Continence Research Review™

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In this issue:

Abbreviations used in this issue:

aSKNA = average skin sympathetic nerve activity;
AUC = area under the receiver operating curve;
BPH = benign prostatic hyperplasia; **IVES** = intravesical electrical stimulation;
OAB = overactive bladder;
Parasacral TENS = parasacral transcutaneous electrical neural stimulation;
PMNE = primary monosymptomatic nocturnal enuresis; **PW** = pulse width;
SNM = sacral neuromodulation; **SUI** = stress urinary incontinence;
TTNS = transcutaneous tibial nerve electrical stimulation;
UAB = underactive bladder; **UTI** = urinary tract infection;
UUI = urgency urinary incontinence; **VS** = vaginal electrical stimulation.

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Welcome to issue 11 of Continence Research Review.

This review begins with an interesting study that discusses the efficacy and safety of intravesical electrical stimulation with underactive bladder patients, providing some promising results. Another study evaluates the effectiveness of parasacral transcutaneous electrical neural stimulation plus urotherapy in children with primary monosymptomatic nocturnal enuresis, determining if it is a better form of treatment than urotherapy alone. This review also touches base on how skin sympathetic nerve activity can be a potential biomarker for diagnosing overactive bladder.

We hope you enjoy this update in continence research, and we look forward to receiving comments and feedback.

Best regards,

Associate Professor Bill Lynch
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Randomized controlled trial of intravesical electrical stimulation for underactive bladder

Authors: Liao L et al.

Summary: Within this study, researchers evaluated the efficacy and safety of intravesical electrical stimulation (IVES) for patients with underactive bladder (UAB), using a novel device. A total of 76 patients were investigated and were randomly allocated to one of two groups, 38 receiving conventional IVES and 38 receiving IVES with an open circuit. Post-void residual urine volume was measured after 4 weeks of treatment to determine the primary efficacy. At four weeks of treatment, the mean post-void residual urine volumes for the trial and control group were -97.1 (107.5) mL and -10.5 (86.7) mL, respectively ($P<0.01$), with per-protocol set results being similar: -102.9 (100.0) mL vs 0.7 (82.5) mL ($P<0.01$). In the full-analysis set and per-protocol set, maximum urinary flow rate significantly increased at 4 weeks ($P=0.04$ and $P=0.03$), and bladder voiding efficacy also increased for both groups ($P<0.01$ and $P<0.01$). There were no substantial differences in the number of 24-h clean intermittent catheterization procedures, in patient perception of bladder condition-scale scores or American urological association symptom index quality of life scores between the groups. There were 6 total AEs (4 in trial group, 2 in control), however were not severe. Results highlight a benefit of this novel IVES device for UAB patients, but that further research is required.

Comment: The UAB is increasingly being recognised as a major urological issue, causing significant morbidity in the general community. This novel technique offers both hope for patients and validates that positive results can be achieved in this generally poorly responsive group of patients. Researchers should be encouraged to continue validation of this technique, hopefully expanding to multi-centre trials. The neurostimulation space is definitely proving a rich and productive area at addressing bladder issues that have been relatively resistant to many therapies.

Reference: BJU Int. 2023;131(3):321-329.
Abstract

Updates to surgical treatment of female stress urinary incontinence (SUI): AUA/SUFU guideline (2023)

Authors: Kobashi KC et al.

Summary: Researchers aimed to produce a clinical structure for diagnosing, counselling and treating women with stress urinary incontinence (SUI). Evidence is derived primarily from the SUI guideline, with it's original data being obtained by the systemic literature review, conducted by the ECRI institute. The importance of differentiation between index and non-index patients was maintained by the Panel. Index patients are healthy females with minimal or no prolapse who want surgical therapy as treatment of pure SUI or stress-predominant mixed urinary incontinence. However non-index patients are females with factors impacting their treatment options and outcomes. This can include high grade prolapse (grade 3 or 4), urgency-predominant mixed incontinence as well as neurogenic lower urinary tract dysfunction. Researchers state that whilst there have been gains within the field that support new methods for the diagnosis and treatment of SUI patients, the field is still expanding, and it is of importance to keep up to date to provide patients with the highest levels of care.

