2015 ANNUAL MEETING HIGHLIGHTS

Overactive Bladder

Course #021IC
Botulinum Toxin: Why Use It, How to Do It, What are the Results?

Course #040PG
Urodynamic Evaluation and Advances in Management of Adult Neurogenic Bladder: A Case Based Approach

Course #058IC
The Role of Sacral Neuromodulation in Urological Practice

Course #079PG
Foundations of Female Urology

Forums
A Decade of Pharmacotherapy for OAB: What Have We Learned?
Second Opinion Cases: Refractory Overactive Bladder and Female Incontinence

Plenary Sessions
Point-Counterpoint: Refractory Overactive Bladder (OAB) with Pelvic Organ Prolapse (POP)
Panel Discussion: Special Considerations for Treating OAB in the Elderly: A Practical Approach
Take Home Message: Female Urology/Incontinence/Urodynamics

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Statement of Need
Overactive bladder (OAB) represents a growing referral for urologists; increases in our aging population as well as awareness of new advances in managing lower urinary tract symptoms are associated with a higher prevalence of OAB. With growth in practice referrals comes an increase of refractory cases to conservative management options that integrate behavior modification, pharmacotherapy and minimally invasive treatments. The treatment of OAB has evolved, with a number of second line therapies that need to be incorporated into the treatment armamentarium.

Target Audience
Urologists, urologists in training and nonphysician providers involved in urology.

Course #021IC: Botulinum Toxin: Why Use It, How to Do It, What are the Results?

Learning Objectives
At the conclusion of this CME activity, participants should be able to:
• Cite the mechanism of action of botulinum toxin
• Describe the role of the toxin as a form of treatment for the bladder, sphincter and prostate
• Identify limitations and potential complications of botulinum toxin treatment
• Examine patient types who may benefit from treatment with botulinum toxin
• Compare and contrast injection techniques

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Course #040PG: Urodynamic Evaluation and Advances in Management of Adult Neurogenic Bladder: A Case Based Approach

Learning Objectives
At the conclusion of this CME activity, participants should be able to:
• Become confident in the urodynamic evaluation of adult neurogenic lower urinary tract conditions
• Become proficient in the comprehensive and contemporary management of neurogenic lower urinary tract conditions
• Obtain instruction on the currently accepted and evidence-based follow-up management of adult patients with neurogenic lower urinary tract conditions

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▼ Continued on page 2
CME Information
▼ Continued from page 1

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Course #058IC: The Role of Sacral
Neuromodulation in Urological
Practice

Learning Objectives
At the conclusion of this CME activity,
participants should be able to:
• Summarize the basic elements of
  sacral neuromodulation (SNM)
• Translate the theory of neuromodu-
lation to the pathophysiology of
  voiding dysfunction
• Differentiate when SNM may be
  appropriate for patients in clinical
practice
• Review new and potential future
  indications and weigh therapeutic
  alternatives
• Exemplify troubleshooting and best
  practice techniques

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Course #079PG: Foundations of
Female Urology

Learning Objectives
At the conclusion of this CME activity,
participants should be able to:
• Cite the basic concepts of pelvic
  floor anatomy and how certain
defects cause pelvic organ prolapse
• Distinguish the different prolapse
  surgeries and the certain types of
  pelvic floor defects they correct
• Interpret the latest concepts regard-
ing the pathophysiology and surgical
  treatment of stress urinary inconti-
nence as well as integrate guidelines
  into clinical management
• Enumerate the basic principles of
  urodynamic testing in women with
  pelvic organ prolapse and integrate
guidelines into clinical management
• Incorporate the diagnosis and man-
  agement of OAB and integrate
guidelines into treatment

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Botulinum Toxin: Why Use It, How to Do It, What are the Results?

Michael B. Chancellor, MD, Course Director

I first started using botulinum toxin (BoNT) in 1998 out of frustration from not being able to help 3 women with multiple sclerosis and refractory neurogenic detrusor overactivity (NDO). They did not want to undergo bladder augmentation surgery and did want to try bladder BoNT injection. The injection worked and the pilot success led me to research and teaching on the use of the world’s most powerful medicine to treat refractory lower urinary conditions.1

There are now 2 approved urological indications for botulinum toxin (BoNT) in the United States. 1) OnabotulinumtoxinA (onaBoNTA) 200 U is used for the treatment of urinary incontinence due to detrusor overactivity associated with a neurological condition in adults who have an inadequate response to or are intolerant of an anticholinergic medication. 2) OnaBoNTA 100 U is used for the treatment of overactive bladder (OAB) with symptoms of urinary incontinence, urgency and frequency in adult patients who have an inadequate response to or are intolerant of an anticholinergic medication. In this course, I review the practical aspects of using BoNT safely and effectively.

Preparing the Patient for Injection

Urinalysis should be checked at the time of the procedure (if the patient has a history of chronic bacteriuria, appropriate preoperative antibiotic coverage is indicated). Anticoagulation medicine should be stopped temporarily and informed consent obtained. The bladder should be empty and local anesthesia should be applied (1% lidocaine solution) with or without sedation.

The bladder should be partially filled to approximately 150 to 200 ml for visualization but avoid over distention. Latex allergy precautions should be considered in the at risk population of NDO. In spinal cord injured patients with lesions above the T6 spinal cord level, precautions to deal with and procedures to minimize the risk of autonomic dysreflexia should be in place. The use of urethral and bladder local anesthesia is helpful, and general anesthesia may need to be considered in select patients.

Injection Technique

For indications of NDO, the recommended dose is 200 U onaBoNTA, the recommended reconstitution volume is 30 ml sterile injectable saline, the recommended volume per injection is 1 ml, the recommended depth of injection is 2 mm intradetrusor, and the recommended injection sites are 30 sites spaced 1 cm apart starting 1 cm above the trigone. For the idiopathic OAB indication the recommended dose is 100 U onaBoNTA, reconstituted in 10 ml saline and injected into 20 sites at 0.5 ml per site (see figure).

Flexible and rigid cystoscopic techniques both work well for BoNT injection. Surgeon preference and institutional practice usually affect the decision of what technique is used.

Flexible cystoscopy. I use flexible cystoscopy in the office for the majority of cases in men and women. The flexible scope accommodates a 27 gauge, 4 mm long flexible injection needle. Office procedures using only local anesthesia are adequate for most of my patients and they appreciate the convenience of an office procedure.

Rigid cystoscope. A scope with a 12 or 30-degree lens bridged with an accessory working element loaded with a 25 gauge needle is recommended. The rigid scope allows for easier orientation within the bladder compared to a flexible cystoscope, the working element facilitates rapid injection into the bladder, and the 25 gauge needle minimizes bleeding and potential backflow from the injection sites.

Preparing the Toxin

Each vial of 100 U onaBoNTA comes in a 10 ml bottle. I do not reconstitute the toxin until I know that infection has been ruled out or an appropriate antibiotic has been started to avoid waste. The unconstituted onaBoNTA vials must be stored in the refrigerator between 2C and 8C (36F to 46F) for up to 36 months. After reconstitution, the vials may be stored in the refrigerator at 2C to 8C (36F to 46F) for up to 24 hours. After this period they should be disposed. OnaBoNTA should not be frozen after reconstitution. It should be used immediately and should not be stored in the syringe. Typical doses in adult patients treated with abobotulinumtoxinA range between 500 and 1,000 U, and for rimabotulinumtoxinB range between 2,500 and 15,000 U (ie 5,000 U is most common).

