# EAU meeting report

11-15 March 2016 Munich, Germany

<table>
<thead>
<tr>
<th>Abstract sessions</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>New diagnostic tools in male LUTS</td>
<td>3</td>
</tr>
<tr>
<td>New horizons in LUTS</td>
<td>4</td>
</tr>
<tr>
<td>Advances in nocturia</td>
<td>4</td>
</tr>
<tr>
<td>LUTS pharmacotherapy: Any news?</td>
<td>6</td>
</tr>
<tr>
<td>Men's sexual health: Focus on premature ejaculation, hypogonadism and lower urinary tract and ejaculatory dysfunction</td>
<td>7</td>
</tr>
<tr>
<td>Prostate cancer screening and early detection</td>
<td>8</td>
</tr>
<tr>
<td>Plenary sessions</td>
<td>9</td>
</tr>
<tr>
<td>Ageing and the lower urinary tract</td>
<td>9</td>
</tr>
<tr>
<td>Healthy LUT and ageing: A contradiction?</td>
<td>9</td>
</tr>
<tr>
<td>Drug therapy in the elderly: Which are the good drugs?</td>
<td>10</td>
</tr>
<tr>
<td>Industry-sponsored symposia</td>
<td>11</td>
</tr>
<tr>
<td>Evolving concepts in the management of male LUTS/BPH</td>
<td>11</td>
</tr>
<tr>
<td>Understanding personalised medical management for BPH patients at risk of progression</td>
<td>12</td>
</tr>
<tr>
<td>Unravelling the mysteries of male LUTS to aid individualised therapy</td>
<td>13</td>
</tr>
<tr>
<td>Abbreviations &amp; References</td>
<td>14</td>
</tr>
</tbody>
</table>
At this year’s European Association of Urology (EAU) in Munich there were around 13,000 participants from 118 countries worldwide. All aspects of urology from the latest medical innovations to hands-on training courses were covered. With regard to male lower urinary tract symptoms (LUTS) related to benign prostate hyperplasia (BPH), there were active discussions and debates regarding its characterisation, relationship and optimal management.

During the abstract sessions, a number of key topics were addressed, including the identification of new tools for the diagnosis of LUTS, changes in prescribing patterns for the management of LUTS/BPH, identification and appropriate management of nocturia, the use of testosterone to address male sexual health needs in those diagnosed with LUTS and the importance of early screening and detection of prostate cancer (PCa).

In addition, the characterisation of aging associated LUTS and the appropriate treatment of the aging patient with LUTS was addressed in a plenary session.

There were also three industry-sponsored symposia relating to the management of LUTS/BPH from Recordati, GSK and Astellas.
Abstract sessions

New diagnostic tools in male LUTS

The EAU guidelines provide clear guidance on the initial assessment of men with LUTS, which include the following as routine:\(^2\)

- Medical history
- Validated symptom score questionnaire with quality of life (QOL) question(s)
- Physical examination including digital rectal examination
- Urinalysis
- Post-void residual urine (PVR)
- Uroflowmetry

In addition, micturition frequency-volume charts (FVC) or bladder diaries should be used to assess male LUTS with a prominent storage component or nocturia.\(^2\) Prostate-specific antigen (PSA) should be measured only if a diagnosis of PCa will change the management or if PSA can assist in decision-making for patients at risk of symptom progression and complications.\(^2\)

In the session addressing new tools for diagnosing LUTS, Lorenzo et al. presented a visual tool that correlates with the maximum flow rate (\(Q_{\text{max}}\)) and could replace the classical uroflowmetry in selected situations (Lorenzo RR et al. Correlation between uroflowmetry and a new visual pictogram (Figure) in male with lower urinary tract symptoms: analogical uroflowmetry (ANUF). Eur Urol Suppl 2016;15(3):e99).

The results from using this tool were found to correlate significantly with clinically measured \(Q_{\text{max}}\).

This study concluded that this tool was easy and useful tool for the diagnosis and follow-up of LUTS but that further studies on its use are needed.

The impact of statins on prostate cell growth has also been investigated by Han et al. They hypothesised that statins may affect prostate cell growth and survival by lowering cholesterol levels in the prostate (Han J-Y et al. Impact of treatment with statin on prostate volume and lower urinary tract symptoms: 3-Year follow-up. Eur Urol Suppl 2016;15(3):e105). When the impact of stain use (n=45) on prostate volume (PV) related LUTS was retrospectively reviewed in patients ≥40 years old with confirmed BPH who had been followed for at least 3 years, a significant difference in PV was observed vs. non-statin users (n=118) (1.67 vs. 0.15cm\(^3\)/year, p=0.045). However, there was no difference between the groups for prostate transition zone volume, change in PSA levels or total International Prostate Symptom Score (IPSS) score.

This study concluded that statins, although effective in reducing PV, were not effective in the overall treatment of men with LUTS. This study suggests statin therapy would not be expected to mask the presence of LUTS.
In a Korean Prostate Health Council Screening Programme, the impact of body mass index (BMI) on PSA, IPSS, PV was analysed in 15,435 men with PSA <10ng/mL and aged >50 years (mean 72 years) (Choi SM et al. The relationship between body mass index and benign prostate hyperplasia in large scale community based cohort. Eur Urol Suppl 2016;15(3);e108). BMI negatively correlated with PSA (r=-0.056, p<0.001), total IPSS (r=-0.095, p<0.001) and IPSS-QOL subscore (r=-0.079, p<0.001).

Choi et al concluded that BMI was negatively associated with serum PSA level, total and QOL IPSS and positively associated with PV, and should be taken into account in screening patients presenting with LUTS.

