# *Management of refractory overactive bladder in adults*

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*Urologists experience frustration in the treatment of refractory overactive bladder for a multitude of reasons. Clinical failure experienced in managing these patients can lead to long office interactions and feelings of inadequacy for both patient and provider. With newer, technically straightforward interventions, this population can be approached with confidence. Appropriately timed diagnostics are essential in identifying neoplastic, neurogenic, and infectious causes for refractory overactive bladder. When approached in an efficient, stepwise fashion, outcomes can be highly satisfactory for both the patient and the provider.*

**Key Words:** overactive bladder, anticholinergic, refractory, treatment failure

## Introduction

Overactive bladder (OAB) syndrome, also known as urge syndrome or urgency frequency syndrome, is a symptom complex defined by the International Continence Society as "urgency, with or without incontinence, usually with frequency and nocturia.'[1] The most important management consideration is the fact that the syndrome is a symptom complex - the etiology varies widely. The most common cause remains "idiopathic". Benign causes include increasing age, pelvic floor spasm, atrophic urethritis, and irritants such as tobacco abuse, caffeine, or diet sodas. Causes warranting further work-up need to be considered at every step in management. These include neurologic disease, diabetes, bladder stones, infection, bladder or adjacent organ cancer, fistula, as well as obstruction by the prostate, pelvic organ prolapse, or prior surgery.

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Initial management of OAB after a benign history, physical exam, post void residual, and urinalysis (negative for blood or infection), includes behavioral and medical therapy. When these initial interventions fail, it is advisable to seek a more complex or ominous cause. If further pathology is not identified, effective third line tools are available to help even the most severe of patients. The goal of this discussion is to provide a brief guide for initial management of overactive bladder followed by an in depth discussion of refractory overactive bladder.

## Bladder function

Complex voiding dysfunction can be understood in the context of the bladder's simple functions. The role of the bladder is to store and to empty urine.

*Storage:* the bladder should store urine at low pressures allowing for easy antegrade efflux from the kidneys down the ureters into the bladder. Storage should occur without leakage or bothersome bladder sensations.

*Emptying:* When it is a convenient time to urinate, bladder emptying should be initiated voluntarily by the cerebral cortex, through the pontine micturition

center, the bulbospinal tracts, and the sacral reflex arc. The detrusor should contract, the pelvic floor should relax, and the bladder should empty fully without reflux to the kidneys.

## Bladder dysfunction

Interruption of the neural, vascular, anatomic, and muscular mileu of the bladder can lead to irritating frequency, urgency and urge incontinence, diminished quality of life, loss of work role, infection, and in severely compromised systems, renal failure or death. In addition, some causes of OAB have their own distinct ramifications. This manuscript aims for pragmatism in identifying the dangerous bladder (e.g. high pressure storage) and serious etiologies of OAB (e.g. multiple sclerosis). It should be emphasized that although psychological overlay can exist in this population, it is extremely risky to recommend psychological consultation as the only intervention.

## History

The interview is often painstaking due to the subjectiveness of urinary symptoms, poor recall for a habitual activity, and the extraneous unwanted detail elicited during the discussion (e.g. what time the patient wakes up). Intake forms, standardized measures, and voiding diaries can save time and add accuracy in the initial and follow-up visits. Active questioning should characterize prior surgeries, bowel function, history of pelvic organ prolapse, presence of neurological disease, and adherence to routine health screening, e.g. colonoscopy (a current exam decreases suspicion of fistula). The voiding diary can identify excess fluid or caffeine intake, or nocturnal polyuria (> 35% of daily urine production occurring at night[2]).