After the Injection

I instruct my patients that they may notice some pain and blood-tinged urine, as well as possible difficulty urinating. These symptoms should resolve within 24 to 48 hours and they should contact my office if they have any questions or concerns. I discuss the appropriate antibiotic coverage and risk of infection with patients who often have more bladder infections. It may take several days to notice a gradual improvement in OAB symptoms. It generally takes several days for a patient to notice impaired voiding and I would instruct that patient to start self-catheterization if clinically necessary. Office followup in about 2 weeks with urinalysis and post-void residual urine check are recommended.
The efficacy of onaBoNTA in reducing urinary leakage and other OAB symptoms was up to 6 months’ duration. Improvements in frequency of urination and the amount of urine voided also occurred with onaBoNTA treatment compared to placebo at week 12. The most common side effects reported with onaBoNTA in clinical studies included urinary tract infection (18% vs 6% with placebo), dysuria (9% vs 7% with placebo), which means painful or difficult urination, and urinary retention (6% vs 0% with placebo), which is a temporary inability to fully empty the bladder which requires clean intermittent catheterization. Urinary retention was more likely to develop in patients with diabetes mellitus treated with botulinum toxin.

How Long Does BoNT Last?

It generally takes about 1 to 2 weeks for my patients to notice some relief of symptoms. If the injection helps, he or she will experience further improvement that usually reaches a maximal benefit at about 1 month. The beneficial effect is usually maintained for 6 to 9 months. Subsequently, urination or catheterization frequency starts to increase and incontinence recurs. I tell my patients to look for these signals and to contact my office to schedule repeat injections.

I wait 3 months before repeat injections even if patients report partial improvement and request repeat injections sooner. One warning is not to exceed 400 U onaBoNTA in a 3-month period. This is important if the patient is receiving BoNT injection from another physician to a different part of his or her body.

What is the Risk of Antibody Formation?

Failure to respond to BoNT injection might result from the presence of pre-existing BoNT antibodies (BoNT-AB, primary failure) or the production of BoNT-ABs in response to BoNT injection (secondary failure). The incidence of onaBoNTA antibody formation is low, at only about 1%. I have not had a case of documented positive BoNT-AB since I first used BoNT in 1998, and I generally perform the FronTalis Antibody Test for clinical confirmation when a patient reports that BoNT is not working after previous successful injections.

When to do Next Injection and How Much to Inject?

For the majority of patients who notice a benefit with bladder BoNT therapy, I use the same dose with repeat injections. Most neurologically impaired patients have had consistent improvement using the same dose and I have noticed this for more than 12 years. If the patient finds benefit but incontinence did not adequately resolve with 100 U onaBoNTA, I may consider going up to 150 or 200 U onaBoNTA with the next injection. Alternatively, in patients with NDO who do not do perform self-catheterization but have noticed retention or incomplete bladder emptying, I generally start at 100 U onaBoNTA. Dose titration is possible and helpful but, in my experience, the percentage of patients who will need dose adjustment up or down is small.

Conclusions

Here are some final considerations to remember for the safe clinical use of botulinum toxin.

• A boxed warning is part of the prescribing information of botulinum toxin in the United States to highlight that BoNT may spread from the area of injection to produce systemic effects consistent with botulism.

• Understand that BoNT products are not interchangeable. The doses expressed in units are not comparable from one BoNT product to the next.

• Symptoms such as unexpected loss of strength or muscle weakness, hoarseness or trouble talking (dysphonia), trouble saying words clearly (dysarthria), loss of bladder

What are the Results?

The neurogenic detrusor overactivity indication received regulatory approval in 2011. A total of 691 patients with spinal cord injury or multiple sclerosis who had an inadequate response or were intolerant of 1 or more anticholinergic medications were enrolled in phase 3 studies. These patients were randomized to receive 200 U onaBoNTA (227), 300 U onaBoNTA (223) or placebo (241). In both studies, significant improvement in the primary efficacy variable of change from baseline in weekly UI episode frequency was achieved with 200 U onaBoNTA vs placebo. The 300 U dose was not better than 200 U but had more side effects. Improvement was seen after 2 weeks and the average duration of response was approximately 9 to 10 months.

OnaBoNTA treatment was associated with significant improvements in maximal cystometric capacity of approximately 150 ml. Among patients who were not catheterizing at baseline before treatment, catheterization for urinary retention was initiated in 30.6% after treatment with 200 U onaBoNTA vs 6.7% of those on placebo. The most frequently reported adverse reactions within 12 weeks included urinary tract infection (24%), urinary retention (17%), hematuria (4%), fatigue (4%) and insomnia (2%).

The idiopathic detrusor overactivity indication received regulatory approval in 2013. Phase 3 studies demonstrated the safety and efficacy of onaBoNTA in patients with OAB whose symptoms were not adequately managed with anticholinergic medications. OnaBoNTA reduced the daily frequency of urinary leakage episodes from baseline by approximately 50% or more by week 12 vs placebo (reduction of 2.5 episodes from baseline of 5.5 in study 1 and reduction of 3 episodes from baseline of 5.5 in study 2 for those treated with onaBoNTA vs a reduction of 0.9 episodes from a baseline of 5.1 in study 1 and a reduction of 1.1 from a baseline of 5.7 in study 2 for those treated with placebo).
control, trouble breathing, trouble swallowing, double vision, blurred vision and drooping eyelids may occur.

- Understand that swallowing and breathing difficulties can be life threatening, and there have been reports of deaths related to the effect of spread of BoNT.
- Be aware that children treated for spasticity are at greatest risk for these symptoms, but symptoms can also occur in adults treated for spasticity and other conditions.
- Realize that cases of toxin spread have occurred at BoNT doses comparable to those used to treat cervical dystonia and at lower doses.


Urodynamic Evaluation and Advances in Management of Adult Neurogenic Bladder: A Case Based Approach

Hari Tunuguntla, MD, MS, MCh, Course Director; Angelo E. Gousse, MD and Stephen R. Kraus, MD, Faculty

Introduction

Neurological conditions are a common cause of urological symptoms and lower urinary tract dysfunction. Lower urinary tract symptoms including urinary incontinence contribute to significant clinical, social and economic burdens for the patient, caregiver and health care system. Prompt recognition and timely management of neurogenic lower urinary tract dysfunction (NLUTD) are important to prevent potentially irreversible adverse outcomes, especially in patients with high risk lower urinary tract features, including high detrusor leak point pressure and low detrusor compliance.

High risk NLUTD is common in spinal cord injury (SCI), multiple sclerosis and spina bifida. These patients are at increased risk for renal failure, kidney and bladder stones, urinary tract infection (UTI) and vesicoureteral reflux (VUR). Treatment objectives in NLUTD include preventing upper tract deterioration, minimizing infection risk and maximizing quality of life by restoring socially acceptable continence. Current advances in urinary tract monitoring, antibiotics and patient treatment have significantly contributed to an increase in the lifespan of these patients with NLUTD.

Patterns of Voiding Dysfunction

Classification of the primary neurological disorder causing NLUTD as suprapontine, infrapontine-suprasacral, sacral and peripheral lesion helps to predict the type of clinical/urodynamic abnormality, and has therapeutic and prognostic significance. Characterization of the lower urinary tract dysfunction as failure to store and failure to empty is also helpful from a treatment point of view.

Evaluation

A careful history and comprehensive evaluation of the patient assist in determining the type of functional abnormality (failure to store and/or failure to empty). It is important to perform functional (nuclear renal scans, serum creatinine) and anatomical (ultrasound or computerized tomography) evaluation of the upper urinary tract. Lower tract evaluation comprises urodynamic study (UDS), cystogram to rule out VUR and cystoscopy to assess bladder anatomy. Initial evaluation of the patient with NLUTD includes baseline UDS and renal/bladder ultrasound.

Urodynamic Evaluation

Urodynamic assessment helps to characterize voiding dysfunction and identify patients at high risk for upper tract deterioration, facilitating appropriate treatment aimed at the preservation of the renal function. The addition of fluoroscopy (videourodynamic study) helps in the diagnosis of complex lower urinary tract dysfunction by identifying the specific location of an obstructive process, confirming normal bladder neck function, visualizing detrusor-sphincter dyssynergia (DESD) and evaluating anatomical abnormalities in complex cases of incontinence. It is also possible to document cases of VUR during the study.