Comment: This article should probably be regarded as compulsory reading for all urologists who treat female SUI. No matter your opinion on mid-urethral slings, the mesh controversy is not going away. Current views and guidelines reflective on current literature are important tools in providing safe, well-informed treatment and allow full consideration of options and potential problems with patients.

Reference: J Urol. 2023;209(6):1091-1098.
Abstract

Effect of pharmacotherapy for overactive bladder on the incidence of and factors related to urinary tract infection: A systematic review and meta-analysis

Authors: Tsubouchi K et al.

Summary: Within this study, researchers investigated the effects in which pharmacotherapy has for overactive bladder (OAB) and whether it impacts the pathogenesis of urinary tract infection (UTI). A total of 35,939 patients were included from 33 trials, of which 29 trials were antimuscarinic agents versus placebo and 9 were beta 3-adrenoceptor agonists versus placebo. It was identified that after 1-3 months of treatment, that the rate of URI in patients treated with antimuscarinic agents was significantly higher (RR: 1.23, 95% CI 1.04 to 1.42, P=0.796). Antimuscarinic agents were also shown to significantly increase the risk of urinary retention, dysuria and/or increased residual urine volume (2.88, 1.79 to 4.63, P<0.001), however patients receiving beta 3-adrenoceptor agonists did not display such results (1.26, 0.38 to 4.14, P=0.708). Researchers state that the use of antimuscarinic agents was proven to significantly increase the incidence of UTI, lower urinary tract symptoms as well as dysfunction. Beta 3-adrenoceptor agonists however did not increase these risks and may be safer than antimuscarinic agents.

Comment: This is an extremely interesting article, that challenges some of our existing preconceptions concerning pharmacotherapy for the OAB. It has been well established that there is an increased association of OAB and detrusor overactivity with UTI. The increase in the incidence of UTI, after the initiation of anti-muscarinic therapy, has not been as evident. Urinary retention is specifically claimed to be very low risk. The finding that both are significantly increased with anti-muscarinic therapy is both surprising and will directly affect considerations in patients for whom such treatment is contemplated. The fact that there is not a similar association with beta-3 agonists certainly changes the decision algorithm. This article provokes thought for further research.

Reference: J Urol. 2023;210(1):32-33.
Abstract

Parasacral transcutaneous electrical neural stimulation versus urotherapy in primary monosymptomatic enuresis: A prospective randomized clinical trial

Authors: Oliveira LF et al.

Summary: Researchers aimed to compare the use of parasacral transcutaneous electrical neural stimulation (parasacral TENS) with urotherapy, to urotherapy alone, in children with primary monosymptomatic nocturnal enuresis (PMNE). A total of 72 children with PMNE, over the age of 5, were enrolled. Each child was randomly allocated to one of two groups, one group being treated with urotherapy and scapular stimulation and the other being treated with urotherapy and parasacral TENS. Both groups had 20 sessions total, 3 times a week, for a duration of 20 minutes each, with a frequency of 10 Hz and 700 μS pulse (width and intensity determined by patient threshold). A total of 28 enuretic children (14 girls [50%], mean age 9.09 ± 2.23 years) completed the study, with no significant mean age difference between groups. The mean percentage of dry nights within the experimental group before treatment was 36%, after the 20th session was 49%, after 15 days 54%, 30 days 54%, 60 days 54% and 90 days 57%. For the control group, these percentages were 28%, 39%, 37%, 35%, 36% and 36%, respectively. It is highlighted that parasacral TENS plus urotherapy improves the percentage of dry nights in children with PMNE, but that no patient had a complete reduction of symptoms.

Comment: This is an interesting study, both for its success in improving the number of dry nights for children suffering from PMNE, but also as a further indication that "neurostimulation" has a role to play in all forms of bladder dysfunction that are suspected to be neurologically driven. The more clinically positive results in all forms can only encourage further research in this area, which will impact the quality of life for many of our patients.

Reference: Neurourol Urodyn. 2023 May 26.
Abstract

The impact of postinjection urinary tract infection on efficacy of intravesical onabotulinumtoxinA—A secondary analysis

Authors: Hanna MG et al.

