the Hon Pierre CHAN, Dr York CHOW, Prof Chak-sing LAU, Dr Chor-chiu LAU, Dr Cissy YU, our President Dr Mario CHAK and our Executive Committee members.

Everyone was thoroughly absorbed in the Bingo hosted by our very own Bingo Masters, Mr Benjamin LEE & Mr William TSUI. Our guests turned into the stars of the evening in the Best Costume Awards and Dance Fever Competition. The atmosphere of the evening was brought to a climax with the countdown party and pop classics performed by Dr Mario CHAK, Dr Ludwig TSOI, Ms Sally POON and our EXCO members.

After midnight, everyone was still enjoying themselves, especially during the Lucky Draw. Fabulous prizes this year included the Luxury Prize of a "World Dream 5-night Discovery in a Palace Deluxe Suite for 4 persons" that was worth \$60,000, the Premier Prize of a "World Dream 5-night Discovery in a Balcony Deluxe Suite for 3 persons" that was worth \$30,000, and delightful prizes such as Decorte AQ Meliority Facial Care Gift Sets, AQ Bio Sanitizer Gift Set, and Nespresso Coffee Machine.

All in all, it was a beautiful night during which we shared our joy and excitement together. We express our sincere gratitude to all our sponsors, and thank all our guests for joining us on this memorable occasion.











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11	★ Certificate Course on Care for Advanced Diseases 12	★ HKMA Yau Tsim Mong Community Network - Update on Liver Tumours ★ Certificate Course on Understanding and Treating Sex Offenders for Medical & Helping Professionals 2019 13	★ The Hong Kong Neurosurgical Society Monthly Academic Meeting – To be confirmed ★ HKMA & Hong Kong Society of Biological Psychiatry - Certificate Course in Psychiatry for Community Primary Care Doctors (Session 5) - Medication I 14	★ HKMA Hong Kong East Community Network - State of Quo of Lipid Management 15	★ HKMA Kowloon City Community Network - Treatment of Nasal Polyps and Allergic Rhinitis 16	17
18	★ FMSHK Executive Committee Meeting ★ FMSHK Council Meeting 19	★ HKMA Kowloon West Community Network – Update on Management of Food Allergy in Children ★ Certificate Course on Understanding and Treating Sex Offenders for Medical & Helping Professionals 2019 20	★ HKMA Central, Western & Southern Community Network – Intensifying Blood Pressure Control 21	★ HKMA Kowloon East Community Network – Roles and Benefits of GLP1-Insulin Combo in Modern T2DM Management 22	23	24
25	26	27	★ HKMA Central, Western & Southern Community Network – Update on DM Management 28	29	★ HKMA Yau Tsim Mong Community Network - Management of Lung Cancer: Update in EGFR Targeted Treatment 30	31