Neurological lesions above the pon-
The majority of patients with incomplete lesions below T10 and about a fifth of patients with lesions above T11, have been shown to retain filling sensation before vesical pressure reached 25 cm H2O, highlighting the potential for sensation dependent bladder emptying in patients with SCI.

Antimuscarinics are the first line choice in managing neurogenic detrusor overactivity (NDO), improving compliance and preventing upper urinary tract damage. Patients with SCI tolerate higher doses better.

Bladder chemodenervation with onabotulinum toxin A (BoNT-A) is a minimally invasive treatment for patients with NDO with significant improvements in mean number of incontinence episodes and other clinical and urodynamic parameters with a mean duration of 36 to 42 weeks. Bladder augmentation is now reserved for patients with DO or impaired compliance in whom treatment with BoNT-A fails. BoNT-A is also an option for chemical denervation of the external sphincter in patients with high bladder outlet resistance.

**Surgical Management**

Surgical options are indicated in high risk NLUTD refractory to the previously mentioned conservative treatments.

**External Sphincterotomy**

Patients with DESD, UTI, upper tract damage, antimuscarinic dysreflexia or CIC failure are candidates for external urethral sphincterotomy combined with an external collection device. A single incision is made at the 12 o’clock position through mucosal and muscular layers proximal to the verumontanum to the proximal bulbar urethra. Patients who are unable to attain adequate detrusor contraction do not experience improvement. In addition, reoperation rates with sphincterotomy are high (15% to 40%).

**Augmentation Cystoplasty**

Augmentation cystoplasty is a definitive treatment option for refractory NDO and intractable incontinence, as well as for upper tract dysfunction due to increased bladder pressures, helping to achieve continence with protection of the upper urinary tract. Common long-term complications include bladder stones and UTIs, with a risk of metabolic abnormalities, specifically hyperchloremic acidosis.

**Ileal Conduit**

Ileal conduit is used in patients with NLUTD with or without cystectomy to provide continuous drainage. It may be considered in quadriplegic patients who wish to be independent or in patients with recurrent UTI with an indwelling catheter. This is useful in patients with a small bladder with severe detrusor overactivity. Ileovesicostomy circumvents ureteral reimplantation.

**Stress Urinary Incontinence**

Female patients with neurogenic SUI may be treated with transurethral bulking agent injection, pubovaginal sling, mid urethral slings and bladder neck closure with urinary diversion, whereas men are treated with urethral sling or artificial urinary sphincter. Followup of these patients is important to detect subsequent development of high-pressure bladder. Puboprostatic slings placed around the urethra distal to the prostate are associated with an 83% rate of success but require an abdominal incision. Bladder neck closure is used as a last resort, reserved for a urethra that is unsalvageable.

**Followup**

Per the Consortium for Spinal Cord Medicine guidelines, patients with SCI should undergo an annual urological evaluation. However, there is no consensus on the type of evaluation or the optimal frequency of followup evaluation. Annual history, physical examination, blood urea nitrogen/creatinine, plain x-ray of the kidneys, ureters and bladder (KUB) and renal ultrasound scan are obtained. Urodynamic study is repeated every 5 to 10 years or as clinically indicated. Screening urinalysis and urine culture are not routinely...
performed. The sensitivity of KUB for detecting urinary tract stones is 14% to 54% and may be omitted as a screening tool (expert opinion). Treatment failures may be missed if based on clinical symptoms alone.

Table. Followup of patients with NLUTD

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level of Evidence</th>
<th>Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk pts – physical examination + urinalysis every 6 mos</td>
<td>4</td>
<td>A</td>
</tr>
<tr>
<td>High risk pts – assess upper urinary tract every 6 mos</td>
<td>4</td>
<td>A</td>
</tr>
<tr>
<td>Any significant clinical change(s) indicate further specialized evaluation</td>
<td>4</td>
<td>A</td>
</tr>
<tr>
<td>Urodynamics is a mandatory baseline + should be done at regular intervals</td>
<td>3</td>
<td>A</td>
</tr>
</tbody>
</table>


Conclusions

A comprehensive neurourological diagnosis and evaluation of bladder dysfunction are important to formulate effective and individualized treatments in NLUTD. Spinal cord lesions above T6 may be associated with autonomic dysreflexia. NLUTD secondary to diabetes mellitus is associated with failure to empty, and pernicious anemia is associated with high post-void residual volume and loss of bladder sensation. Myelodysplasia is associated with open and fixed sphincter.

All patients should undergo a baseline renal bladder ultrasound and UDS, the latter constituting a significant part of the baseline evaluation and followup of NLUTD. History, physical examination and renal bladder ultrasound should be repeated annually. Spinal cord injury, advanced multiple sclerosis and spina bifida are associated with an increased risk of upper urinary tract damage. Patients should be frequently monitored given their predisposition for urinary calculi, UTIs, malignancy and deterioration of upper tracts. UDS may be repeated as clinically indicated.

Management of NLUTD is aimed at the preservation of the upper and lower urinary tract. A risk and patient oriented approach coupled with regular and lifelong urological followup improves outcomes, prevents complications and potentially results in an optimized quality of life and life expectancy.

Bibliography


Third Line Therapies

An increasing number of options can be used as a complement or alternative to anticholinergic drugs, such as sacral neuromodulation (SNM), percutaneous tibial nerve stimulation (PTNS) and intravesical botulinum toxin (BoNT). Which one to choose? I use all of them depending on the situation. This course presumes the more conservative or first and second line options have been insufficient. I will detail the use of sacral neuromodulation in patients who do not respond adequately and will discuss the positioning of SNM relative to PTNS and BoNT.

Sacral Neuromodulation

SNM involves chronic modulation of the S3 and, less frequently, the S4 nerve via a transforaminal route. Modulation implies the therapy is thought to act indirectly, via a central afferent mechanism, targeting reflex centers in the spinal cord and pons, influencing reflexes between the bladder, urethral sphincter and pelvic floor. Stimulation implies a more direct effect on efferent motorneurons, as in functional electrical stimulation.

The therapy, marketed internationally as InterStim®, uses an implantable system including a lead electrode and an implantable neurostimulator (INS). There is typically a trial or screening phase using a percutaneous lead lasting for 3 to 7 days (percutaneous nerve evaluation) or a staged lead implant when a chronic lead is implanted surgically. The therapy may be trialed for up to several weeks, and if successful, the lead may then be converted for long-term use by connecting to an INS.

Present and Future Indications for SNM

In the United States, the FDA (Food and Drug Administration) approved indications for SNM include patients with refractory OAB, and idiopathic, nonobstructive urinary retention (NOUR). SNM is also approved for the indication of fecal incontinence (FI). It may be successfully used for OAB and NOUR indications since it is not a bladder specific therapy, and works at a central level on the “on-off” switch for pelvic reflexes. While FDA labeling stipulates SNM is only approved for patients with non-neurogenic bladder, those with a neurogenic basis of their complaints have been successfully treated and reported in the literature.

Many of our patients with refractory urinary complaints also have significant and disabling bowel complaints, and the selection of SNM is likely to have a beneficial effect on both conditions. These are not limited to FI, but also include fecal urgency and frequency, constipation/anismus and dyschezia. Thus, the benefits of therapy should be appropriately weighed vs intravesical BoNT for this potential in patients with relevant gastrointestinal (GI) symptoms.

Therapeutic Efficacy and Complications

Recent publication of the InSite trial showed SNM to be superior to anticholinergics after an inadequate response to 2 drugs. At 12 months, SNM was shown to remain safe and effective. There have been hundreds of other publications in the peer reviewed literature regarding SNM. In general, randomized controlled trials/case series reports show an approximately 80%/70% success rate, defined by at least a 50% decrease in relevant voiding parameters. Studies also demonstrate significant improvement of quality of life, decreased use and cost of therapeutic alternatives, and long-term benefit.