New horizons in LUTS

Two surveys have provided the first real-world data on prescribing patterns, incidence of adverse drug reactions (ADRs) and treatment effectiveness in Japanese patients (± concomitant cardiovascular [CV] disorders) prescribed mirabegron (MIRA) for the treatment of overactive bladder (OAB) (Kato D et al. Safety and effectiveness of mirabegron in patients with overactive bladder (OAB): Results of two Japanese post-marketing surveys. Eur Urol Suppl 2016;15(3);e278). When OAB Symptom Score (OABSS), IPSS-QOL, residual urine volume and incidence of ADRs were assessed at 12 weeks in Survey 1 (n=9,795 [46.8% male]; MIRA dose 25mg [11.2%], 50mg [84.8%] or 100mg [<0.1%; unlicensed dose]), 63.6% of patients achieved the 3-point minimal clinically important change (MCIC) in mean OABSS score and IPSS-QOL scores decreased significantly (p<0.001) vs. baseline; ADRs were reported in 6% of patients. In Survey 2 (n=236 patients [61.9% male] with a concomitant history of, or current, mild-to-moderate CV disease; MIRA dose 25mg [17.8%] or 50mg [78.8%]), MIRA was considered to be effective by clinicians in 83.3% of patients and the incidence of CV ADRs was 5.51%.

Kato et al concluded that, in the clinical setting, MIRA was well tolerated with no unanticipated ADR and was an effective treatment for Japanese patients with OAB, including those with concomitant CV disorders.

Advances in nocturia

Nocturia is a common and bothersome symptom that may impose detrimental impacts on sleep quality, mood and overall health (Yoshida M et al. Mirabegron improves nocturia and nocturia associated QoL and sleep quality. Eur Urol Suppl 2016;15(3);e538). Yoshida et al explained that the multifactorial aetiology of nocturia makes it a challenging clinical entity. OAB and nocturia are clearly associated, although the relationship is not reciprocal. For that reason, antimuscarinics (AM) may be used. AM reduce nocturia by increasing bladder capacity, which may benefit patients whose awakenings are associated with urgency. Agents that selectively activate the β3-adrenoceptor subtype, such as MIRA, could treat the symptoms of OAB via a mechanism of action that is distinct from AM therapies. In a prospective multicentre study in 58 female OAB patients, MIRA 50mg/day for 12 weeks, significantly decreased OABSS. The total IPSS score, QOL index, voiding symptoms and storage symptoms also improved significantly. After 12 weeks, MIRA significantly improved nocturnal frequency, nocturnal urine volume per void, urine volume of the first nocturnal voiding and nocturia QOL (N-QOL) scores, and increased hours of undisturbed sleep (from 160.6 to 203.8 min). In addition, the Pittsburgh Sleep Quality Index (PSQI) was significantly improved from as early as 4 weeks (p<0.01 at all time points).

This study showed that MIRA improved nocturnal frequency by increasing nocturnal bladder capacity, and improved QOL by increasing sleep quality in patients suffering from nocturia.
Pathophysiologically, nocturnal polyuria (NP) is a possible cause of nocturia (Weiss J et al. Diagnosing nocturnal polyuria (NP)-based on self-reported nocturnal void volume and fluid intake in clinical practice: Results from a real-world treatment survey in Europe and the USA. (Eur Urol Suppl 2016;15(3);e536). The International Continence Society has defined NP as nocturnal urine volume ≥33% of total daily urine volume, while 24-hour output remains normal. Many patients with OAB and BPH may have coexisting NP. Timing of LUTS may assist in identifying patients with NP. Weiss et al presented data from the Adelphi LUTS Disease Specific Programme from France, Germany, Spain, UK and USA, which included 5,335 patients. This study showed that self-reported data on nocturnal void volume and fluid intake could be useful in clinical practice to diagnose NP. In this survey, NP patients reported that they always (26.6%) or usually (59.5%) pass a significant volume of urine at night. The estimated void volume in NP patients was 38% of the total daily void volume while for other patients it was <33%. NP patients also had a more limited fluid intake before travelling and sleeping.

This study concluded that bladder/voiding diaries are not being utilised fully, suggesting the need for refinement or better awareness among both patients and physicians. Self-reported data on nocturnal void volume and fluid intake may be a useful additional tool in clinical practice to diagnose NP.

De Nunzio explained that smoking, hypertension, abdominal obesity and metabolic abnormalities have been considered individual factors involved in LUTS pathogenesis. (De Nunzio C et al. Metabolic abnormalities linked to an increased cardiovascular risk are associated with higher storage lower urinary tract symptoms. Eur Urol Suppl 2016;15(3);e541). All of these factors are used to define individual CV risk (CVR). In a study to evaluate the association between CVR and LUTS in 509 patients with BPH, 61% were found to have a moderate/high CVR and 25% presented with a metabolic syndrome. With regards to LUTS, 58% had moderate/severe symptoms and 55% had moderate/severe storage. Patients with moderate/severe CVR had significantly higher IPSS (p=0.01) and storage IPSS (sIPSS, p=0.05). The presence of CVR was associated with an increased risk of IPSS >7 (Odds ratio [OR]=1.737, 95% confidence interval [95%CI]=1.085-2.783; p=0.022) and a significantly increased risk of a sIPSS subscore >3 (OR=1.6, 95%CI=1.001-2.555; p=0.04).

This study showed that moderate/high CVR is associated with an increased risk of LUTS, particularly storage LUTS.