Summary: This trial investigated the difference in treatment responses between women who did and did not develop a UTI within 14 days after intravesical onobotulinumtoxin A injections. Patient's enrolled were receiving this treatment for refractory urgency urinary incontinence (UUI) and were grouped based on UTI presence or absence. From a total of 187 patients who received onabotulinumtoxin A, 10 (5.3%) experienced UTI within 14 days of injection, and 177 (94.7%) did not. There were no substantial differences between groups in terms of demographics, mean UUI episodes per day (no UTI [5.37 ± 2.65] vs. UTI [6.40 ± 3.02], P=0.24), or other diary parameters. There were also no differences between groups in terms of mean daily UUI episodes at 1 month (no UTI [-4.29 ± 3.02], P=0.24] vs. UTI [-3.74 ± 2.01]; mean difference [95% CI -0.55, -2.39 to 1.28], P:0.55) or at 6 months (no UTI [-3.63 ± 2.89] vs. UTI [-2.15 ± 3.18]; mean difference [-1.48, -3.44 to 0.48], P:0.14). Researchers state that UTI, after an intravesical injection of onabotulinumtoxin A, was not significantly associated with inferior treatment responses at 1 or 6 months.

Comment: This study is welcome information for those who regularly administer intravesical onabotulinumtoxin A. It always seemed intuitive that an infection in the post-treatment period would decrease the effectiveness achieved. In this study, patients who suffered an infection within 14 days of onabotulinumtoxin A injection were followed closely and it was subsequently found they did not have inferior results to those patients who had not suffered an infection. Knowledge of this lack of inferiority will help influence ongoing therapy options in those who have not experienced the expected improvement in urinary symptoms after onabotulinumtoxin A therapy.

Reference: Neurourol Urodyn. 2023 Apr 22.
Abstract

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.

Transcutaneous tibial nerve electrical stimulation versus vaginal electrical stimulation in women with overactive bladder syndrome: Is there a role for short-term interventions?

Authors: Mayer de Oliveira Nunes J et al

Summary: Within this trial, researchers compared the use of vaginal electrical stimulation (VS) and transcutaneous tibial nerve electrical stimulation (TTNS) in women who have OAB. A total of 69 patients were assessed and were randomly allocated to receive either VS, TTNS or no treatment for a duration of 6 weeks. It was identified that both TTNS (mean difference = -4.2; 95% CI -6.5 to -1.9) and VS (-3.8; -6.0 to -1.6) was associated with a reduction of international consultation on incontinence questionnaire OAB scores and discomfort sensations (-3.9; -6.2 to -1.7; P<0.001 for TTNS and -2.8; -5.0 to -0.6; P=0.01 for VS) at 6 weeks, in comparison to the control group (P<0.001). However, international consultation on incontinence questionnaire OAB scores only remained low in the TTNS group, when compared to the control group (-3.6; -6.0 to -1.2; P=0.00) 1 month post treatment. It was further identified that discomfort symptoms for both groups improved (TTNS [-3.2; -5.2 to -1.2; P<0.001] and VS group [-2.6; -4.7 to -0.6; P=0.01]) when compared to the control group. Researchers state that these short-term interventions of TTNS and VS were both successful in the treatment of OAB in women.

Comment: This study shows encouraging results for TTNS for the treatment of the OAB. Using VS as a direct comparator, this study did demonstrate effectiveness and suggested the positive effects were ongoing for at least one month after the therapy regime. Transcutaneous therapies are always more enticing than percutaneous therapies to patients. This increases compliance and adherence to protocols and hence improved effectiveness. Transcutaneous therapies are cheap, and patients can readily be taught self-administration, so further evidence to the positive knowledge base is welcome. This study also continues the theme of effectiveness of "neurostimulation" on the OAB.

Reference: Neurourol Urodyn. 2023 Apr 12.
Abstract

Development of a machine learning-based predictive model for prediction of success or failure of medical management for benign prostatic hyperplasia

Authors: Pham K et al.

Summary: This study aimed to develop a novel predictive model to aid in the identification of whether patients will or will not respond to the medical management of benign prostatic hyperplasia (BPH). Data was derived from the Medical Therapy of Prostatic Symptoms study, with results from initial data sets of 2,172 patients who had BPH and were being treated with doxazosin (group 1), finasteride (group 2) or a combination of therapy (group 3). K-fold stratified cross-validation was used for each group and boosted support vector machines for further refinement. Optimal operating points were determined once the area under the receiver operating curve (AUC) was calculated. Within the entire cohort, it was identified that the AUC for the boosted support vector machine model was 0.698, and that for group 1 the AUC was 0.729, group 2 was 0.719 and group 3 was 0.698. This data allowed for the development of a predictive model that had acceptable rates of discrimination of medical management success for this patient population.