The degree of improvement, even among the patients with the most severe baseline symptoms, has been shown to be greater than among patients successfully treated in OAB drug trials (based on package inserts/FDA submitted trials). Similarly, the degree of improvement seen among patients treated with PTNS appears to be about half as much among patients who are less symptomatic to start with. Randomized head-to-head trials have not been reported.

SNM vs BoNT or PTNS

Much discussion has been focused on the relative merits of intravesical BoNT vs SNM in urological patients. I use both in my practice, and believe that the therapies have different strengths and weaknesses which should be considered when discussing with patients (Appendix 1). In general, patients with significant bowel symptoms, pelvic pain and nonobstructive urinary retention are more likely to benefit from SNM, while elderly patients, those with progressive neurogenic bladder, those likely to need body magnetic resonance imaging (MRI) or those in whom a trial of SNM has failed are more ideally suited for BoNT.

Unlike BoNT, there is likely to be a benefit from PTNS for bowel symptoms. Patients who have demonstrable detrusor overactivity on urodynamic study, including those with more severe symptoms, are likely to experience a greater benefit from SNM than PTNS. Equivalent long-term efficacy of PTNS vs SNM has not been demonstrated, and there has not been a study conclusively demonstrating that the outcome of PTNS predicts the outcome of SNM. Of course, patient preference is paramount in choosing among these options.

Troubleshooting SNM

Typical problems encountered with SNM are summarized in Appendix 2. Recent studies have demonstrated a reoperation risk due to complications of less than 20% using modern techniques. There are several troubleshooting tips for dealing with common dilemmas.

Infection Prevention. A recent multi-center study has demonstrated the rate of infection of SNM devices to be 3%. Perioperative antibiotics, similar to those used with other urological prosthetics, are a must. Patients shower preoperatively with Hibiclens®, and alcohol and Duraprep™ are used intraoperatively. Other intraoperative considerations include the use of an Ioban™ drape,
making sure the incision is sufficiently deep, the lead extension tunnel is as long as possible during a staged trial, and the excess lead is handled in a way to allow normal apposition of subcutaneous tissues. Evidence of a chronic, draining sinus is typically associated with implant infection. Once infection is obvious, all implanted components and the surrounding capsule must be removed, with incisions allowed to heal (usually 3 months) before re-implantation, if elected.

Lead Problems. Lead migration or lead fracture can be causes of decreasing efficacy. A fall or trauma is often responsible for these issues. Impedances greater than 4,000 Ω at 1 or more sites are indicative of fracture, while less than 50 Ω or equalization of impedances implies fluid in a connection site. Anteroposterior and lateral sacral films can be helpful in identifying these issues. While lead migration is rare, forward migration can occur in very thin patients who had a “knuckle” of lead in the presacral area. Care to lay the lead down flat beneath the skin (by making a larger than normal or a “skipping” incision) can prevent this complication.

Pain at INS Site. Using the small INS making a deep pocket parallel to the skin surface, just large enough to fit the device, and with careful hemostasis, can be helpful in avoiding INS pain. It is important to place the device below the posterior superior iliac crest and lateral to the sacral edge to prevent direct compression over bone.

Pregnancy. While there is no direct evidence of problems from SNM during pregnancy, it is recommended that the device be turned off throughout term or as soon as pregnancy is known. Some patients may refuse because of the return of severe symptoms. In general, limitation of use during the first trimester and turning down stimulation levels are prudent steps. I believe strong consideration of an elective C-section should be given for patients treated with SNM who have demonstrated pelvic floor hypertonus.

MRI with SNM. Most patients with intact systems using InterStim II INS can have MRI of the head or extremities only when using a send and receive MRI coil. The current SNM devices are not fully MRI compliant and axial MRI scans remain contraindicated. It is the lead and not the generator that represents the greatest risk to the patient during these studies. A connected lead is safer than a disconnected one. Care should be taken to remove the entire lead when necessary and patients should be informed of retained leads when present. Careful counseling and informed consent are needed if MRI is considered for patients treated with SNM.

Conclusions

Urologists commonly care for patients with drug refractory voiding complaints. First line alternatives include behavioral therapy, biofeedback and physical therapy. Other options, including SNM, PTNS and intravesical BoNT, are important considerations for optimal benefit. The techniques, patient selection guidelines and troubleshooting measures discussed should help achieve a successful outcome.
Illustrated how SUI is diagnosed and characterized by abdominal leak point pressure. An overview of the pertinent AUA guidelines on adult urodynamics was presented.

Dr. Rosenblum followed with a discussion of the pathophysiology and treatment of SUI. She reviewed in great detail the anatomy of urethral support. She emphasized that defects in urethral support may lead to urethral hypermobility and predispose one to SUI. She went on to say that “not all women with hypermobility leak urine” and that it appears that “any women with SUI must have some degree of intrinsic sphincter deficiency.” The AUA update on SUI was presented, and the standard evaluation with history and physical examination, stress test, urinalysis, post-void residual and assessment of bother was outlined for the audience.

Dr. Rosenblum then reviewed the “acceptable” surgical procedures for SUI, including retropubic suspensions, pubovaginal slings, mid urethral slings (MUSs) and urethral injection therapy. She noted the decreasing numbers of Burch procedures being performed but reaffirmed that in women with urethral hypermobility undergoing abdominal surgery these operations may still be used successfully. However, most in the audience agreed that even in this setting they would still proceed to MUS.

She noted that the best outcomes data in the surgical management of SUI were for sling procedures. “Slings have the highest degree of efficacy, but it must be noted that MUS procedures have similar efficacy of the pubovaginal sling with less perioperative morbidity.” After these comprehensive lectures, videos of the retropubic and obturator MUSs as well as the pubovaginal sling were reviewed with the audience.

Dr. Winters started the second session by reviewing normal pelvic anatomy and defining the various defects creating most commonly seen prolapse conditions, stating that “the etiology of POP is multifactorial, ranging from childbirth to disorders of connective tissue.” He concluded by illustrating the commonly performed prolapse procedures and the vaginal support defects they correct.

Dr. Winters noted the importance of the apex in vaginal support, stressing that “if present, apical support defects must be corrected to achieve successful outcomes.” After the lecture on prolapse, instructional videos on abdominal sacral colpopexy, transvaginal prolapse correction and colpocleisis procedures were presented.

The third and final session included lectures designed to enhance practices devoted to female urology. Dr. Kraus presented a number of ideas geared to creating a practice environment conducive to female urology. He stated that “small things matter. Even the waiting room appearance is important if we are to make our offices more comfortable to women.”

In the final lecture, Dr. Kraus highlighted the most common presentations of transvaginal mesh surgery and illustrated principles guiding surgical management. For erosions in the bladder he noted, “minimally invasive techniques are still quite feasible, and their application is at the discretion of the surgeon.” At all times, surgeons should adhere to “sound reconstructive principles.” Dr. Kraus emphasized early intervention for women who are in retention after MUS and that there is no need to wait “as commonly done for pubovaginal sling procedures.”

At this point, Drs. Rosenblum and Winters guided the participants through various clinical scenarios in the area of female urology and a clinical review of the AUA OAB guidelines. A question and answer period completed this dynamic and highly interactive session. The instructional videos in each of the sessions emphasized the teaching points and are likely to facilitate their future practice.
It was my privilege to moderate this session at the 2015 Annual Meeting, and I will summarize the important points made by each speaker.

**Origin of the Term Overactive Bladder**

Dr. Paul Abrams pointed out that use of the term overactive bladder (OAB) originated in 1997 as an alternative to the term “unstable bladder.” The term was first used in the title of a symposium in 1997, “Introduction to the Overactive Bladder: From Basic Science to Clinical Management.” It was ultimately adopted in 2002 by the Standardization Subcommittee of the International Continence Society and officially defined as “urinary urgency usually accompanied by frequency and nocturia, with or without urge urinary incontinence, in the absence of urinary tract infection or other obvious cause.”