Although α1-blockers (AB) can improve nocturia in men with LUTS, the symptoms do not always completely resolve (Cho KJ et al. Efficacy and safety of desmopressin “add-on” therapy in men with persistent nocturia under alpha-blocker monotherapy for lower urinary tract symptoms: A randomised, double-blind, placebo-controlled study. Eur Urol Suppl 2016;15(3);e543). The efficacy and safety of desmopressin add-on therapy in men with persistent nocturia on AB monotherapy for LUTS was assessed by Cho et al in a randomised, double-blind, placebo-controlled study of desmopressin 0.2mg (n=47) vs. placebo (n=39) for 8 weeks. The primary endpoint was the change in the mean number of nocturia episodes from baseline. Secondary endpoints included the proportion of patients with a decreased number of nocturia episodes by ≥50%, nocturnal urine volume, NP index, IPSS, nocturnal hesitancy, International Consultation on Incontinence Questionnaire-Nocturia (ICIQ-N), perception of benefit with treatment, satisfaction and willingness to continue. Safety assessments included ADR. Desmopressin was significantly superior to placebo in terms of change from baseline in the mean number of nocturia episodes (-1.13 ± 0.92 vs. -0.68 ± 0.79, p=0.034), change in nocturnal urine volume (p<0.001), change in total IPSS (p=0.041), change in NP index (p=0.001), change in ICIQ-N (p=0.001) and willingness to continue treatment (p=0.025). The incidence of ADR was comparable between treatment groups.

This randomised, double-blind, placebo-controlled study concluded that desmopressin 0.2mg add-on therapy in men with persistent nocturia on AB monotherapy for LUTS was effective and well tolerated.
The long-term efficacy and safety of an anticholinergic agent combined with an AB vs. AB monotherapy in patients with BPH complicated by OAB (n=120) has been assessed by Matsukawa et al in a single-centre, randomised, prospective urodynamic study (Matsukawa Y et al. Long term efficacy of a combination therapy with an anticholinergic agent and an alpha-1-blocker for patients with benign prostatic enlargement complicated by overactive bladder: A randomized, prospective, comparative trial using a urodynamic study. Eur Urol Suppl 2016;15(3);e867). Patients received silodosin at 8mg/day (n=53) or silodosin at 8mg/day and propiverine at 20mg/day (n=51). Changes vs. baseline in IPSS, IPSS-QOL and OABSS at 12 weeks and 1 year were assessed. IPSS and OABSS significantly improved in both groups at 12 weeks and 1 year (p<0.01), with significantly greater improvements in IPSS-QOL and OABSS in the combined therapy group vs. monotherapy group at 1 year (p=0.01 and p=0.04, respectively). Both groups showed significant improvements in storage function, but the combined therapy resulted in significantly greater improvements in terms of the incidence of detrusor overactivity (DO) and maximum cystometric capacity (MCC). Urodynamic voiding function significantly improved in both groups at 12 weeks and 1 year after treatment without significant intergroup difference. None of the patients had urinary retention, and there were no significant differences in ADR between the two groups.

The combination of an AB and 5ARI is used to treat BPH (Matsukawa Y et al. Effects of withdrawing the alpha-1 blocker from alpha-1 blocker plus 5-alpha-reductase inhibitor combination therapy on patients with benign prostatic hyperplasia from the perspective of urodynamic study. Eur Urol Suppl 2016;15(3);e869). However, questions remain regarding how long combination therapy should be continued and whether therapeutic effects decrease if combination therapy is changed to single-drug therapy. A urodynamic study by Matsukawa et al to assess the effect of withdrawing AB therapy (silodosin 8mg/day) from combination therapy (silodosin 8mg/day and dutasteride 0.5mg/day) was carried out in patients with BPH. Combination therapy was administered to untreated BPH patients for 1 year, after which the patients were divided into two groups: Group A (n=57) who continued combination therapy and Group B (n=60) who continued with dutasteride 0.5mg/day alone. The changes in subjective symptoms using IPSS and OABSS and changes in storage and voiding function before and 1 year after the division of the patients into two groups were examined. There were no significant differences in changes in IPSS, OABSS and BOO11 between the two groups.

This urodynamic study concluded that the withdrawal of AB from combination therapy for BPH could be considered reasonable. However, the storage function tended to be worse after changing to single drug therapy. Therefore, it was suggested that withdrawal must be carefully performed for patients with storage dysfunction.
Men’s sexual health: Focus on premature ejaculation, hypogonadism and lower urinary tract and ejaculatory dysfunction

Very few controlled studies of long-term testosterone therapy in hypogonadal men are available (Haider A et al. Long-term effects on urinary function in hypogonadal men treated with testosterone undecanoate injections (TU) vs. untreated controls from a single urologist’s office: Real-life data from a registry study. *Eur Urol Suppl* 2016;15(3):e1005). A registry (n=656) was established to assess long-term effectiveness and safety of testosterone undecanoate injections (TU, 1,000mg/12 weeks) in a urological setting in comparison to an untreated hypogonadal control group. 360 men received parenteral TU (Group A) and 296 men opted against testosterone and served as controls (Group B). Median follow-up in both groups was 7 years. Measurements were taken at least twice a year, and 8-year data were analysed (Table).

**Men’s sexual health: Focus on premature ejaculation, hypogonadism and lower urinary tract and ejaculatory dysfunction**

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<tr>
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<th>GROUP A (TU)</th>
<th>GROUP B (TU)</th>
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<td>Baseline 8 years</td>
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<td>Total cholesterol (mg/dL)</td>
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<td>16-17 (p&lt;0.0001)</td>
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<tr>
<td>PV (mL)</td>
<td>28.2</td>
<td>31.1 (p=0.001)</td>
<td>34.5</td>
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<td>PVR (mL)</td>
<td>67.3</td>
<td>13.7</td>
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<td>International Index of Erectile function (IIEF)</td>
<td>18.51</td>
<td>25.94</td>
<td>26.47</td>
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**Men’s sexual health: Focus on premature ejaculation, hypogonadism and lower urinary tract and ejaculatory dysfunction**

Haider et al concluded that long-term testosterone undecanoate therapy in hypogonadal men resulted in significant improvement in urinary function vs. baseline and controls who experienced worsening independent of prostate size. Long-term TU was well tolerated and a high adherence rate suggested a high level of patient satisfaction.

