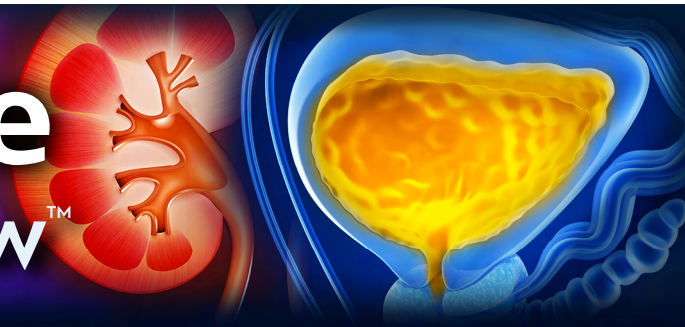


# Continence Research Review™



Making Education Easy

Issue 13 - 2024

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- Continence problems and mental health in adolescents from a UK cohort
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- Serum testosterone and dihydrotestosterone for incidence and progression of LUTS
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- Efficacy and safety of an onabotulinumtoxinA injection paradigm for refractory OAB
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- Injection site number and outcomes of intradetrusor onabotulinumtoxinA for OAB

### Abbreviations used in this issue:

AE = adverse event; BPH = benign prostate hyperplasia;  
DRA = detrusor relaxing agent; OAB = overactive bladder;  
LUTS = lower urinary tract symptoms; NDO = neurogenic detrusor overactivity.

## Welcome to issue 13 of Continence Research Review.

In this month's issue, we cover a series of studies providing comprehensive insights into various aspects of continence research. These include the therapeutic benefits and safety of oral detrusor relaxing agents for neurogenic detrusor overactivity, mental health considerations for adolescents with continence problems, and the intricate relationship between hormonal levels and lower urinary tract symptoms. Additionally, we include a series of studies on the efficacy and safety of onabotulinumtoxinA for overactive bladder syndrome. We conclude this month's issue with a study utilising functional MRI to identify subtypes in the overactive bladder during bladder filling; this study emphasised the role of sensorimotor-prefrontal connectivity in those with higher urinary symptoms.

We hope that you enjoy this month's issue of Continence Research Review, and as always we look forward to receiving your feedback.

Best regards,

**Associate Professor Bill Lynch**

[bill.lynych@researchreview.com.au](mailto:bill.lynych@researchreview.com.au)

### Detrusor relaxing agents for neurogenic detrusor overactivity

**Authors:** Zhou Z et al.

**Summary:** This study aimed to assess the therapeutic benefits and safety of oral detrusor relaxing agents (DRA) in treating neurogenic detrusor overactivity (NDO). A comprehensive search identified 23 randomised controlled trials involving 1697 patients. Compared to a placebo, oral DRAs demonstrated clinical benefits but exhibited more adverse events (AEs) in treating NDO. Subgroup analysis revealed that antimuscarinics improved urodynamic and bladder diary outcomes but had higher rates of AEs like xerostomia. Mirabegron showed improvements with fewer bothersome side effects. Bayesian network meta-analysis indicated no superiority or inferiority among antimuscarinics or mirabegron. Overall the study concluded that, oral DRAs exhibited therapeutic efficacy, but the choice between antimuscarinics and mirabegron should consider their specific benefits and side-effect profiles in managing NDO.

**Comment:** Systematic reviews are always helpful in summarising and collating data to make better-informed clinical decisions. This review is useful in reinforcing that there are similar symptomatic benefits from both antimuscarinics and Mirabegron (the only beta-3 agonist available for comparison in this review). The latter has fewer side effects. The conclusion that further random controlled trials are required is justified. Still, I feel it probably does support using Mirabegron as a first-line agent in appropriate circumstances, even if the evidence is somewhat limited.