Later, it was generally agreed that urge incontinence should be renamed urgency incontinence. Since urgency is the primary symptom without which the parent term cannot be used, it is appropriate to define urgency as “the complaint of a sudden, compelling desire to pass urine which is difficult to defer.” This definition of overactive bladder can be applied not only to the overactive bladder syndrome but also to urge syndrome or urgency-frequency syndrome. Data from the EPIC study (2005) determined an overall overactive bladder prevalence of 11.8% in individuals age 18 to 70+. The prevalence increases with age especially after age 60, accounting for the larger prevalence numbers appearing in series which count only adults older than age 40.

Overactive bladder is not synonymous with detrusor overactivity, the latter being a urodynamic diagnosis and the former being a symptomatic diagnosis. The original idea behind the term OAB was that it should be readily recognizable and understandable by specialists and all primary care providers, and should describe a group of symptoms that, in the absence of another identifiable pathological cause, can be treated empirically with simple measures (behavioral modification and pharmacotherapy) without the need for an extensive evaluation, as long as there exists a list of symptoms or signs that should prompt referral to a specialist.

Dr. Abrams concluded by describing the difference between urgency and urge to void, the former being a symptom and the latter being an expression in common use, synonymous with the desire to void, which we all experience. To avoid confusion, it was suggested to avoid the expression “urge to void.”

**Overactive Bladder: A Critical Evaluation**

Dr. Jerry Blaivas described some of the well-known difficulties with the definition of overactive bladder. The first point related to whether urgency was in fact correctly described as a “sudden” compelling desire. Urgency does not have to be sudden, as suddenness does not distinguish OAB from nonOAB, and as normal people experience urgency. Urgency can be graded by several different scores or scales and these can be helpful in describing the severity of symptomatology.

The phrase “if there is no proven infection or other pathology” was also discussed as being somewhat confusing. The current definition of overactive bladder suggests a pathophysiology related to detrusor overactivity, but Dr. Blaivas pointed out that there are many instances of urgency without a urodynamic demonstration of detrusor overactivity. He concluded that the definition of OAB was flawed and much too restrictive, and that OAB was actually a symptom complex with a differential diagnosis. He also thought that the International Continence Society definition of urgency should be changed to “a compelling desire or urge to void which is difficult or uncomfortable to defer.”

**Have Antimuscarinics Stood the Test of Time?**

Dr. Marcus Drake described the range of antimuscarinic products available and their evolution dating back to 1975 (oral oxybutynin). Through the years, with the introduction of different products with various characteristics, the efficacy and safety overall had been improved. The introduction of flexible dosing represented a distinct improvement for at least a proportion of patients with overactive bladder.

Data certainly have shown that antimuscarinics are capable of improving all of the relevant parameters related to overactive bladder symptoms, including urgency episodes, urgency incontinence episodes, pad use, micturition frequency and quality of life. Caution is needed with these medications in several situations such as gastroesophageal reflux, inflammatory bowel disease, myasthenia gravis, certain cardiac abnormalities and poorly controlled closed angle glaucoma.

However, he also pointed out that the use of antimuscarinics in men who have only storage symptoms or residual storage symptoms after treatment with an alpha blocker and/or 5-alpha reductase inhibitor was now an accepted form of treatment, especially the use of flexible dose antimuscarinics, which allow the treatment regimen to better balance efficacy and tolerability in individual patients.

Solid data have resulted in evidence-
based recommendations to treat men with primarily storage lower urinary tract symptoms (LUTS) with antimuscarinic monotherapy and, for men with storage LUTS and voiding dysfunction, to start initial management by targeting the voiding issues and then adding an antimuscarinic if storage symptoms remain troublesome.

Acute urinary retention was cited as being “probably an issue” with such management only for patients with prominent storage symptoms in conjunction with severe bladder outlet obstruction. The possible association of the cumulative use of strong anticholinergics and the incidence of dementia was also addressed.

When data suggested such an association, it was most likely the overall anticholinergic load that was the risk factor. In the 5th International Consultation on Incontinence (2013), the International Scientific Committee recommended that in cognitively intact frail older people, antimuscarinics may be added to conservative therapy of urgency urinary incontinence, with grades of recommendations of A to C depending on the agent.

Although there have been some head-to-head trials of antimuscarinics for the treatment of overactive bladder, there were few, if any, such trials which compared the newer entrants to the market against each other. The long-term persistence with antimuscarinic therapy is relatively poor, a disturbing factoid that has been reported on numerous times in the literature. After 1 year of therapy, various estimates put the percentage of people who continue to take their bladder antimuscarinic as 20% to 30% or less. The lack of persistence is ascribed to poor resolution of symptoms, poor balance of efficacy and adverse events, and the failure of the medication to address issues that matter to the patient, which may vary from patient to patient. These may include impairment at work, of travel, of sex, of sleep and other personal issues.

Finally, Dr. Drake described some of his own tricks for maximizing efficacy, such as combining an extended release tablet for 24-hour coverage with an immediate release tablet used flexibly to cover individual priorities. However, he warned the patient that this is an unlicensed approach.

Clinical Trials vs Real World Experience of Anticholinergics

Dr. Sender Herschorn first pointed out the comorbidities associated with OAB such as obesity, hypertension, depression, asthma, chronic constipation and neurological conditions. He cited various studies showing worse sexual function in respondents with OAB, a more common unemployment status or impaired status at work, and described the considerable economic cost of overactive bladder based on a 2015 estimate of a cost of $1,944 per capita. He then went on to discuss some of the actual results with antimuscarinic drugs in terms of leakage episode reduction, perception of cure or improvement and global adverse events. There seems to be a trade-off between efficacy and adverse events, at least according to some reports.

My take home message from this portion of the talk was that one had to critically evaluate clinical significance as well as statistical significance, at least as these apply to efficacy parameters. Some long-term persistence results were cited as being considerably higher than what is usually assumed to be persistence of these agents. However, being familiar with some of these studies, it should be noted that many of these counted only patients who elected to enter extension trials after the completion of a study.

Dr. Herschorn cited a systematic review of long-term adherence that put the median persistence at 12 months at 12% to 39%, at 18 months 8% to 15%, at 24 months 6% to 12% and at 36 months 0% to 16%. In discussing the reason for poor persistence, he pointed out that many patients were dissatisfied because of unrealistic treatment expectations, a message to all of us who treat patients with OAB. In his conclusion, he cited progress in many aspects of OAB, its high prevalence and costly measurable impact on society, but he noted “discrepancy in pharmaceutical reporting of clinical trials and real world data.”

Beta-3 Agonists: Will they Fill the Void?

Dr. Victor Nitti began by discussing a survey of patients with OAB who had discontinued antimuscarinics, the prime reason being a lack of expected efficacy and a prominent reason being side effects. He then discussed the AUA/SUFU guideline for the diagnosis and treatment of nonneurogenic overactive bladder in adults, and that behavioral therapies should be offered as first line therapy and antimuscarinics or oral beta-3 adrenoceptor agonists as second line therapy, with an evidence strength grade of B for the oral medications.

He discussed the pharmacology of beta-3 receptor agonists, pointing out that the bladder and urothelium contain 3 types of beta receptors but 95% of these in humans are of the beta-3 subtype. Agonists of this subtype cause significant relaxation of human bladder muscle strips and because of their profile they would avoid the undesirable adverse events of increased heart rate and muscle tremors.

Currently, there is one beta-3 receptor agonist on the market and one with encouraging phase 2 studies in development. He discussed the various phase 3 studies on the efficacy and adverse event profile of mirabegron, pointing out favorable results of the phase 3 studies in terms of reduction in incontinence episodes and reduction in micturition. Changes also occurred in the number of urgency episodes, mean level of urgency and average voided volume (the latter, an increase). Changes in blood pressure and pulse rate did occur with some doses but these were minimal.

As with antimuscarinics, mirabegron
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appeared safe in men with lower urinary tract symptoms and bladder outlet obstruction. Whether mirabegron has an efficacy similar to that of antimuscarinics awaits direct comparison studies. There are definite advantages over the antimuscarinics with respect to adverse events. Dry mouth and constipation are essentially nonexistent compared to placebo.

