

## What's new in functional urology research?

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### The addition of mirabegron to solifenacin for incontinent overactive bladder (OAB) results in an acceptable cardiovascular profile

Oral pharmacotherapies for the treatment of OAB include antimuscarinics such as solifenacin and the beta-3 adrenoceptor ( $\beta$ 3AR) agonist mirabegron. Although both classes of drugs are similarly effective, the antimuscarinics have been associated with bothersome anticholinergic side effects, such as dry mouth and constipation, that can lead to treatment discontinuation. The randomized, double-blind, multicentre, phase 3 BESIDE study showed that add-on therapy with mirabegron 50 mg for 12 weeks provided additional improvements in OAB symptoms for incontinent OAB patients who experience an insufficient response to solifenacin 5 mg compared with solifenacin 5 mg or 10 mg monotherapy.<sup>1</sup> Since antimuscarinics and  $\beta$ 3AR agonists are both potentially autonomically active, the BESIDE investigators examined cardiovascular outcomes in this study population, and reported these results at EAU 2016.<sup>2</sup> Key parameters of blood pressure and pulse rate were assessed at screening, baseline, and intervals throughout the study. Electrocardiogram (ECG) results were also assessed at screening, baseline, and end of study. No clinically meaningful differences in blood pressure or heart rate were observed between the treatment groups, and there were no significant changes in ECG properties. These results provide some assurance that the addition of mirabegron to solifenacin in patients with incontinent OAB who have an inadequate response to solifenacin does not increase risk of cardiovascular adverse events.

### $\beta$ 3ARs may be expressed in sensory nerves

The  $\beta$ 3AR agonist mirabegron has long been thought to ameliorate symptoms of OAB, such as urinary urgency or urgency incontinence, by targeting the  $\beta$ 3AR and causing detrusor muscle relaxation. However, it has been suggested

that these therapies may also reduce activity in sensory nerves. Immunohistochemistry of cadaveric organs was conducted by a group from Portugal and the U.K., showing that immunoreactivity for  $\beta$ 3AR was present throughout the human bladder in both the mucosa in nerve fibres intermingled on the connective tissue and in the muscular layer, on nerve fibres present along smooth muscle bundles.<sup>3</sup> Surprisingly, no immunoreaction was detected in smooth muscle cells, suggesting that this is not the therapeutic target for  $\beta$ 3AR agonists. The hypothesis that the therapeutic effects of  $\beta$ 3AR agonists actually occur through modulation of the bladder neural circuits rather than a direct effect on smooth muscle cells warrants further exploration.

### Botulinum toxin type A effective in decreasing urgency urinary incontinence in patients with idiopathic OAB

Studies comparing the effectiveness of botulinum toxin type A and anticholinergics for the treatment of urgency urinary incontinence are lacking. Everaert, on behalf of colleagues from other countries, presented results of a prospective, multicentre, randomized, controlled trial evaluating the efficacy and safety of botulinum toxin type A 100 U or solifenacin 5/10 mg vs. placebo in 356 solifenacin-naive patients with idiopathic OAB and urinary incontinence who were inadequately managed by one or more anticholinergic agent.<sup>4</sup> At study entry, patients reported an average of 4.94 urge incontinence episodes (UIE)/day at baseline. After 12 weeks of treatment, daily UIE were significantly reduced by both botulinum toxin type A and solifenacin; however, these reductions were significantly greater with botulinum toxin type A (Table 1). The proportions of patients who achieved 100%, 75% or higher, and 50% or higher reductions in daily UIE were also higher among botulinum- and solifenacin-treated patients than placebo-treated patients. Again, these rates were higher among botulinum-treated patients than solifenacin-treated patients — significantly so for reductions of 50% or higher and 75% or higher. No new safety signals were observed during the study.

**Table 1. Change from baseline in urinary incontinent episodes (UIE)/day and proportions of patients achieving 100%, 75% or greater, and 50% or greater reductions in UIE<sup>a</sup>**

Parameter, n (%)	Botulinum toxin type A 100 U (n=145)	Solifenacin 5/10 mg (n=151)	Placebo (n=61)
LS mean change from baseline in UIE/day	-3.19 <sup>a,b</sup>	-2.56 <sup>a</sup>	-1.33
Proportion of patients achieving 100% UIE reduction	33.8% <sup>a,c</sup>	24.5% <sup>d</sup>	11.7%
Proportion of patients achieving ≥ 75% UIE reduction	55.2% <sup>a,e</sup>	43.0% <sup>f</sup>	21.7%
Proportion of patients achieving ≥ 50% UIE reduction	77.2% <sup>a,g</sup>	64.9% <sup>a</sup>	33.3%

LS: Least squares

<sup>a</sup>p<0.001 vs. placebo; <sup>b</sup>p=0.022 vs. solifenacin; <sup>c</sup>p=0.107 vs. solifenacin; <sup>d</sup>p=0.028 vs. placebo; <sup>e</sup>p=0.047 vs. solifenacin; <sup>f</sup>p=0.003 vs. placebo; <sup>g</sup>p=0.025 vs. solifenacin.

### Mirabegron improves nocturia and nocturia-associated quality of life in affected women

Nocturia can negatively impact quality of sleep, mood, and overall health. However, limited options are available to treat this common, bothersome symptom. Yoshida and colleagues from Japan presented results of their prospective, multicentre study evaluating the effects of mirabegron 50 mg/day on nocturia, nocturia-associated quality of life (QOL) and sleep quality in 60 female patients with OAB and nocturia.<sup>5</sup> After 12 weeks of treatment, mirabegron significantly improved total International Prostate Symptom Score (IPSS), QOL index, voiding symptoms and storage symptoms, as well as nocturnal frequency, nocturnal urine volume per void, urine volume of the first nocturnal voiding and nocturia-QOL scores. Mirabegron also increased hours of undisturbed sleep, from 160.6 to 203.8 minutes. In addition, Pittsburgh Sleep Quality Index scores were improved significantly after treatment. These preliminary data suggest that mirabegron should be evaluated further to explore its effects on nocturia and QOL.