**Men’s sexual health: Focus on premature ejaculation, hypogonadism and lower urinary tract and ejaculatory dysfunction**

5ARIs have sexual side effects, including erectile dysfunction (ED), loss of libido and ejaculatory dysfunction (Park HJ et al. Can concomitant dutasteride reduce the effect of testosterone replacement therapy in men with late-onset hypogonadism? A 24-week, randomized, parallel study. *Eur Urol Suppl* 2016;15(3):e1006). A 24-week, randomised, parallel study of the clinical outcomes in men age >40 years with symptomatic BPH with aging male symptoms (AMS) who were taking stable doses of AB 4 weeks before participation, examined the effect of dutasteride 0.5mg once daily plus a transdermal gel containing 10g testosterone (DT group, n=30) vs. the transdermal gel alone (T group, n=30). The primary outcomes were the change in the AMS score, sexual desire (Question 17, AMS score) and erectile function (IIEF). Secondary outcomes were post-treatment IPSS, peak urinary flow rate and PVR. Both groups showed significant improvements from baseline in all primary outcome parameters. However, there were no significant differences in the AMS total score (DT –5.2 vs. T –5.0; p=0.55), sexual desire (DT –2.5 vs. T –2.3; p=0.23) and IIEF-5 score (DT –2.1 vs. T –1.9; p=0.13) between groups. The extent of IPSS, Qmax and PVR improvement from baseline to 24 weeks was similar in both groups. PV decreased significantly in the DT group vs. the T group (DT –2.1 cc vs. T +0.6 cc, p<0.01).

This randomised, parallel study concluded that tadalafil plus testosterone was superior to tadalafil alone in improving LUTS in men with BPH and low testosterone levels.

**Men’s sexual health: Focus on premature ejaculation, hypogonadism and lower urinary tract and ejaculatory dysfunction**

This randomised, parallel study, conducted by Park et al, concluded that concomitant dutasteride did not reduce the effect of testosterone replacement therapy in men with late-onset hypogonadism.

**Men’s sexual health: Focus on premature ejaculation, hypogonadism and lower urinary tract and ejaculatory dysfunction**

Tadalafil is effective for treating LUTS secondary to BPH (Park HJ et al. Does concomitant testosterone replacement improve the response of tadalafil 5mg once daily in men with lower urinary tract symptoms? *Eur Urol Suppl* 2016;15(3):e1013). A randomised, parallel study conducted by Park et al in men aged ≥40 years with symptomatic BPH and T levels <300ng/dL investigated the effect of testosterone (T) transdermal gel (10g) in combination with tadalafil (5mg once daily) (n=44) vs. tadalafil alone (n=46) over 12 weeks. The primary outcomes were post-treatment IPSS, peak urinary flow rate and PVR. Secondary outcomes were changes in IIEF-EF domain scores, Global Assessment Questionnaire (GAQ) scores and Life Satisfaction Checklist (LSC) scores. There were no significant differences in the level of improvement of IPSS, Qmax and PVR between the treatment groups. However, there were significant greater improvements from baseline in the IPSS storage subscore, the IPSS-QOL score, IIEF-EF domain score, GAQ and LSC for tadalafil + T vs. tadalafil alone (p<0.01 for all). The ADR were similar to those of previous reported.
Prostate cancer screening and early detection

Although the main cause of LUTS is BPH, a small proportion of men have LUTS that is directly attributable to PCa. Digital rectal examination gives an evaluation of prostate size, which is relevant in particular to BPH management, and along with PSA testing is essential in differentiating clinically between BPH and PCa.

The validity of using PSA screening to identify patients with PCa has been in debate for some time. This was investigated by Arnsrud Godtman et al in an 18-year follow up of the Gothenburg screening trial (Arnsrud Godtman R et al. 18-year follow up of the Gothenburg randomized population-based prostate cancer screening trial. Eur Urol Suppl 2016;15(3);e87). The trial enrolled 20,000 men (10,000 to screening group and 10,000 to control group [no screening]) and found that screening for PSA every second year identified a greater cumulative PCa incidence and less cumulative PCa mortality in the screening group vs. the control group (14.2% vs. 9.8% [HR 1.51, 95%CI: 1.39,1.64] and 0.81% vs. 1.25% [HR 0.65, 95%CI: 0.49,0.86]), suggesting that PSA screening is worthwhile.

This study concluded that an organised PSA screening programme could increase PCa identification and effectively reduce PCa mortality.

Little is known about the association between family history and PSA among men of very young age. Herkommer et al analysed this relationship in the German PROBASE screening trial, which enrolled 5,818 45-year old men (Herkommer K et al. The association between family history and prostate-specific antigen from a large group of 45-year old men embarking on prostate cancer screening: Results from the PROBASE trial. Eur Urol Suppl 2016;15(3);e89). Men were randomised for PSA screening either at the time of enrolment or 5 years later. In the group screened at 45 years of age, 11.1% had ≥1 first-degree relative diagnosed with PCa. A significant relationship between family history and increased PSA levels was observed (p<0.001) (Table).

This is the largest study to date of 45-year old men to demonstrate higher PSA levels among men with a family history of PCa. This study supports current European and American recommendations for earlier screening among men with first-degree family history of PCa.