Dr. Nitti’s personal observations were that some patients responded preferentially to antimuscarinics and some to beta-3 agonists. Some patients responded well to both and some patients responded best to combination therapy (not yet approved by the Food and Drug Administration). He thought the side effect profile definitely favored the beta-3 agonists. He cited one study which suggested that by combining a dose of beta-3 agonist with the lower dose of a flexible dose antimuscarinic, an efficacy equal to the higher dose antimuscarinic could be achieved without a corresponding increase in adverse events.

Finally, he cited a late breaking abstract which reported that an add-on treatment with mirabegron provided additional benefit to a dose of 5 or 10 mg solifenacin in incontinent patients with overactive bladder with an insufficient response to 5 mg solifenacin.

With respect to combination therapy, finding the optimal dose combination and whether add-on is better than initial combination therapy remains to be explored. Other areas awaiting investigation include the combination of an alpha blocker with a beta-3 agonist for male lower tract symptoms which include overactive bladder. The question of whether persistence is better than with antimuscarinics has not yet been explored. He suggested that combining a beta-3 agonist with botulinum toxin or neuromodulation might represent a further advance in efficacy.

What is New in the Pipeline
In his usual expert way, Dr. Karl-Erik Andersson ended the session. He cited current targets including muscarinic receptors and beta-3 agonists and afferent and efferent neurotransmission (botulinum toxin). He described 3 new antimuscarinics in the pipeline, one of which was a highly selective M3 receptor antagonist, one which combines a non-selective muscarinic receptor antagonist and a sodium channel blockade agent to inhibit afferent pathways, and one that combines tolterodine and pilocarpine, presumably to reduce dry mouth and constipation.

He also described 2 beta-3 agonists in development. He discussed developments in botulinum toxin therapy as possibly including liposome encapsulation and methods to increase neurotoxin persistence.

The list of potential future therapies/targets is long, and includes purinergic receptor antagonists (especially P2X3), TRP (transient receptor potential) antagonists, agents affecting the cannabinoid system (agonists, antagonists), centrally acting drugs, prostanoid receptor antagonists, nerve growth factor inhibitors, rho-kinase inhibitors, vitamin D3 receptor agonists, potassium channel openers, monoamine reuptake inhibitors, opioid receptor agonists, agents acting on serotonin receptors, drugs acting on the nitric oxide/cyclic guanosine monophosphate system and modulators of the GABAB receptor.

In a pithy statement that summarizes the status of a lot of these hoped for developments, he quoted Francisco Cruz, “In conclusion, TRP receptors are a reality that still need an enormous amount of work and dedication before becoming therapeutically useful. And that may take more time than we anticipate at the moment.”

Second Opinion Cases: Refractory Overactive Bladder and Female Incontinence

Gary Lemack, MD, Panel Leader

This panel on urinary incontinence in women featured presentations by Dr. Ariana Smith and Dr. David Ginsberg. The panelists discussed common management dilemmas in stress urinary incontinence (SUI) and overactive bladder (OAB).

Urinary incontinence (UI) prevalence estimates in women vary widely depending on the definition used and the population studied, although it has been estimated that 53% of American women have some form of incontinence with at least 10% reporting weekly incontinence episodes. While a variety of sociodemographic and physical risk factors have been identified, age, parity, body mass index, smoking and comorbid conditions (ie type 2 diabetes, depression) are among the factors most commonly associated with UI.

Overactive bladder remains one of the most bothersome conditions reported by American women. A structured management algorithm has been developed by the AUA/SUFU, which highlights the appropriate diagnostic strategy as well as a stepwise approach to treatment. Dr. Ginsberg pointed out that the minimal evaluation required includes a thorough history (including documenting current medications), physical examination (including pelvic examination) and urinalysis.

Other tools (post-void residual volume [PVR], questionnaire, voiding diaries) may be helpful in the initial assessment for some patients, but other invasive studies such as urodynamics (UDS) are likely not necessary in the baseline evaluation of the patient with nonnervenous bladder. While pelvic organ
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pulspage (POP) can certainly coexist in women with OAB, moderate stage POP (ie stage 1, 2) should not be repaired with the intention to improve OAB unless POP symptoms (bulge, pressure) are also bothersome for the patient.

If symptoms are bothersome enough for the patient to desire treatment, the initial approach to OAB should be non-invasive, focusing on behavioral modification (ie dietary modifications, timed voiding, fluid management, learning urge suppression techniques). Medical therapy (antimuscarinic or beta-agonist) can be initiated at the initial consultation or after evaluating the impact of behavioral techniques.

Once daily medical formulations are generally associated with fewer side effects and typically recommended as first line agents. An adequate period of therapy to assess response is 4 to 6 weeks for oral therapy and 8 to 12 weeks for behavioral modification. If the initial trial of oral therapy is insufficient (inadequate response vs bothersome side effects), options include a higher dose of the same agent, an alternative agent in the same class or a different class of oral therapy.

More complex cases may require additional evaluation, particularly those with minimal response at all to therapy, those with coexisting SUI and those with advanced POP. While UDS may certainly have a role in the evaluation of these patients, no widely accepted UDS parameters have been identified to clearly direct therapy in patients who do not respond to initial treatments.

For those women who seek additional treatment, sacral neuromodulation, percutaneous tibial nerve stimulation and intradetrusor onabotulinumtoxinA injections are all currently approved. While there is no reason to believe these modalities would not be effective as first line treatments, in general they are reserved for patients with inadequate response to initial therapies based, in part, on the design of the original clinical trials for each.

Dr. Ginsberg pointed out that each of the different therapies might appeal to different patients based on their personal expectations and risk aversion profile and that no universal recommendation can be made. After a thorough discussion of each modality, any of these options will likely lead to adequate improvement in the majority of patients.

Dr. Smith discussed treatment of the “index” patient with SUI as well as more complex cases. Referring to the 2009 AUA guidelines on the evaluation and management of SUI (which are currently in the process of being updated), Dr. Smith noted that an initial evaluation consisting of a thorough history, physical examination, urinalysis, assessment of bladder emptying (PVR) and demonstration of SUI during examination (typically a supine stress test) may suffice in most patients before embarking on surgical therapy.²

In a multi-institutional trial Nager et al, on behalf of the Urinary Incontinence Treatment Network, noted that the addition of UDS to standard pre-operative testing (examination, supine stress test, assessment of bladder emptying, urinalysis) in women with demonstrable SUI, symptomatology suggestive of SUI alone or stress predominant mixed UI, and minimal PVR, did not improve surgical outcomes.³

The choice of sling type may take into account a variety of considerations. While overall stress specific outcomes might be superior after retropubic mid urethral sling (RMUS), these procedures are associated with more intraoperative bladder perforation and a higher likelihood of postoperative voiding dysfunction than transobturator MUS (TMUS). Single incision slings, while widely used, still do not have the same high quality long-term data compared to MUS. Therefore, direct comparisons of long-term outcomes are not possible.

In women with persistent incontinence after MUS, further diagnostic testing may be helpful. UDS may be useful in distinguishing true persistent SUI from urgency UI due to detrusor overactivity. Outcomes of retropubic procedures (fascial sling or RMUS) appear to be superior to TMUS in women with persistent or recurrent SUI, and are generally advocated for this patient population. Bulking agents, while having an inferior outcome overall, may have a select role in such patients wishing to avoid another open surgical procedure.

In patients with symptoms of bladder outlet obstruction after MUS (typically voiding dysfunction or de novo urinary urgency), early intervention is advocated by most (by 4 to 6 weeks). In these cases, evaluation with UDS is not necessary and prompt intervention (sling loosening, sling incision) is generally recommended. Office based dilations are generally considered ineffective at relaxing an obstructed sling and sling incisions are typically associated with recurrent incontinence rates of 20%, even when performed in the first month after initial placement. Health care providers are referred to the OAB and SUI guidelines for further information on optimizing clinical management.