**Reference:** *BJU Int.* 2024;133:25-33

[Abstract](#)

### Continence problems and mental health in adolescents from a UK cohort

**Authors:** Gordon K et al.

**Summary:** This prospective cohort study aimed to explore the link between incontinence/lower urinary tract symptoms (LUTS) and mental health problems in adolescents. They analysed a population-based sample of 7,332 young people, the study found that daytime wetting and voiding postponement exhibited the strongest associations with mental health issues. All incontinence subtypes/LUTS were linked to increased odds of generalised anxiety disorder, higher anxiety scores, common mental disorders, depression, depressive symptoms, self-harm thoughts, and disordered eating. The associations remained significant after adjusting for various factors. However, the study's limitations include a lack of generalisability to certain demographic groups and non-UK populations. Overall, the findings suggest a noteworthy connection between continence issues in adolescence and adverse mental health outcomes.

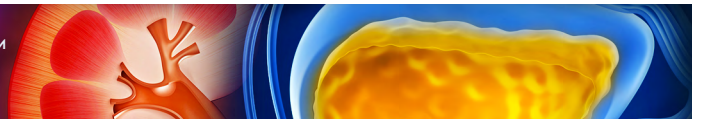
**Comment:** I think this study warrants attention in that it provides objective data on what, I suspect, we all thought was a self-evident truism. Incontinence is a significant issue that profoundly affects well-being and quality of life. The young (especially adolescents in their formative years) feel the social implications even more profoundly. The association with mental health problems highlights even further the need for attention to be given to this area of urological and general health.

**Reference:** *Eur Urol.* 2023;84:463-70

[Abstract](#)



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## Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia

**Authors:** Sandhu JS et al.

**Summary:** This American Urological Association Guideline amendment focuses on evidence-based management of male LUTS secondary to benign prostatic hyperplasia (BPH). The Minnesota Evidence Review Team thoroughly searched relevant studies, updating the guideline in 2023 to include literature from September 2020 to October 2022. Strength ratings (A, B, C) were assigned based on the evidence supporting strong, moderate, or conditional recommendations. Changes to the guideline include updated information on combination therapy, photoselective vaporisation, water vapour thermal therapy, laser enucleation, and prostatic artery embolisation. A new statement on temporarily implanted prostatic devices was added, and information on transurethral needle ablation and transurethral microwave thermotherapy was moved to the background section. The guideline aims to serve as a valuable reference for clinicians managing LUTS/BPH.

**Comment:** A very useful update on current approaches to the management of BPH with particular reference to drug combinations and including newer interventional techniques. A level of evidence is always handy when assessing the utilisation of various regimes. This is essential for all urologists – little more to be said.

**Reference:** *J Urol.* 2024;211:11-9

[Abstract](#)

## Serum testosterone and dihydrotestosterone and incidence and progression of lower urinary tract symptoms

**Authors:** Daniels JP et al.

**Summary:** This study aimed to investigate the relationship between serum testosterone or dihydrotestosterone levels and the incidence or progression of LUTS in men. Analysing data from the REDUCE trial, involved 3009 asymptomatic men and 2145 symptomatic men, the study found no evidence to support the hypothesis that elevated serum testosterone or dihydrotestosterone is a risk factor for LUTS incidence in asymptomatic men or LUTS progression in symptomatic men. The analysis, conducted using Cox models and adjusting for various factors, revealed no significant associations, and the results were consistent across both dutasteride and placebo arms. Therefore, this study challenges the previously suggested link between serum androgens and the development or worsening of lower urinary tract symptoms in middle-aged men.

**Comment:** This further analysis of the REDUCE data provides relevant information for both patients and physicians. Higher (and lower) testosterone and dihydrotestosterone levels have no effect on lower urinary tract symptoms and no effect on PSA, prostate volume or IPSS. There was no association with progression on any parameter either. Therefore, the physician need not be concerned with testosterone influencing symptomatic or physical parameters of BPH. Serum testosterone probably has little use in BPH research, though, of course, tissue androgen levels may be a different matter.

**Reference:** *J Urol.* 2024;211:101-10

[Abstract](#)

## Naturalistic bladder filling reveals subtypes in overactive bladder syndrome that differentially engages urinary urgency-related brain circuits.