How PSA is discussed and who is likely to receive counselling regarding PSA screening can vary. This was analysed by Hanna et al using the latest 2014 Behavioural Risk Factor Surveillance System (BRFSS) dataset in 130,592 men aged ≥40 years without a history of PCa (Hanna N et al. Informed decision-making for prostate-specific antigen screening. Eur Urol Suppl 2016;15(3);e94). When patients were asked whether they had a discussion regarding the advantages or disadvantages of PSA screening, 58%, 28% and 60% stated having been counselled on the advantages, disadvantages or either, respectively.

In multiple-variable logistic regression analyses predicting the receipt of any informed decision-making, Black vs. White (OR=1.87), older men (OR=2.16), higher income (OR=1.34 and 1.59 for 25-50,000$/year and >50,000$/year, respectively) and education level (OR=1.54 and 2.40 for high school and college graduate, respectively) were identified as independent predictors (p<0.001). Patients from other race (defined as other than non-Hispanic White and Black) (OR=0.75) were less likely to receive counselling. As a result, sociodemographic characteristics including age, ethnicity, marital status, education, health status and income were significant independent predictors for receiving counselling (p<0.001).

This study concluded that disadvantages of PSA screening were less frequently discussed than the advantages and that there were important sociodemographic characteristics associated with PSA screening informed decision-making.
Plenary sessions
Aging and the lower urinary tract

In this plenary session, two state-of-the-art lectures addressed important questions regarding the causes and appropriate management of aging patients with LUTS/BPH.

Healthy LUT and ageing: A contradiction?

Dr Wein elegantly presented the multiple pathophysiological aspects of aging that can affect the urinary tract. He described how aging patients can expect changes such as altered bladder sensation, decreased contractility of the detrusor muscles, decreased urethral blood flow and sphincter atrophy. In addition, peripheral and central neurological changes as well as the aging endocrine system can impact on the urinary tract. The analogy Dr Wein painted was a picture of unpredictability, with the aging individual either sailing off peacefully into the sunset or facing a perfect storm of age-related urological complications. He explained how the morphological, metabolic, hormonal, environmental, physiological and pharmacological changes in the LUT, as well as changes in cerebral control and integration all play a potential role.

Dr Wein explained that an increase in the prevalence of both storage and voiding symptoms correlates with increasing age. Ischaemia and oxidative stress result from direct damage (including distension), followed by reperfusion injury, which in turn can lead to neurodegeneration4, inflammation4, and other functional abnormalities5,8. These oxidative changes can result in detrusor over- or under-activity2,4,5,6,7. Multiple pathological pathways can then impact on the urinary tract.

The cellular changes associated with aging are particularly interesting. These include the development of a dense band pattern in the detrusor muscle, with dense sarcolemmal and depleted caveolae8. The latter may cause a decrease in cellular signalling. These changes can be associated with DO, detrusor underactivity and BOO. The relationship between these structural and functional changes is unclear. Aging individuals may be asymptomatic, but may also present with a delayed desire to void resulting in a reduction of afferent nerve activity that can lead to early termination of detrusor contraction and decreased voiding efficiency.

Within the central nervous system (CNS), the insular cortex, hypothalamus, periaqueductal gray and pontine micturition centre are all involved in the voiding reflex4. The elderly may have underperfusion of the cerebral cortex, which could explain altered bladder sensation and urgency urinary incontinence, and an associated change in the central connectivity or peripheral bladder afferents. In addition, a decrease in vasopressin secretion is associated with increasing age and consequently an increased risk of NP.

The insight provided by this excellent plenary lecture was that multiple possible mechanisms can impact on the aging lower urinary tract. While this means there is currently no 'silver bullet' treatment, it makes sense that an approach using appropriate combination therapy would show incremental benefit over monotherapy.
Drug therapy in the elderly: Which are the good drugs?

Dr Wagg explained that, although there are many efficacious therapies available to treat LUTS, the evidence for these has largely come from studies that excluded the very elderly or high-risk patients. It is therefore necessary to extrapolate these data to the elderly patient population, which must take into account increased polypharmacy in these patients and a need for well-tolerated therapies. While elderly patients tend to be more adherent to therapies than younger patients, they also view urinary incontinence medication preferable to take ‘as needed’ rather than routinely. There have been a number of studies investigating the efficacy and tolerability of AM in older patients. One of the important safety factors addressed in these studies was the impact on cognition. Impact on cognition is affected by the ability of the AM to bind acetylcholine receptors (particularly M1) in the CNS, which depends upon the permeability of the blood-brain barrier (BBB). The tendency of the BBB in elderly patients is to be more ‘leaky’ than in younger patients, but is also influenced by the pharmacological characteristics of the drug (molecular size, lipophilicity and chemical changes in vivo) and whether or not the drug is a substrate for the p-glycoproteins, which actively transport the drug from the CNS. Oxybutynin is the most effective AM, it is also the one most likely to cross the BBB and affect cognitive function. The positive association between AM exposure and dementia over the long-term has been shown to correlate, not surprisingly, with higher daily doses.

The Fit for the Aged (FORTA) classification, introduced in 2008, has rated therapies in degrees of suitability for older patients. This approach classifies only three drugs used for LUTS as beneficial (category B, with proven or obvious efficacy in the elderly, but limited extent of effect or safety concerns), namely dutasteride, fesoterodine and finasteride (Table). Interestingly, other drug classes commonly used for the treatment of LUTS are listed under ‘Caution (category C)’ or ‘Don’t (category D)’ in elderly patients.