## Physical exam

In addition to the standard physical exam, a few details add minutes to the initial visit but can save hours in patient care. Ambulatory status, body mass index, and hygiene are obvious at first glance. More subtle findings include shuffling gait (suggestive of Parkinson's), fear of the physical exam (pelvic floor spasm), atrophy of calf muscles (tethered cord), and pedal edema (nocturnal polyuria). Genitourinary examination must include evaluation for prolapse in women, Figure 1, most specifically an obstructing cystocele. The standing position should be considered at the end of the exam to further characterize apical descent, as vault or uterine prolapse significantly impact surgical management options for cystocele. The apex can be characterized by asking the patient to maximally strain while holding the fingers gently on the vault or cervix. Examination of the levator muscles in both men and women is straightforward. The muscles can be appreciated posterolaterally during digital vaginal or rectal exam. The puborectalis, for example, passes posterior to the rectum close to the perineal body. Manual pressure is perceived as uncomfortable and can reproduce symptoms experienced clinically. Digital rectal examination will also reveal the presence of hypotonic sphincter tone, impacted hard stool, or, in women, a lax perineal body.

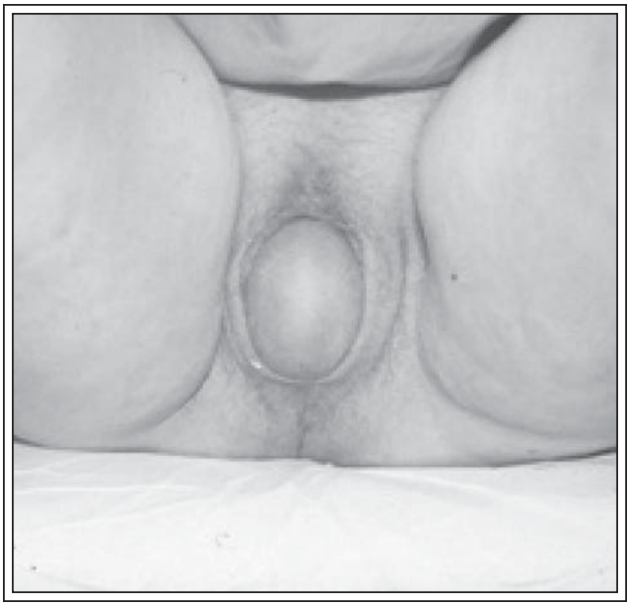

**Figure 1.** Pelvic organ prolapse, unspecified compartment.

Neurological exam is performed to a level of detail commensurate with index of suspicion. Sensation of the perineum derives from S3-5, the anterior scrotum and labia from thoraco-lumbar roots, and the posterior scrotum and labia from sacral roots. The bulbocavernosus reflex tests the integrity of the sacral 2-4 central and peripheral pathways. The cremesteric tests L1-L2. The abdominal reflex tests T6-L2 and is only present if there is an upper motor neuron lesion. The anal wink interrogates S2-5.

## Chart review

Prior creatinine, PSA, urine samples, upper urinary tract imaging, cystoscopy, urodynamics, and interventions should be noted or archived at the first visit. Many patients with refractory OAB present with a string of

prior physicians due to non-resolution of symptoms. Imaging and operative notes are documented at multiple sites and the patient's recall for prior medications may be incomplete. Some of this information may save time or improve patient care in later visits. Efforts to find the information should match projected relevance (e.g. a medication previously worked but the patient could not afford it).

## Coexisting diagnoses

### *Incontinence and infection*

Incontinence and urinary tract infection (UTI) directly impact the workup. Incontinence can be characterized as urge urinary incontinence (defined as an involuntary leakage accompanied by or immediately preceded by urgency), stress urinary incontinence (involuntary leakage on effort or exertion), and mixed urinary incontinence (a combination of the latter two).[1] In addition, overflow incontinence denotes overflow of urine from a poorly emptying bladder when the bladder reaches maximum capacity, and unawares incontinence refers to leakage perceived only once the skin or clothing is wet. Incontinence can often help point toward a particular diagnosis in OAB. For example, in detrusor overactivity with hypocontractility, the bladder fails to store (overactivity) and fails to empty (hypocontractility). Leakage is both urge and overflow. Diagnosis is by urodynamic testing and treatment involves a combination of timed voiding, anticholinergic therapy, intermittent catheterization, or neuromodulation. Adult tethered cord often presents with incontinence.[3]