### The addition of desmopressin to alpha-blocker therapy is effective and well-tolerated in men with persistent nocturia

Alpha-blockers have been used to treat symptoms of nocturia in men, resulting in measurable, albeit modest, improvements in symptoms related to bladder outlet obstruction. Recently, there has been increased interest in the use of desmopressin, a synthetic analogue of arginine vasopressin, to treat this bothersome condition. A group of researchers from Korea investigated the efficacy and safety of desmopressin add-on therapy for men with persistent nocturia despite treatment with an alpha-blocker for lower urinary tract symptoms (LUTS).<sup>6</sup> This placebo-controlled study enrolled men 40–65

years of age with LUTS who had been taking an alpha-blocker for a minimum of eight weeks and who were experiencing nocturia two or more times per night. The men were randomly assigned to treatment with either desmopressin 0.2 mg add-on therapy (n=47) or placebo (n=39). Men who received desmopressin add-on therapy experienced significantly greater reductions in nocturnal urine volume (-283.6 vs. -112.6; p<0.001), Nocturnal Polyuria Index (NPI) (-13.9 vs. 5.9; p=0.001), IPSS total score (-5.2 vs. -2.5; p=0.042), IPSS Nocturia score (-1.4 vs. -0.6; p=0.004), and International Consultation on Incontinence Questionnaire-Nocturia (ICIQ-N) score (-3.3 vs. -1.6; p=0.001). There were no significant differences in adverse events between the two groups. Interestingly, there were no significant differences between the two groups with respect to patients' perceptions of treatments, with similar proportions perceiving "much benefit" or feeling "very satisfied" with the treatment. However, significantly more patients treated with desmopressin add-on therapy were "very willing to continue treatment" (82.9% vs. 61.5%; p=0.025), suggesting that patients tolerated the combination therapy well.

### Prostatic urethral lift offers rapid, durable improvements in LUTS with minimal adverse effects

The LIFT study was a prospective, randomized study comparing prostatic urethral lift (n=140) with sham procedure (n=66) in men with symptomatic LUTS in 19 centres across the U.S., Canada, and Australia. At three months, the urethral lift outperformed sham procedure, with an 88% reduction in IPSS compared with sham (p=0.003).<sup>7</sup> Medium- to long-term outcomes from the LIFT study were presented at EAU 2016,<sup>8</sup> and showed that this response remained relatively persistent throughout four years of followup. After four years, IPSS remained improved by 41% compared with baseline, peak flow remained improved by 62% compared with baseline, and 86.4% of patients still did not require additional treatment for their LUTS symptoms. This high-quality, randomized study highlights several advantages of the prostatic urethral lift, including rapid, durable symptom relief and preservation of sexual function. Durability will continue to be assessed through protocol-driven followup through to five years.

### Urodynamics remain an important tool for identifying bladder outlet obstruction

Voiding function is often defined by the bladder outlet obstruction index (BOOI) and bladder contractility index (BCI). To establish whether there is a relationship between free flow (FF) at the maximum flow rate and these two indices, a group from the Bristol Urological Institute in the U.K. retrospectively analyzed 1717 men who underwent both FF

and pressure/flow studies in their institution between 2010 and 2015, with similar voided volumes recorded for both measures.<sup>9</sup> Among men with a FF of less than 10 mL/s, 60% were obstructed; however, surprisingly, 15% were not obstructed. Conversely, 65% of men with a FF of more than 15 mL/s were unobstructed as expected, but 15% were obstructed. There was no association between FF and BCI, but the majority of men were categorized as having normal BCI. These results show that, regardless of the FF cut-point, there are a significant number of false negatives and false positives for obstruction, underscoring the importance of considering invasive urodynamics before embarking on prostate de-obstructing surgery.

### Adverse life events are associated with depression in men with LUTS

LUTS and depression commonly coexist in elderly men, negatively impacting QOL. Using data from the multicentre, population-based European Male Ageing Study, researchers sought to further clarify the nature of this relationship by evaluating adverse life events (ALEs) as potential moderators and the inflammatory reaction as an underlying biological mechanism.<sup>10</sup> Gacci and colleagues reported their results from 3369 men who were assessed by means of several self-reported questionnaires, including the IPSS, the Beck's Depression Inventory-II (BDI-II), and the Adverse Life Events Scale. Information was also collected about their general health, lifestyle, and medical comorbidities. Biological markers, including prostate-specific antigen (PSA), testosterone, and C-reactive protein were recorded.

BDI scores were strongly associated with the IPSS total score ( $R^2$  0.44;  $\beta=0.13$ ;  $p<0.001$ ), as well as with the IPSS voiding score (Spearman rho 0.26;  $p<0.001$ ) and storage (Spearman rho 0.25;  $p<0.001$ ) subscales. Moreover, having at least one ALE was associated with a higher risk of developing LUTS compared with having no ALE (OR 1.28, 95% CI 1.09–1.50;  $p=0.002$ ), and the LUTS-depression

association increased as a function of the number of ALEs ( $F=22.62$ ;  $b=0.061$ ;  $p<0.001$ ). C-reactive protein was found to facilitate the association between LUTS and depression, suggesting activation of the central inflammatory signaling as a biological pathway underlying the association. These results serve as a caution that men with LUTS and a history of ALEs may be vulnerable to depressive symptoms.

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