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<thead>
<tr>
<th>Absolutely (A)</th>
<th>Beneficial (B)</th>
<th>Caution (C)</th>
<th>Don’t (D)</th>
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<td>Trospium</td>
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*a* Indispensable drug, clear-cut benefit in terms of efficacy/safety ratio proven in elderly patients for a given indication

*b* Drugs with proven or obvious efficacy in the elderly, but limited extent of effect or safety concerns

*c* Drugs with questionable efficacy/safety profiles in the elderly, to be avoided or omitted in the presence of too many drugs, lack of benefits or emerging side effects; review/find alternatives

*d* Avoid in the elderly; omit first, review/find alternatives
Evolving concepts in the management of male LUTS/BPH

**Recordati sponsored symposium**

Saturday 12th March 2016

C Roehrborn, FR Cruz, F Fusco

This symposium addressed the diagnosis and treatment of LUTS/BPH, with a focus on AB therapy.

This symposium highlighted the increasing problem of LUTS/BPH due to increased life expectancy in the developed world. It was stated that from 2000 to 2005 the number of patients aged 65 years or older, suffering from BPH in the worldwide population increased by 11%. As a result, it is even more imperative to correctly diagnose and manage this condition. There are a number of global guidelines for the assessment of LUTS/BPH, which can be used as tools to categorise patients with complicated and uncomplicated LUTS. This can help to determine disease severity, appropriate treatment, predict outcome and prevent harm.

It was also noted that nocturia is a component of LUTS that can significantly impact on patient QOL. Professor Roehrborn explained that its causes are multifactorial, and it is defined as the interruption of sleep ≥1 times at night to void, which is preceded and followed by sleep. Nocturia is independently associated with increased morbidity and mortality.

One of the main tools for investigating the impact of LUTS on patient QOL is the IPSS. This tool incorporates a number of questions. However, Professor Roehrborn explained that the question relating to nocturia has been found to be ambiguous (Q7). The question asks, “In the past month how many times did you typically get up at night to urinate?” This confuses many patients, who do not realise the information needed is the average number of times they get up in a single night. For example, 1 out of 6 patients scored on the IPSS Q7 a 5 while the voiding log reported either no or 1-3 episodes only. Therefore, IPSS Q7 is not suitable for accurate nocturia assessment and many clinicians also use FVC.

Several therapies have been investigated for the treatment of nocturia. The CombAT trial, where the combination of dutasteride (5ARI) and tamsulosin (AB) has been shown to provide greater improvements and less worsening of nocturia compared with either dutasteride or tamsulosin as monotherapy over a period of 4 years was discussed. It was also explained that a fixed dose combination of the AM solifenacin plus tamsulosin has also been shown to be more effective than tamsulosin alone or placebo in the NEPTUNE trial. Although AB monotherapy overall appears to have a relatively weak effect on nocturia symptoms, a pooled analysis of three randomised controlled trials of silodosin, an AB with selectivity for the α1A receptor, showed a consistent and significant improvement in bothersome nocturia (≥2 nocturnal episodes) in men with LUTS/BPH. It was explained that the SiRE trial (silodosin 8mg every day/daily for 24 weeks) showed a lower prevalence of bothersome symptoms with FVC than with Q7 of the IPSS. Also, it was shown that monitoring fluid intake is important, as patients who increase their fluid intake will do less well on therapy. It is important to distinguish between patients with and without NP (defined as night time urine output >20% of the daily total in young adults and >33% in older adults), as silodosin has no effect on NP.

The urodynamic outcomes for AB treatment in patients with benign prostatic obstruction (BPO) are a matter of debate as only a small change in Qmax has been observed despite significant improvements in IPSS. A meta-analysis of 25 urodynamic studies showed a significant change with AB treatment versus control for the BOOI (p<0.0001), with the largest individual effect seen for silodosin versus other AB (-30.45 vs. -6.69 to -19.41). This is thought to be due to its selectivity for the α1A receptor. The reason why the change in Qmax is small is because the improvement in the BOOI is believed to be mainly due to the reduction in detrusor pressure at Qmax.

The use of AB monotherapy as a foundation drug for LUTS/BPH for any patient with a symptom severity score who
are bothered was discussed. It is acknowledged that the combination of AB and 5ARI is needed in men at risk of progression.23 This risk correlates with PSA level, which in turn has shown to directly correlate with PV.23 Randomised controlled studies (REDUCE24, MTOPS25) have shown that, in study populations, PV increases by around 4-5% per year and that this increase is most dependent on baseline PSA levels. With a low PSA (<1.5ng/mL) at baseline, using PSA as a surrogate marker for PV, the annual growth rate of the prostate would be expected to be around 1mL/year or 2-3%. This means that a 30mL prostate would increase from 30mL to 40mL in 10 years. In other words, the PSA value stratifies expected prostate growth and therefore risk of progression. This would suggest that initial therapy decisions should be based on PSA level regardless of age, symptom severity and Qmax. Patients with a PV <40mL at baseline can be successfully treated with AB monotherapy.26 Conversely, larger prostate glands with higher PSA values should be treated using 5ARI plus AB combination therapy.23

It was explained that, in nearly all published studies, storage symptoms account for about 40% and voiding symptoms for about 60% of total symptom burden. Therefore, the average patient presenting for medical therapy will not benefit in total IPSS and voiding symptoms from the addition of antimuscarinics (SATURN and NEPTUNE: except in patients with very high voiding and urgency, who may benefit from addition antimuscarinics). The additive effect of combining an AB and phosphodiesterase-5 inhibitor is only modest at best (from small non-placebo controlled studies).

### Understanding personalised medical management for BPH patients at risk of progression

**GSK sponsored symposium**

Sunday 13th March 2016

P Hammerer, A Tubaro, C Roehrborn

This symposium discussed the personalised medical management of BPH taking into consideration patients expectations and robust evidence supporting a risk of progression stratification approach.

BPH is considered as one of the most important factors in older men contributing to the pathophysiology of LUTS, which can have a significant impact on patient quality of life in those with moderate-to-severe symptoms. However, each patient experiences his symptoms differently, and the degree to which the patients are bothered by their symptoms may vary.