**Authors:** Mawla I et al.

**Summary:** This study aimed to investigate the association between brain function and urinary urgency in participants with OAB. Using functional MRI scans during a bladder-filling paradigm, participants rated urgency levels. Latent class trajectory models identified two subtypes: OAB-1 and CON-1 (unresponsive to bladder filling) and OAB-2 (highly responsive, mostly OAB participants). OAB-2 individuals had significantly higher urinary symptoms but not pain or psychosocial measures. Neuroimaging analysis revealed differences in brain network connectivity between subtypes, with OAB-2 showing distinct changes related to bladder filling and voided volume. Sensorimotor to dorsomedial/dorsolateral prefrontal connectivity emerged as a key factor mediating the relationship between voided volume stimulus and urgency perception in OAB-2. This study highlights the existence of different OAB subtypes with varying pathophysiological mechanisms, particularly emphasising the role of sensorimotor-prefrontal connectivity in those with higher urinary symptoms.

**Comment:** This is a very exciting study. It identified patients complaining of symptoms of an overactive bladder and recruited a control group for comparative analysis. The study was conducted in the setting of “natural” bladder filling and resulted in identifying two OAB sub-types, with one group identifying little urgency change (OAB-1) with bladder volume whilst the other reported marked urgency change (OAB-2). OAB-1 and controls had different functional MRI results than the OAB-2 group, with good correlations reported. It seems sensorimotor-prefrontal connectivity is a key locus in those with higher urgency profiles. Identification of a brain segment functioning differently in the OAB-2 group will potentially allow directed research into that area and, hopefully, the development of more effective agents for the management of the overactive bladder.

**Reference:** *J Urol.* 2024;211:111-123

[Abstract](#)

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## RESEARCH REVIEW™

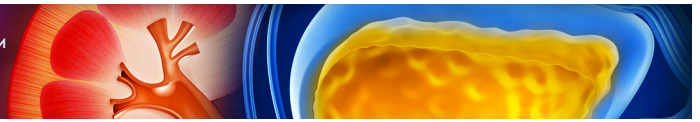
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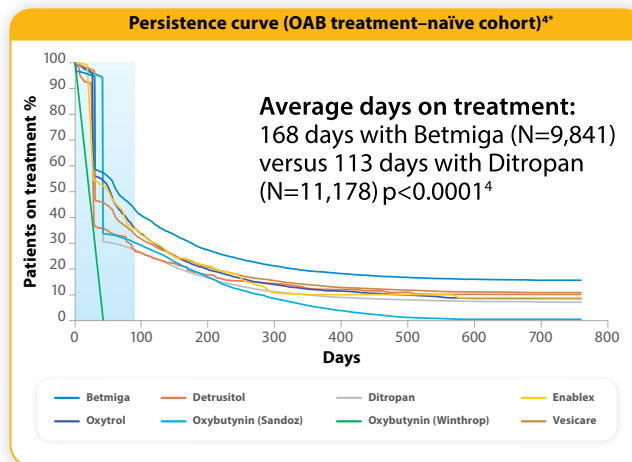


Figure adapted from IQVIA NostraData LRx<sup>4</sup>

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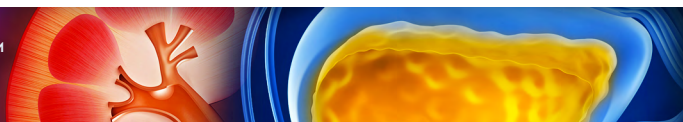
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**Abbreviation:** OAB, overactive bladder.

**References:** **1.** Betmiga (mirabegron) Australian Approved Product Information, 14th July 2021. **2.** Yeowell G, Smith P, Nazir J, *et al.* Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB): a systematic literature review. *BMJ Open* 2018;8:e021889. **3.** Conjoint USANZ and UGSA Guidelines on the Management of Adult Non-Neurogenic Overactive Bladder. 2015. Available online: <https://www.usanz.org.au/info-resources/position-statements-guidelines/management-adult-non-neurogenic-overactive-bladder> (accessed March 2022). **4.** IQVIA NostraData LRx. December 2020.