Date / Time	Function	Enquiry / Remarks
1 THU 7:00PM	Certificate Course in Allergy 2019 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
5 MON 7:00PM	Certificate Course on Care for Advanced Diseases Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
6 TUE 1:00 PM	HKMA-HKS&H CME Programme 2018 -2019 – Common Pitfalls in the Interpretation of Autoimmune Serological Tests Organiser: Hong Kong Medical Association; Hong Kong Sanatorium & Hospital; Speaker: Dr. LEE Ka Wing Gavin; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	HKMA CME Dept Tel: 2527 8285 1 CME Point
1:00 PM	HKMA Kowloon West Community Network – Biological Therapy for Moderate to Severe Atopic Dermatitis Organiser: HKMA Kowloon West Community Network; Speaker: Dr. HO Ka Keung; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chuen	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	Certificate Course on Understanding and Treating Sex Offenders for Medical & Helping Professionals 2019 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
9:00 PM	HKMA Council Meeting Organiser: The Hong Kong Medical Association; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Christine WONG Tel: 2527 8285
7 WED 1:00PM	HKMA Central, Western & Southern Community Network - Common Breast Problems Organiser: HKMA Central, Western & Southern Community Network; Speaker: Dr. CHENG Yuh Meei; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Miss Antonia LEE Tel: 2527 8285 1 CME Point
1:00PM	HKMA New Territories West Community Network – Geriatric Paradox - How Does It Change Your Practice in Primary Care? Organiser: HKMA-New Territories West Community Network, HA-NT West Cluster - Dept. of Family Medicine & Primary Health Care; Speaker: Dr. AU YEUNG Tung Wai; Venue: SB1036, Tuen Mun Hospital, Tsing Chung Koon Road, Tuen Mun	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00PM	Certificate Course in Clinical Cytogenetics and Genetics 2019 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
8 THU 1:00 PM	HKMA Kowloon East Community Network: The Three Highs – A Cardiologist's Perspective Organiser: HKMA Kowloon East Community Network; Speaker: Dr. LEE Kar Fai, Victor; Venue: Lei Garden Restaurant, Shop no. L5-8, apm, Kwun Tong, No. 418 Kwun Tong Road, Kwun Tong, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
7:00 PM	Certificate Course in Allergy 2019 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
12 MON 7:00 PM	Certificate Course on Care for Advanced Diseases Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
13 TUE 1:00 PM	HKMA Yau Tsim Mong Community Network - Update on Liver Tumours Organiser: HKMA Yau Tsim Mong Community Network; Speaker: Dr. YEUNG Yuk Pang; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
7:00 PM	Certificate Course on Understanding and Treating Sex Offenders for Medical & Helping Professionals 2019 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
14 WED 7:30 PM	The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed Organiser: Hong Kong Neurosurgical Society; Speaker: Dr CHAN Nok Lun, Norren; Chairman: Dr CHEUNG Fung Ching; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital	1.5 points College of Surgeons of Hong Kong Name: Dr. WONG Sui To Tel: 2595 6456 Fax. No.: 2965 4061
1:00 PM	HKMA & Hong Kong Society of Biological Psychiatry - Certificate Course in Psychiatry for Community Primary Care Doctors (Session 5) - Medication I Organiser: Hong Kong Medical Association; Hong Kong Society of Biological Psychiatry; Speaker: Discussants / Moderator: Dr. WONG Ming Cheuk/ Dr. MAK Ki Yan/ Prof. TANG Siu Wa; Venue: Tang Room, 3/FL, Sheraton Hong Kong Hotel & Towers, 20 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 2 CME Point
15 THU 1:00 PM	HKMA Hong Kong East Community Network - State of Quo of Lipid Management Organiser: HKMA Hong Kong East Community Network; Speaker: Dr. WONG Bun Lap, Bernard; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
16 FRI 1:00 PM	HKMA Kowloon City Community Network - Treatment of Nasal Polyps and Allergic Rhinitis Organiser: HKMA Kowloon City Community Network; Speaker: Dr. CHUNG Yiu Kei, Geoffrey; Venue: President's Room, Spotlight Recreation Club, 4/F, Screen World, Site 8, Whampoa Garden, Hunghom, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
19 MON 7:00 PM	FMSHK Executive Committee Meeting Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898



Date / Time	Function	Enquiry / Remarks
19 MON 8:00 PM	FMSHK Council Meeting Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
20 TUE 1:00 PM	HKMA Kowloon West Community Network – Update on Management of Food Allergy in Children Organiser: HKMA Kowloon West Community Network; Speaker: Dr. CHONG Chun Yin, Patrick; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chuen	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	Certificate Course on Understanding and Treating Sex Offenders for Medical & Helping Professionals 2019 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Vienna LAM Tel: 2527 8898
21 WED 1:00 PM	HKMA Central, Western & Southern Community Network – Intensifying Blood Pressure Control Organiser: HKMA Central, Western & Southern Community Network; Speaker: Dr. LEE Kin Tong, Joe; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Miss Antonia LEE Tel: 2527 8285 1 CME Point
22 THU 1:00 PM	HKMA Kowloon East Community Network – Roles and Benefits of GLP1-Insulin Combo in Modern T2DM Management Organiser: HKMA Kowloon East Community Network; Speaker: Dr. LAM King Yun, Joanne; Venue: V Cuisine, 6/F, Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O	Ms. Candice TONG Tel: 2527 8285 1 CME Point
28 WED 1:00 PM	HKMA Central, Western & Southern Community Network – Update on DM Management Organiser: HKMA Central, Western & Southern Community Network; Speaker: Dr. CHEUNG Yun Ning, Elaine; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Miss Antonia LEE Tel: 2527 8285 1 CME Point
30 FRI 1:00 PM	HKMA Yau Tsim Mong Community Network - Management of Lung Cancer: Update in EGFR Targeted Treatment Organiser: HKMA Yau Tsim Mong Community Network; Speaker: Dr. LEE Kun Min; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point