For a patient presenting with LUTS, it is important to consider differential diagnoses, as there are other causes besides BPH. Today there are well-recognised factors used to help to establish the risk profile for disease progression in patients with BPH, which enable better-informed decisions and optimal medical management. These risk factors include increasing age, LUTS severity, reduced urinary flow rate, enlarged prostate and increased PSA.

To ensure optimal management of BPH, it is important to listen to the patients’ concerns and to explain and reassure them regarding their condition and how it can be best managed according to their individual needs. Importantly, the right patient expectations should be agreed from the outset and counselling is critical. The latter is particularly important, as data was presented to show that adherence to BPH medical treatment is only around 30% after 1 year. Low adherence levels are associated with increased hospitalisation and need for surgery. The reasons for lack of adherence are varied, including lack of symptom resolution or their improvement and ADRs. In order to improve adherence, the importance of counselling patients to stay on therapy even if symptoms improve and the need to regularly follow up patients to review their medical therapy was emphasised. AB, 5ARI and their combination are a recognised standard medical treatment for patients with bothersome LUTS due to BPH. Monotherapy with AB has been shown to be associated with a greater risk of hospitalisation versus 5ARI alone or in combination. There are also differences in the degree of efficacy between individual therapies. The 5ARI dutasteride has been shown to be more effective than finasteride in reducing BPH-related hospitalisation (p=0.0025).27

In the long term, AB do not decrease the risk of acute urinary retention (AUR) and need for surgery, as they have no effect on PV, which has been observed in clinical practice to continue to increase at a rate of around 4-5%/year. Therefore, it was suggested that combination therapy with a 5ARI should be considered.

In the CombAT trial, a combination of dutasteride 0.5mg and tamsulosin 0.4mg resulted in significant improvements in LUTS and QOL, and a reduction in the risk of AUR or BPH-related surgery compared to tamsulosin monotherapy at 4 years. These improvements were observed regardless of baseline PSA levels.28

In the CONDUCT trial, which enrolled treatment-naïve moderate BPH patients, a fixed dose combination of dutasteride 0.5mg and tamsulosin 0.4mg plus lifestyle advice resulted in rapid and significant symptom improvement, and reduced the risk of clinical progression over a 2-year period versus watchful waiting (WW) with escalation to tamsulosin monotherapy.29 Further analysis of the study population found that some men with moderate symptom severity at risk for progression did well with lifestyle advice alone over 2 years. The most relevant distinguishing characteristic was a lower
BII suggestive of less bother from LUTS/BPH. Guidelines have long since recommended conservative management for men with mild LUTS and those with moderate LUTS who are not bothered, a recommendation supported by the CONDUCT study findings.

Evidence from the CombAT and CONDUCT trials support the use of dutasteride plus tamsulosin in combination for BPH patients at risk of progression to improve symptoms, slow disease progression and improve QOL.

Unravelling the mysteries of male LUTS to aid individualised therapy

Astellas sponsored symposium
Monday 14th March 2016
M Oelke, T Bschleipfer, J Rees, FV der Aa

LUTS are multifactorial and occur due to a complex interaction between the bladder and the outflow tract. Factors that affect the function of the bladder, prostate and urethra can contribute to LUTS. The prevalence of LUTS increases with age and is associated with a significant reduction in patient QOL. LUTS may be variably characterised by storage (irritative), voiding (obstructive) and post-micturition symptoms. Of these, storage symptoms (frequency, urgency and nocturia) tend to be the most bothersome.

It was explained that it is important to distinguish between LUTS associated with normal aging (BPH) versus those associated with abnormal processes resulting from BOO secondary to BPH. With age, all men experience an increase in PV and a decrease in Qmax, believed to be caused by structural changes in the bladder, including muscle atrophy, collagenosis and appearance of dense band patterns associated with incomplete dysjunction patterns. In contrast, abnormal changes resulting from BOO include morphological and functional modifications in the epithelium, smooth muscle cells in the bladder wall, in the extracellular matrix, as well as in the neuronal network, which in turn result in detrusor dysfunction.

Treatment of LUTS due to BPH aims at improving patient QOL by reducing symptom-related bother. Treatment of BOO aims at relieving BPH complications, but also aims at relieving LUTS associated with detrusor dysfunction.

It was suggested that the management of LUTS should take a holistic approach rather than take an urocentric approach. In the UK, Dr Rees stated that patients presenting with LUTS are largely managed in primary care unless complications occur. Initial assessment involves talking to patients about their symptoms and to what degree they bother them, as well as asking them to complete a FVC, which has been found to be more practically useful than undertaking an IPSS. The biggest concern for men presenting with LUTS is the risk of PCa, and so a determination of the PSA level is often offered to alleviate this concern but also to determine the risk of progression and to direct medical management of BPH. The guidelines are conflicting with regards recommendations for measuring PVR at the initial assessment. In primary care, measurement of PVR when a patient first presents with LUTS has not been found to be useful.

With regards to medical management, Dr Rees went on to discuss how it is important to reassure patients that LUTS/BPH is a part of the natural aging process and to manage their expectations with regards to treatment. Lifestyle advice and identifying comorbidities, such as ED are important, as LUTS/BPH is often a component of a wider metabolic syndrome.

In real-life practice, there is a difference between statistically significant and clinically significant medical treatment. In clinical trials, combination therapy has been shown to be statistically significant. However, for this to be interpreted as a change in symptoms noticeable by patients in clinical practice, a minimally important difference of at least 3 points on the IPSS is needed.

In the clinical management of LUTS/BPH, there is also the question of AB withdrawal to be considered. In the SMART trial, men with lower IPSS did not notice a difference in their symptoms with AB withdrawal, suggesting these patients can be considered for AB withdrawal.