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## Longitudinal fluctuations in treatment response after onabotulinumtoxinA and sacral neuromodulation for refractory urgency incontinence

**Authors:** Hendrickson WK et al.

**Summary:** This study aimed to compare treatment response fluctuations over six months between onabotulinumtoxinA and sacral neuromodulation for urgency incontinence using Markov models. They analysed data from a randomised trial with 357 participants, the study found that, after onabotulinumtoxinA, 61% reported persistent objective success, compared to 51% with sacral neuromodulation. OnabotulinumtoxinA recipients had lower 30-day transition probabilities from objective and subjective success to failure. Over six months, 2 in 5 women experienced symptom fluctuations, with onabotulinumtoxinA showing a lower likelihood of transitioning from success to failure within 30 days compared to sacral neuromodulation. Both treatments had a 20%-40% probability of women returning to subjective and objective success after failure. Markov's models provided valuable insights into how symptoms fluctuate following urgent incontinence treatment.

**Comment:** This is an intriguing study, if somewhat difficult to follow (well, at least to me) with regards to Markov modelling. However, it does provide some important insights into the treatment of urgency incontinence with both onabotulinumtoxinA and sacral neuromodulation. Firstly, a percentage of patients move from treatment success to failure over a 30-day transition period, with the onabotulinumtoxinA patients being slightly less likely to be in this group. Similarly, a percentage of patients move from failure to success. These fluctuations were both subjective and objective measurements, so they were particularly relevant. It would seem that early decisions concerning success or failure should not be made with either modality. It should be noted that 200iu was utilised onabotulinumtoxinA dose, and the study did not allow for programming tweaking with regard to sacral neuromodulation. As most would use 100iu (initially at least), this may have resulted in a slight bias to the better results for onabotulinumtoxinA.

**Reference:** *J Urol.* 2024;211:134-43

[Abstract](#)

## Efficacy and safety of an alternative onabotulinumtoxinA injection paradigm for refractory overactive bladder

**Authors:** MacDiarmid S et al.

**Summary:** This phase 4, double-blind study assessed the efficacy and safety of an alternative 10-injection-site paradigm of onabotulinumtoxinA for OAB. Patients with OAB and urinary incontinence were randomised to onabotulinumtoxinA or placebo. At week 12, onabotulinumtoxinA significantly reduced the daily frequency of incontinence episodes, micturitions, nocturia, and urgency compared to placebo. OnabotulinumtoxinA also improved treatment benefits and quality of life. Only 2.6% of onabotulinumtoxinA patients used intermittent catheterisation during the study. AEs included urinary tract infection, dysuria, and productive cough, with a higher UTI rate in the onabotulinumtoxinA group. The study suggests that the 10-injection-site paradigm is effective and may reduce the need for clean intermittent catheterisation in OAB patients.

**Comment:** It is refreshing to realise that groups are re-looking at established regimes for existing treatment modalities. Whilst not earth-shattering, this study does highlight that we have more flexibility with botulinum toxin A than we often appreciate. Perhaps we need to think outside the box more frequently for patients who do not respond or react in the expected fashion.

**Reference:** *Neurourol Urodyn.* 2024;43:31-43

[Abstract](#)

## Multimorbidity associated with urinary incontinence among older women and men with complex needs in Aotearoa | New Zealand

**Authors:** Schluter PJ et al.

**Summary:** This study aimed to explore the association between multimorbidity and urinary incontinence in community-living older adults with complex needs. They analysed data from 140,401 participants aged 65 and older in New Zealand, with a median of 3 chronic conditions, the study found that 77.9% had multimorbidity. Overall, 42.2% of females and 32.9% of males reported urinary incontinence. Adjusted analyses revealed that the prevalence of urinary incontinence was 1.21 times higher in females and 1.18 times higher in males with multimorbidity compared to those without. Despite the modest effect sizes, the study suggests a significant association between multimorbidity and urinary incontinence in this population, highlighting the challenges in capturing all relevant chronic conditions in epidemiological investigations.