Point-Counterpoint: Refractory Overactive Bladder (OAB) with Pelvic Organ Prolapse (POP)

Kathleen Kobashi, MD, Moderator

Overactive bladder (OAB) is a prevalent problem that by 2018 is projected to affect more than 500 million people worldwide. The prevalence of OAB and pelvic organ prolapse (POP) increases with age, but clearly these 2 conditions can exist concomitantly or independently of each other. When OAB is complicated by the presence of moderate to high grade POP (or vice versa), careful evaluation and consideration of the potential causes of the OAB are critical to provide patients with optimal care. In this point-counterpoint session, we discussed the clinical dilemma of which to treat first when OAB and POP coexist.

The prevalence of OAB is higher in patients with POP and conversely POP is a known risk factor for OAB. Independent risk factors for OAB include symptomatic POP, prior anti-incontinence/POP surgery, age greater than 75, being overweight, postmenopausal status and smoking. Some have suggested that repair of prolapse can result in resolution of the OAB, and this is based largely on the theory that high grade prolapse can cause urethral kinking and consequent bladder outlet obstruction and secondary OAB.

The question at hand is to determine whether a given patient’s primary concern is an anatomical or a functional one. Other important considerations include the degree of bother the patient’s symptoms are causing her. Is it necessary to treat the prolapse at all or is it reasonable to simply proceed with treatment of the OAB, understanding the risk of precipitating retention in patients who may have a degree of bladder outlet obstruction due to the prolapse?

The panel used a case illustration to facilitate the discussion on treating the OAB (Dr. Ann Gormley) or the prolapse (Dr. Sandip Vasavada) first. The case was a 58-year-old woman with stage 2 anterior prolapse to 1 cm beyond the hymenal ring. She described bothersome urinary urgency requiring 2 pads a day and mild obstructive voiding symptoms, and she had no subjective or objective stress incontinence. Urodynamics showed a bladder capacity of 400 cc with low amplitude detrusor overactivity (DO) and a pressure-flow study equivocal for obstruction.

OAB symptoms include urinary frequency and/or urgency with or without incontinence. The AUA/SUFU OAB guidelines provide a stepwise approach to the treatment of straightforward OAB, broken down into 3 main tiers. First line treatments include behavioral therapies. Second line treatments include oral antimuscarinics or beta-3 agonists. Third line treatments include neuromodulation, either biological with intradetrusor onabotulinumtoxinA (100 U) or electrical with peripheral tibial nerve stimulation or sacral neuromodulation.

Much of Dr. Gormley’s presentation in favor of treating the OAB first was founded on the flaws in the literature supporting treating POP first. The best review evaluating the relationship of POP and OAB included 917 studies on OAB, DO and POP. There were 46 studies that met the inclusion criteria. Only 2 drug studies were included, 1 of which focused on tolterodine in patients with stage 1 vs stage 2 or greater POP. After treatment, only 14% of patients with stage 1 POP had OAB vs 39% of those with higher grade POP. This group postulated that the POP must provide some causative effect on bladder function to result in OAB, the symptoms of which would not improve without treatment of the POP.

In the BE-DRI study Richter et al examined the predictors of outcomes in the treatment of urgency incontinence. They sought to determine which women could stop treatment and still remain continent. The findings suggested that the 1 factor associated with success was greater anterior wall POP, leading them to hypothesize that POP causes kinking of the urethra. This prevents urine from reaching the proximal urethra, which in turn causes DO. These reports represented 2 distinct drug studies with directly opposing conclusions.

Looking at surgical trials, studies have suggested that OAB symptoms improve after POP surgery. However, there is significant variability in the studies that are available in the literature and, thus, that were included in de Boer’s review. A key consideration suggested by the AUA panelists and several authors was patient bother. In other words, if the OAB symptoms are more bothersome than the POP, many suggest consideration of primary treatment of the OAB per the OAB guidelines.

Another study dichotomized POP based on stage, and found that patients with higher grade POP had greater persistence of OAB symptoms after POP surgery. The investigators concluded that this was related to irreversible structural changes in the detrusor muscle due to the POP.

Dr. Vasavada advocated for the treatment of POP first. Limitations on first and second line therapies include poor compliance, high cost and adverse effects, in addition to limited improvement in symptoms even without concomitant POP. Additionally, the potential of POP to cause OAB would lead one to consider treating the POP first. “Unkinking” of the bladder may allow relief of obstruction and, subsequently, less OAB.

Reduction of POP has resulted in improvement of OAB, whether it be...
Panel Discussion: Special Considerations for Treating OAB in the Elderly

Kevin Pranikoff, MD, Moderator

Overactive bladder (OAB) is common in older adults, and is associated with substantial impairment in mental health and health related quality of life (HR-QOL). Since the prevalence of OAB increases with age, identifying and treating OAB in the elderly is important as it is usually associated with an increased risk of falls, fractures and mortality. The use of botulinum toxin A (BoNT-A) in this vulnerable population was discussed by Dr. Hann-Chorng Kuo.

The first line treatment for OAB should start with lifestyle modification followed by the second line of pharmacotherapy. However, conservative treatment and antimuscarinics (AMS) may result in insufficient improvement and low compliance because of bothersome adverse events. Intravesical injection of BoNT-A is effective for idiopathic detrusor overactivity (DO) refractory to AMS. Several randomized placebo controlled studies have proven that BoNT-A 100 U is well tolerated, and displays significantly and clinically relevant improvements in all OAB symptoms and HR-QOL in patients inadequately treated with AMS. Improvement of urgency severity is significantly associated with a higher success rate at 3 months and longer therapeutic duration after intravesical BoNT-A injection for DO. Repeated BoNT-A injections for refractory OAB are safe and effective.

The most common reasons for discontinuing injections were poor efficacy and issues related to clean intermittent catheterization. Safety is a major concern, especially in elderly individuals. Although safety and efficacy were similar between elderly patients without frailty and younger patients, an increased risk of a large post-void residual (PVR) and a lower long-term success rate in frail elderly patients were noted. Male gender, baseline PVR greater than 100 ml and presence of comorbidities are independent risk factors for a higher incidence of acute urinary retention or large PVR after treatment.

Overactive bladder symptoms are the most common urinary symptoms experienced by individuals with Parkinson's disease (PD). Because of common comorbid conditions related to PD such as autonomic dysfunction, constipation, increased fall risk, sleep dysfunction and cognitive impairment, persons with PD may be more vulnerable to medication side effects. Dr. Camille Vaughan reviewed a practical approach to the initial management of OAB in the setting of PD.

Providers may consider a brief cognitive screening test, such as the Mini-Cog in order to guide treatment options. The presence of cognitive impairment may cue the provider to be more cautious about prescribing medications with strong anticholinergic properties that could impact cognition, such as AMS. Lifestyle modification and behavioral therapy are reasonable initial approach-
es to OAB symptoms in persons with PD. Fluid management includes maintaining adequate fluid intake to promote bowel regularity and hydration, while modifying the type and timing of fluid to include sips throughout the day and a reduction in caffeine and alcohol intake, if needed.

A pilot study published in 2011 suggests that pelvic floor muscle exercises may be beneficial for OAB symptoms in the setting of PD. Optimization of comorbid conditions such as constipation or sleep dysfunction may also improve symptoms attributed to the lower urinary tract.

When lifestyle modification and behavioral therapy are not sufficient, medications are a next step. The overall anticholinergic burden of current antiparkinsonian therapy as well as the potential for cognitive side effects and constipation should be considered carefully before adding AMS. Generally the risk of these side effects is decreased in extended release or transdermal preparations.

A 2015 study of solifenacin provides preliminary evidence for its efficacy in persons with PD and OAB, and is the first study to evaluate any antimuscarinic in a well-defined cohort of patients with PD. A beta-3 agonist could be considered as an alternative to antimuscarinic therapy and may have less potential to cause cognitive or bowel side effects.