Primary treatment is symptom focussed and can be determined according to whether patients experience symptoms associated with voiding, storage, post-micturition, or a combination of these.

The treatment strategy for LUTS/BPH can be divided into WW, medical treatment and surgery, according to symptoms, patient needs and preferences. WW, including lifestyle advice, is recommended for patients with mild symptoms or moderate symptoms that are not causing them bother. The majority of these patients are satisfied with this type of management at 5 years.

Regardless of PV, all patients with moderate to severe LUTS should be offered medical therapy.

For those at risk of progression, combination therapy with AB and 5ARI is the recommended approach. It was suggested that AM with or without an AB should be considered in patients with storage symptoms unless they have a high PVR.
Abbreviations

AB - α1-blocker
ADRs - Adverse drug reactions
AMS - Aging male symptoms
AM - Antimuscarinics
5ARI - 5-α-reductase inhibitor
AUR - Acute urinary retention
BRFSS - Behavioural Risk Factor Surveillance System
BPH - Benign prostate hyperplasia
BPO - Benign prostatic obstruction
BOO - Bladder outlet obstruction
BOOI - Bladder outlet obstruction index
BBB - Blood-brain barrier
BMI - Body mass index
BII - BPH impact index
CV - Cardiovascular
CNS - Central nervous system
CVR - CV risk
DO - Detrusor overactivity
ED - Erectile dysfunction
FORTA - Fit for the Aged
FVC - Frequency-volume charts
GAQ - Global Assessment Questionnaire
ICIQ-N - International Consultation on Incontinence Questionnaire-Nocturia
IEF - International Index of Erectile Function
IPSS - International Prostate Symptom Score
LSC - Life Satisfaction Checklist
LUT - Lower urinary tract
LUTS - Lower urinary tract symptoms
MCC - Maximum cystometric capacity
Qmax - Maximum flow rate
Qd - Every day/daily
MCIC - Minimal clinically important change
MIRA - Mirabegron
N-QOL - Nocturia QOL
NP - Nocturnal polyuria
OABSS - OAB Symptom Score
OAB - Overactive bladder
PSQI - Pittsburgh Sleep Quality Index
PVR - Post-void residual urine
PCa - Prostate cancer
PV - Prostate volume
PSA - Prostate-specific antigen
QOL - Quality of life
WW - Watchful waiting

References

5 Young JS et al. BJU Int 2014;111:355-361.
15 Roehrborn CG. Rev Urol 2005;7(Suppl 9); S3-S14.
20 Novara G et al. BJU Int 2014;114:427-433
Duodart Abbreviated PI

**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.

**Dosage and administration:** The recommended dose of Duodart is one capsule (0.5 mg dutasteride/ 0.4 mg tamsulosin) taken orally approximately 30 minutes after the same meal each day. The capsules should be swallowed whole and not chewed or opened.

For full information please refer to MOH approved Prescribing Information.

**Succinct safety information:**

**Contraindication:** women and children and adolescents. patients with hypersensitivity to dutasteride, other 5-alpha reductase inhibitors, tamsulosin (including tamsulosin-induced angio-edema), soya, peanut or any of the other excipients. Patients with severe hepatic impairment. patients with a history of orthostatic hypotension.

**Warning and Precaution for use:** Cardiac failure In two 4-year clinical studies (REDUCE & CombAT), the incidence of cardiac failure was higher among subjects taking the combination of Avodart and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. The incidence in both trials was low (≤1%).

Prostate cancer (PCa) and high-grade tumours (HGT): In the REDUCE study The percentage of subjects diagnosed with gleason 8-10 cancers was consistent across study time periods (Years 1-2 and Years 3-4) in the dutasteride group (0/5% in each time period), while in the placebo group, the percentage of subjects diagnosed with gleason 8-10 cancers was lower during Years 3-4 than in Years 1-2 (<0.1% versus 0.5% respectively). No HGT has been seen in 2-year follow up to the REDUCE study. The relationship between dutasteride and high grade prostate cancer is not clear.

Hepatic impairment: Dutasteride was not studied in patients with liver disease.

Breast cancer: In the 2-year clinical trials, and in the 2-year, open label extension, there were 2 cases of breast cancer reported in dutasteride-treated patients, and 1 case in a placebo-treated patient. Currently it is not clear if there is a causal relationship between the occurrence of male breast cancer and long term use of dutasteride.

Orthostatic hypotension: 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.

**Strong Inhibitors of CYP3A4**
Tamsulosin containing products, including duodart, should not be co-administered with strong CYP3A4 inhibitors (e.g. ketoconazole) as this can significantly increase tamsulosin exposure.

Inhibitors of CYP2D6 and moderate inhibitors of CYP3A4
Tamsulosin containing products, including duodart, should be used with caution when co-administered with moderate inhibitors of CYP3A4 (e.g. erythromycin), strong (e.g. paroxetine) or moderate (e.g. terbinafine) inhibitors of CYP2D6, or in patients known to be poor metabolizers of CYP2D6, as there is a potential for significant increase in tamsulosin exposure. Tamsulosin: In addition atrial fibrillation, arrhythmia, tachycardia and dyspnoea have been reported in association with tamsulosin use. The frequency of events and the role of tamsulosin in their causation cannot be reliably determined.

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**Adverse reactions:**
- Nervous system disorders (dizziness)
- Cardiac disorders (Cardiac failure (composite term))
- Reproductive system and breast disorders, Psychiatric disorders, Investigations (Impotence, Altered (decreased) libido, Ejaculation disorders, Breast disorder).

These sexual adverse events are associated with dutasteride treatment (including monotherapy and combination with tamsulosin). These adverse events may persist after treatment discontinuation. The role of dutasteride in this persistence is not known.

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