**Comment:** A useful study highlighting both the incidence of urgency incontinence and its association with multimorbidity. It points us to management that actively looks for and treats urgent incontinence, with probable beneficial effects on quality of life.

**Reference:** *Neurourol Urodyn.* 2023;42:1745-1755.

[Abstract](#)

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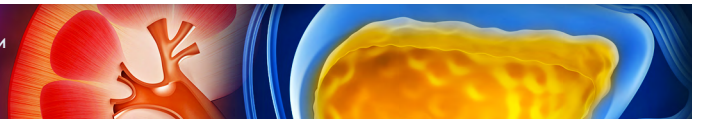
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## A multicenter study evaluating the frequency of use and efficacy of a novel closed-loop wearable tibial neuromodulation system for overactive bladder and urgency urinary incontinence (FREEOAB)

**Authors:** Goudelocke C et al.

**Summary:** This 12-week multicentre study evaluated the effectiveness and safety of a novel wearable neuromodulation system for bladder control in individuals with OAB. The transcutaneous tibial neuromodulation system demonstrated significant reductions in urinary frequency, urgency, and incontinence episodes at 12 weeks. Quality of life improvements exceeded clinically important differences. Long-term results remained robust at 12 months, and device-related AEs were mild with no serious events. Therapy compliance was high at 88.5%, and patients reported overall satisfaction with the device. The Aviation device represents a promising, non-invasive, and patient-centred option for treating OAB and urinary incontinence, offering improved accessibility and ease of use.

**Comment:** Encouraging study for those who manage patients with overactive bladder and incontinence. With side effects limiting the use of non-interventional modalities, any treatment that is easy to use, non-invasive with essentially no side effects and encouraging results warrants attention. "Peripheral" neuromodulation, for want of a better term, seems to fit well in these criteria. It will be interesting to see further developments with both this product and undoubtedly with others under production. Watch this space!

**Reference:** *Urology*. 2024;183:63-69

[Abstract](#)

## Injection site number and outcomes of intradetrusor onabotulinumtoxinA for refractory overactive bladder syndrome

**Authors:** Zdroik A et al.

**Summary:** In this single-blinded randomised trial, the optimal number of onabotulinumtoxinA injections for refractory OAB syndrome was investigated. Patients received either ten injections of 100 units each or 20 injections of 100 units each. The primary outcome was procedural pain, measured on a Numerical Pain Rating Scale immediately after the procedure. Results from 40 enrolled and randomised patients showed no statistically significant difference in median pain scores between the two groups. Patients' perceptions of pain, efficacy, and AEs were comparable, suggesting that the number of injections (10 or 20) did not significantly impact these factors. The study concludes that both injection paradigms are similarly well-tolerated by patients.

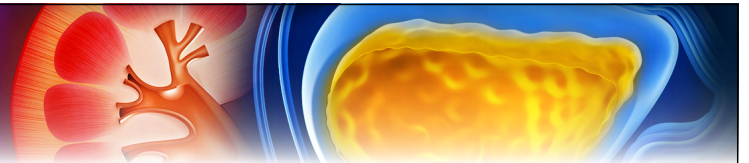
**Comment:** Similar to another study in this issue, this trial highlights that ten injection sites for onabotulinumtoxinA are as effective as 20. Useful information, as previously stated, encourages looking at more flexible regimes to address specific patient needs.

**Reference:** *Int Urogynecol J*. 2024;35:119-26

[Abstract](#)



## Continenace Research Review™



### Independent commentary by Associate Professor Bill Lynch

Bill Lynch is a consultant urologist based in Sydney. He has a particular interest in functional & reconstructive urology, as well as the practical application of technology within the urological discipline. He has published widely and often speaks internationally in these areas. He is associated with The St George Hospital (University of NSW), Sydney and is a founding member of the world-renowned Pelvic Floor Unit at that institution. He is a Clinical Associate Professor of Urology at Macquarie University.



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