Nocturia may represent a somewhat occult presentation for OAB in older men with benign prostatic hyperplasia (BPH), as discussed by Dr. Kevin Pranikoff. In a previous era, it was assumed that nocturia in the presence of BPH was due to bladder outlet obstruction (BOO) with decreased functional bladder capacity. Other possible reasons are also now appreciated including detrusor underactivity and DO with or without BOO. With BOO, one has an increased probability of DO as well as an earlier appearance of DO and higher amplitude of contractions.

Behavioral modification is low risk, and measures such as fluid restriction in the evening, caffeine and alcohol avoidance and leg elevation in the evening along with emptying the bladder at bedtime may be effective. At least 1 study has shown a 50% response. Patients with nocturia and BOO will often have a good response to alpha blocking agents. If they have concomitant DO, they will often respond to the addition of AMS along with alpha blockade.

Treatment of OAB in the elderly requires a nuanced approach. We may be able to avoid AMS where possible using alternative techniques. Where not possible, we may choose them wisely based on evidence where available.

References:

**Take Home Message: Female Urology, Incontinence and Urodynamics**

Gamal M. Ghoniem, MD, FACS, Orange, California, provided the audience with highlights of the AUA meeting on female urology, incontinence and urodynamics. The abstract numbers are indicated in parentheses.

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This review will summarize the presentations at this year’s AUA meeting on topics related to overactive bladder (OAB), neurogenic voiding dysfunction, mesh/female urology, pelvic organ prolapse and impaired bladder contractility/underactive bladder.

**Overactive Bladder**

The majority of treatment and outcome data regarding OAB are limited to clinical trials. However, real-world patterns of OAB care in the U.S. were examined in a multicenter study using a national observational data set (PD27-06). Based on ICD-9 codes for OAB, 46,648 patients were enrolled. In the study, anticholinergic therapy was used in only 34% of females and 19% of males, indicating possible underuse of effective therapy.

OAB third line therapy was a major focus at this year’s meeting. In a crossfire debate on neuromodulation vs botulinum toxin for idiopathic detrusor overactivity...
activity, one party concluded that neuromodulation and neurotoxin injection can be used as first line treatment. Third line therapies clearly provide patients with choice, and patients should be counseled regarding the pros and cons of each therapy.

Botulinum toxin. In an ad hoc analysis phase 3 study investigators examined the results of 227 patients with neurogenic detrusor overactivity (NDO) who completed a 4-year treatment with onabotulinumtoxinA (onaBTXA) and experienced consistent improvement with time (PD1-01).

In another study, asymptomatic bacteriuria significantly increased the risk of urinary tract infection but not urosepsis or hospitalization (458 injections, including OAB 171 and neurogenic detrusor overactivity 278) (PD1-08).

Decreasing the number of injection sites does not seem to decrease efficacy as demonstrated in a rat spinal cord injury model (PD1-03) and in a clinical study (MP89-17). The latter group suggested using 10 sites rather than 20.

Another study compared onaBTXA 200 U to abobotulinum toxin A (aboBTXA 750 U) in 211 consecutive patients with neurogenic bladder and obtained similar results (PD1-04).

In a basic science study, onaBTXA was compared to aboBTXA in mice using immunohistochemical staining of cSNP-25 (MP8-20). A ratio of 1:2 was more suitable for idiopathic OAB to avoid high rates of urinary retention.

A 30% real-world retention rate was found in 103 patients with idiopathic OAB after onaBTXA injections requiring clean intermittent catheterization (PD27-08). The investigators pointed out the need to standardize definitions and define risk factors for better patient counseling.

In a study of other beneficial effects of onaBTXA, injection decreased frequency and severity of autonomic dysreflexia were reported in 17 patients with spinal cord injury above T6 (PD1-06). Improved bladder compliance was also reported in 27 patients with neurogenic bladder (PD1-07). Interestingly, early injection yielded better results.

Neuromodulation. In an examination of quality of life after InterStim® at 3 years in 272 patients, decreased depression and pain and increased sexual function were reported (PD27-07). However, the researchers cited 44% device related adverse events.

Bilateral lead placement seems to be of limited value. The majority of patients with bilateral lead implant for stage I sacral neurostimulation (SNS) ultimately had a unilateral lead (PD27-04). Bilateral lead implant may benefit some patients, although further studies are warranted.

In a study of 244 patients, investigators questioned how many active electrodes in the tined lead are needed to achieve clinical success (PD27-10). It was concluded that at least 1 functional electrode is needed. After stratifying 78 patients (36 age 61 to 80 years), age did not adversely affect outcomes after SNS (PD27-02).

Neurogenic Voiding Dysfunction

In a review of the medical records of 99 of 118 patients with severe cerebral palsy and Gross Motor Function Class System of 4 or 5 during a 10-year period, it was recommended that a nonoperative approach be used in the absence of compelling indications (PD10-08).

Another group used a more restrictive approach to urodynamic testing in patients with multiple sclerosis using the criteria of post-void residual volume greater than 100 ml (PD10-05). They concluded that a Urogenital Distress Inventory-6 score greater than 7 could eliminate 16% of tests.

Another study, lumbar to sacral ventral nerve rerouting in 6 of 8 spinalized cats (spinal cord injury at T9-T10) restored voiding after cutaneous stimulation (MP12-04).

Mesh/Female Urology

A progressive decrease was noted in the proportion of patients undergoing anti-incontinence procedures after Food and Drug Administration (FDA) notification (MP8-07). However, this decrease was balanced by increased use of bulking agents and pubovaginal slings.

Transvaginal mesh (TVM) in the media was studied after the 2011 FDA update, and it was reported that few sites distinguish between TVM for pelvic organ prolapse repair and urinary incontinence surgery (MP81-05). Investigators raised the concern regarding how patients perceive the safety and efficacy of TVM, regardless of the indication. However, at the last SUFU meeting Nitti noted that the majority of litigation cases were from mid urethral slings.

Using the National Surgical Quality Improvement Program (NSQIP) data set, 1,280 procedures were identified with and 5,644 without mesh (PD50-04). Higher bleeding rates requiring blood transfusion and surgical site infection were found in the mesh group, although no differences were noted in other metrics.

Risk factors were analyzed for mesh removal in 59,887 community based patients (PD28-09). Revision rates after stress urinary incontinence surgery were low (1.2% at 1 year, 2.5% at 10 years). As expected, high volume surgeons were associated with less risk while females with multiple sling placement procedures were at high risk.

Pelvic Organ Prolapse

In a crossfire debate on sacrocolpopexy for apical prolapse, it was noted that although the transvaginal approach has been somewhat lost in the debate, this approach may be quite satisfactory for many women. Regardless of the gold standard, patient outcomes and comorbidities should be considered.

In a comparison of open abdominal sacrocolpopexy (ASC) and laparoscopic sacrocolpopexy (LSC) with a median followup of 32 months LSC is equivalent to ASC with decreased morbidity, less blood loss and shorter recovery (MP81-
Impaired Bladder Contractility/
Underactive Bladder

There has been a resurgence of interest in basic and clinical research regarding one of the most neglected areas of voiding dysfunction, that of impaired bladder contractility. Basic science research depends on validated animal models, which still seem to be difficult to achieve. Bilateral pelvic nerve severance or crush has proven to be reliable. One group was successful in developing such a model following hysterectomy in monkeys (severing the pelvic nerve), while inducing obesity yielded conflicting results (MP8-01).

Although one group was successful finding underactive bladder (UB) in obese rats (MP8-04), another group found that a high fat diet resulted in OAB (MP8-07). In addition, the effects of ischemia yielded variable results.

Ischemia produced OAB in 8 weeks and UB in 16 weeks (MP8-08). Conversely, chronic ischemia resulted in OAB and resveratrol protected the bladder from OAB (MP8-14). Finally, in a retrospective analysis of 4,272 urodynamic studies, it was concluded that UB is not a symptom complex and should be based on urodynamic diagnosis (MP89-08).
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