Upcoming Event

1 September 2019	LI SHU PUI SYMPOSIUM 2019 - MANAGEMENT OF CHRONIC MEDICAL CONDITIONS AND REHABILITATION Venue: Ballroom, JW Marriott Hotel Hong Kong, Pacific Place, 88 Queensway, Hong Kong	Website: www.hksh.com/lsp-registration Tel: 2835 8800
22 September 2019	ASM 2019 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Sheraton Hong Kong Hotel	Ms. Cordelia WU Tel: 2527 8898

Certificate Course for Health Care Professionals

• Course No. C338 • CME/CNE Course

Jointly organised by

Best Practices in Quality of Life Evaluation and Assessments 2019



Date	Topics	Speakers
14 Oct	Linguistic and Psychometric Evaluation of QoL Measures	Dr Daniel Fong Associate Professor, School of Nursing The University of Hong Kong
21 Oct	Principles and Concepts of Quality of Life (QoL)	Dr Wendy Wong Assistant Professor, Hong Kong Institute of Integrative Medicine, School of Chinese Medicine The Chinese University of Hong Kong
28 Oct	Using QoL in Health Evaluation	Dr Carlos Wong Assistant Professor (Research), Department of Family Medicine and Primary Care The University of Hong Kong
4 Nov	Assessing QoL in Palliative Care	Dr Raymond Lo Clinical Professor (Hon), Department of Medicine and Therapeutics The Chinese University of Hong Kong
11 Nov	Assessing QoL in Cancer Patients	Dr Winnie So Associate Professor, The Netherlands School of Nursing The Chinese University of Hong Kong
18 Nov	QoL in General Population	Prof Eliza Wong Professor, JC School of Public Health and Primary Care The Chinese University of Hong Kong

Dates : 14, 21, 28 October, 2019 and 4, 11, 18 November, 2019 (Every Monday)

Time : 7:00 pm – 8:30 pm

Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong

Course Fee : HK\$750 (6 sessions)

Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong

Tel: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

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Answers to Radiology Quiz

Answers:

- The density of a nodule determines the risk of malignancy.
 - Calcified and fat-containing nodules are generally benign.
 - Solid nodules are largely benign (93%) and often caused by prior infection.
 - Partially solid nodules are the most worrying with 63% being malignant.
 - Ground glass nodules are notorious for growing slowly. 18% eventually transform into an adenocarcinoma. Even if the nodule is stable, long-term (5 years) follow-up is needed.
- The Fleischner Society provides a set of useful guidelines for managing incidental lung nodules. Action plans are given based on clinical (e.g. smoking status) and radiological parameters (e.g. size and density of the nodule). Generally speaking, follow-up is not needed for nodules <6 mm in low-risk patients.

A summary table and a smartphone app is available here: (<https://fleischner.memberclicks.net/pulmonary-nodule-app>).

For our clinical scenario, follow-ups at 6-12 months and 18-24 months are appropriate.
- In general, FDG-PET scans are not helpful for evaluating nodules <8 mm due to its limited spatial resolution.
- Three major methods exist:
 - CT-guided percutaneous biopsy: more appropriate for peripherally located nodules.
 - Bronchoscopy-guided biopsy: more appropriate for centrally located nodules.
 - VATS wedge resection: more appropriate for highly suspicious nodules; provides treatment in addition to diagnosis.

The need and method of biopsy are best decided by a multidisciplinary team consisting of thoracic surgeons, chest physicians, oncologists, radiologists and pathologists.

- Lung cancer is often discovered late leading to poor survival. Recently, large trials (e.g. NLST, NELSON, MILD) have demonstrated a 20-39% reduction in lung cancer mortality risk for patients who underwent LDCT screening and early curative treatment.

The evidence is evolving and there is a debate as to who should undergo screening. Practically speaking, American guidelines recommend LDCT for patients 1) Aged between 55-80; 2) Have a 30 pack-year smoking history and 3) Currently smoking or haven't abstained for >15 years.

Dr Yan-lin LI

FRCR

Department of Radiology, Queen Mary Hospital

The Federation of Medical Societies of Hong Kong
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Annual Scientific Meeting 2019

Innovative Medical Technology

Date : 22 September 2019 (Sun) Time : 9:00am – 17:00pm

Venue : Ballroom, 3/F, Sheraton Hong Kong Hotel & Towers,
20 Nathan Road, Tsim Sha Tsui, Kowloon

Opening Ceremony

Session I - Practice of Health Service Management

- Opportunities and Challenges in Greater Bay Area
Prof Geoffrey LIEU
Advisor, The Hong Kong College of Health Service Executives
- 101 of Innovative Healthcare - the Role of Medical Entrepreneurs
Dr LIU Shao-haei
President, The Hong Kong College of Health Service Executives