Comment: This article proposes an intriguing approach to the decision process in the adoption of medical therapy for BPH. The concept of a model that could predict response to medical therapy is one much desired by both patients and the prescribing physician. The complexity of the factors considered in this study make its application in a clinical setting impractical, but the fact that predictors could be identified with relative reliability encourages the techniques to be explored further. AI applications will undoubtedly take such studies further, so I think this is a "watch this space" scenario.

Reference: Neurourol Urodyn. 2023;42(4):707-717.
Abstract

Effect of pulse width variations on sacral neuromodulation for overactive bladder symptoms: A prospective randomized crossover feasibility study

Authors: Rueb J et al.

Summary: This trial assessed the effect of two pulse width (PW) settings (60 µs, 420 µs) in comparison to the industry standard (210 µs) on sacral neuromodulation (SNM) efficacy and quality of life. 18 patients (mean age 68 years) were enrolled, with each being previously implanted (mean implant duration 4.4 years) and experienced urge incontinence or urgency-frequency with satisfaction on SNM. Participants completed a 3-day voiding diary, validated questionnaires as well as device interrogations with sensory threshold assessment at baseline. It was identified that PW variations did not produce many differences in overall objective outcomes, but device parameters differed significantly. Shortened PW produced a higher amplitude whilst conserving battery life. After the study, 11 participants chose standard PW, 5 chose extended and 2 chose shortened, with those choosing alternative PW achieving significant reduction in urinary frequency from enrolment (-2.23 voids/day [P=0.015]). Patient's receiving extended PW, who reported "much better" or "very much better" had significant reductions in urinary frequency and nocturia: 5.6 and 0.4, compared to 8.5 and 2.16 at baseline (P=0.005, P=<0.001). Those receiving shortened PW, who also reported "much better" or "very much better" achieved significant reductions in urinary frequency at 5.15, compared to 7.35 (P=0.026). The effectiveness of SNM was unchanged with alternative PW, however, alternative PW was preferred by 39% of patients, and had the greatest improvement in urinary symptoms.

Comment: A study of note for Interstim implanters. Variations in PW may not necessarily lead to any higher objective symptom improvement, but can effect both patient comfort and battery life, thus increasing long term effectiveness and patient compliance. The fact that PW variations do not have a deleterious effect on symptoms, shows that it is definitely worth exploring variations in patient settings. If a patient feels more comfortable with a particular setting, they are far more likely to report a subjective improvement (if not objective), hence experience treatment satisfaction.

Reference: Neurourol Urodyn. 2023;42(4):770-777.
Abstract

Skin sympathetic nerve activity as a potential biomarker for overactive bladder

Authors: Chen Y-C et al.

Summary: Utilising neuECG, researchers assessed autonomic nervous function in both healthy controls and patients with OAB before and after treatment. A total of 52 patients were assessed (newly diagnosed OAB patients [n=23], controls [n=29]). Patient's with OAB were administrated antimuscarinics, and all patient's autonomic function was assessed in the morning using neuECG, determining the average skin sympathetic nerve activity (aSKNA). A higher aSKNA was found in OAB patients (P=0.003) and a lower standard deviation of the normal-to-normal beat intervals as well as lower high-frequency than the controls. Baseline aSKNA also had the highest value when predicting OAB (AUROC = 0.783, P<0.001). However, aSKNA had a negative correlation to first desire and normal desire in urodynamic studies (both P=0.025) and was also reduced after treatment at rest, stress and in recovery phases, compared to those prior to treatment (P=0.046, 0.017 and 0.017, respectively). OAB patients experienced increased sympathetic activity compared to controls, however experienced a decrease post-treatment. Researchers suggest that aSKNA may be a possible biomarker for diagnosing OAB.

Comment: This is a fascinating study in that it explores a minimally invasive objective test that can identify patients with an OAB, and further correlates with successful medical therapy. Further work will undoubtedly follow, but skin sympathetic nerve activity if easily measured looks a promising tool for the future in this space.

Reference: World J Urol. 2023;41(5):1373-1379.
Abstract

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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