Session II A - Respiratory Health

- Approach to Small Lung Nodules
Dr CHU Chung-ming
Specialist in Respiratory Medicine, Honorary Consultant, United Christian Hospital
- Update in Airway Diseases Management
Dr David CL LAM
Clinical Associate Professor, Department of Medicine, Queen Mary Hospital

Session II C - Vaccine & Urology

- Prostate / Vaccine / Nocturia TBC
Speaker TBC
- MRI USG Fusion Biopsy of Prostate
Dr Peter KF CHIU
Associate Consultant, Urology Team, Department of Surgery, Prince of Wales Hospital

Luncheon Symposium

- Mood Disorder
Speaker TBC

Session III A - Dermatology

- Steroid Phobia in Atopic Dermatitis
Speaker TBC
- The Future of Atopic Dermatitis Treatment: Children in Focus
Speaker TBC

Session III C - Care for Advanced Diseases I

- Cancer Pain
Dr Raymond SK LO TBC
Immediate Past President, The Federation of Medical Societies of Hong Kong
- Care for Advanced Diseases related topic
Speaker TBC

Session IV A - Diabetes Mellitus and Renal Health

- Complications of Phosphate in Cardiovascular Morbidities - Challenges to Chronic Kidney Patients and Doctors
Dr Samuel KS FUNG
EXCO Member, The Federation of Medical Societies of Hong Kong
- Diabetic Kidney Disease - A Growing Threat in Asia; Counter-measures
Dr CHENG Yuk-lun
Chairman, Hong Kong Society of Nephrology

Session IV B - Children Health

- Precision Medicine in Epilepsy
Dr Mario WK CHAK
President, The Federation of Medical Societies of Hong Kong

Session IV C - Care for Advanced Diseases II

- Care for Advanced Diseases related topic
Speaker TBC
- Care for Advanced Diseases related topic
Speaker TBC

Session V A - Cardiovascular Diseases

- Cardiology related topic
Dr Michael Pak-hei CHAN
Clinical Assistant Professor, Department of Medicine, The University of Hong Kong
- Lipid Management
Dr Steve SL LI

Session V B - Neurosurgery

- Frameless Stereotactic Radiosurgery from Brain Metastasis to AVM, What Next?
Dr YAM Kwong-yui
Consultant, Department of Neurosurgery, Tuen Mun Hospital
- Epilepsy Surgery: Progress with Technology Advancement
Dr WONG Sui-to
Consultant, Department of Neurosurgery, Tuen Mun Hospital

Session V C - Rheumatology & Immunology

- Allergic Rhinitis
Dr LO Pui-ye
Specialist in ENT
- Rheumatology related topic
Speaker TBC

Registration Fee

HK\$100 Members of Member Societies of FMSHK
HK\$400 Non-members
HK\$50 Medical Student

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 PLACEBO-LIKE DRY MOUTH(1.7%) SIDE EFFECT¹

YOUR **1ST** STEP FOR **MALE LUTS+** PATIENTS
 WITH PROMISING SAFETY PROFILE[#]
 PLACEBO-LIKE DIZZINESS(1.4%) SIDE EFFECT²

A FRESH STEP IN LUTS+ MANAGEMENT

Urgency
 Slow Stream
 Frequency



*OAB: Overactive Bladder + LUTS: Lower Urinary Tract Symptoms
 # α_1 -blockers are often considered the first line drug treatment of male LUTS³

Reference: 1. Chapple C.R. et al. NeuroUrol Urodynam 2013 [doi 10.1002/nau.22505] 2. Chapple C.R. et al. Eur Urol Suppl. 2005; 4:33-44
 3. Gravas S, et al. EAU Guidelines on the Treatment of Non-neurogenic Male LUTS. European Association of Urology, 2017.

Abbreviated prescribing information of Harnal OCAS[®] 0.4 mg Tablets

Version: 002 PJ version: Sep 2013. **Composition:** Tamsulosin HCl **Indication:** Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). **Dosage:** 1 tab daily, can be taken independently of food. **Administration:** Swallow whole, do not chew/crush. **Contraindications:** Hypersensitivity to tamsulosin hydrochloride or to any of the excipients. **Special warnings and special precautions for use:** As with other α_1 -adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with Harnal OCAS[®] 0.4 mg Tablets, as a result of which, rarely, syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared. Before therapy with Harnal OCAS[®] 0.4 mg Tablets is initiated, the patient should be examined in order to exclude the presence of other conditions, which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards. Treatment of patients with a history of orthostatic hypotension should be approached with caution. The treatment of patients with severe renal impairment (creatinine clearance of <10 ml/min) should be approached with caution, as these patients have not been studied. The treatment of patients with severe hepatic dysfunction should be approached with caution. The Intraoperative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract and glaucoma surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin hydrochloride 1-2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not been established. IFIS has also been reported in patients who had discontinued tamsulosin for a longer period prior to the surgery. The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract or glaucoma surgery is scheduled is not recommended. During pre-operative assessment, surgeons and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma surgery are being or have been treated with tamsulosin in order to ensure that appropriate measures will be in place to manage the IFIS during surgery. Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4. Cases of allergic reaction to tamsulosin in patients with a past history of sulfonamide allergy have been reported. If a patient reports a previously experienced sulfa allergy, caution is warranted when administering tamsulosin hydrochloride. **Undesirable effects:** Common (>1% <10%), Uncommon (>0.1% <1%), Rare (>0.01% <0.1%), Very rare (<0.01%). **Cardiac disorder:** Uncommon: Palpitations. **Gastrointestinal disorders:** Uncommon: Constipation, diarrhoea, nausea, vomiting. **General disorders and administration site conditions:** Uncommon: Asthenia. **Nervous system disorders:** Common: Dizziness (1.3%), Uncommon: Headache. **Rare:** Syncope. **Reproductive system and breast disorders:** Common: Ejaculation disorders. **Very rare:** Priapism. **Respiratory, thoracic and mediastinal disorders:** Uncommon: Rhinitis. **Skin and subcutaneous tissue disorders:** Uncommon: Rash, pruritus, urticaria. **Rare:** Angioedema. **Vascular disorders:** Uncommon: Orthostatic hypotension. **Post-marketing experience:** The following events have also been reported during the post-marketing period. These events are reported voluntarily from a population of uncertain size, therefore it is not possible to reliably estimate their frequency: visual disorders (e.g. blurred vision, visual impairment), dermatitis exfoliative, erythema multiforme and epistaxis. During cataract and glaucoma surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been reported. **Full prescribing information is available upon request.**

Abbreviated prescribing information of Betmiga[®] prolonged-release tablets

Version: 003 PJ version: Apr 2016. **Composition:** Mirabegron **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adult including elderly 50 mg once daily with or without food. **Administration:** Swallow whole with liquids. Do not chew/divide/crush. **Contraindications:** Mirabegron is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. - Severe uncontrolled hypertension defined as systolic blood pressure \geq 180 mm Hg and/or diastolic blood pressure \geq 110 mm Hg. **Special warnings and precautions for use:** Renal impairment: Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m²) or patients requiring haemodialysis and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²) concomitantly receiving strong CYP3A inhibitors. Hepatic impairment: Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors. Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure \geq 160 mm Hg or diastolic blood pressure \geq 100 mm Hg). Patients with congenital or acquired QT prolongation: Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinic medications for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga; however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB. **Undesirable effects:** Summary of the safety profile: The safety of Betmiga was evaluated in 8,433 patients with OAB, of which 5,648 received at least one dose of mirabegron in the phase 3 clinical program, and 622 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with Betmiga, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. List of adverse reactions: The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (\geq 1/10); common (\geq 1/100 to <1/10); uncommon (\geq 1/1,000 to <1/10,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Infections and infestations: Common: Urinary tract infection. Uncommon: Vaginal infection, Cystitis. Psychiatric disorders: Not known (cannot be estimated from the available data): Insomnia*. Eye disorders: Rare: Eyelid oedema. Cardiac disorders: Common: Tachycardia. Uncommon: Palpitation. Atrial fibrillation. Vascular disorders: Very rare: Hypertensive crisis*. Gastrointestinal disorders: Common: Nausea*, Constipation*, Diarrhoea*. Uncommon: Dyspepsia, Gastritis. Rare: Lip oedema. Skin and subcutaneous tissue disorders: Uncommon: Urticaria, Rash, Rash macular, Rash papular, Pruritus. Rare: Leukocytoclastic vasculitis, Purpura, Angioedema*. Musculoskeletal and connective tissue disorders: Uncommon: Joint swelling. Reproductive system and breast disorders: Uncommon: Vulvovaginal pruritus. Investigations: Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased. Renal and urinary disorders: Rare: Urinary retention*. Nervous system disorders: Common: Headache*, Dizziness*, observed during post-marketing experience. **Full prescribing information is available upon request.**