Infection should be immediately characterized as culture-positive or culture-negative. All symptomatic episodes should be investigated with a catheterized urine culture in women and midstream or catheterized culture in men. Patients with true culture-positive recurrent urinary tract infection and those in whom data is not reconstructable require a work-up. Upper urinary tract imaging (renal mass protocol in those with hematuria), cystoscopy, and assessment of post void residual should be performed to identify stones, tumors, renal duplication, trabeculation, incomplete emptying, fistulae, foreign bodies from prior surgery, or other pathology. Cystogram can identify more subtle fistulae and voiding cystourethrogram can demonstrate vesicoureteral reflux when further suspicion warrants. Urethral diverticulum is an often-missed cause of recurrent UTI in women. Although the classic triad includes post void dribbling, dysuria, and dyspareunia,[4] it presents most commonly as recurrent urinary tract infection, stress incontinence, pain, and incomplete emptying.[5] Magnetic resonance imaging has superior sensitivity for urethral diverticulum[6] and helps guide surgical planning. In neurological patients who self catheterize, review of catheterization technique should be performed. Catheters should be replaced once a week to prevent surface irregularity, cleaned in a clean-rinsing detergent, and left to dry in open air rather than a plastic bag. Confirmation of emptying on self catheterization can be performed as a quick step at the end of fluoroscopic videourodynamics or in conjunction with office ultrasound. Lastly, patients who self catheterize are often colonized with bacteria. It is only in the presence of symptoms that this colonization is deemed to be an infection.

When symptoms of urinary tract infection are not corroborated by cultures, (it is often the case there are one or two truly positive cultures and the rest are negative), immediate diagnostics are not always necessary. All symptomatic episodes should be cultured. Expressed prostatic secretions should be considered in men and vaginal swab for ureaplasma and mycoplasma in women. Exam of the levator muscles is essential in these patients. Symptoms of UTI can derive from pelvic floor muscle spasm due to cross – sensitization (explained to the patient as "cross talk") along the S 2,3,4 nerve pathways.[7] Relaxation of the musculature via biofeedback or pelvic floor physical therapy can lead to resolution of the episodic symptoms as discussed below. If "UTI" symptoms persist, a workup similar to culture – positive recurrent UTI should be initiated while continuing to gather culture data during episodes. Carcinoma in situ, bladder stones, and urethral diverticula are just a few potential findings.

### *Bladder outlet obstruction*

In both men and women, bladder outlet obstruction can lead to irritative voiding symptoms. Treatment of the bladder with anticholinergics often fails in the setting of obstruction. Conversely, treatment of the bladder outlet (via alpha blockers or surgery) does not always resolve the frequency and urgency resulting from a compromised bladder, especially when the obstruction has been of long duration, Figure 2. Chronic injury in the obstructed bladder is characterized by ischemic damage to nerves, synapses and smooth muscle cells within the bladder wall. This occurs due to initial poor blood flow followed by the generation of reactive oxygen and nitrogen species during reperfusion.[8] These reactive species have been shown to damage plasma and subcellular membranes in animal models. In the human model ischemia has been observed in decompensated bladders. Decreased compliance correlates with decreased blood flow in

human cystometric studies[9] as well as in the rabbit and pig bladder outlet obstruction models.[10,11]

Patients who suffer from significant irritative symptoms in the setting of bladder outlet obstruction should undergo urodynamic testing prior to surgical intervention. In order to avoid dissatisfaction with surgery, patients with decompensated bladder function should be counseled to anticipate continued voiding dysfunction after relief of the obstruction. Reassessment 3-6 months postoperatively allows for maximal detrusor recovery and initiation of further treatment directed at the bladder itself. In 40 women undergoing urethrolysis for iatrogenic bladder outlet obstruction, 56% required either anticholinergics or neuromodulation for refractory overactive bladder.[12] It is obvious why appropriate preoperative counseling is important.

Patients with OAB who failed anticholinergic therapy prior to treatment of the obstruction may now experience success. Randomized trials have shown the superior efficacy of combination therapy using alpha blockage and anticholinergic therapy in men with storage and voiding symptoms.[13]

One often-missed diagnosis in the refractory OAB patient is primary bladder neck obstruction (PBNO).[14]

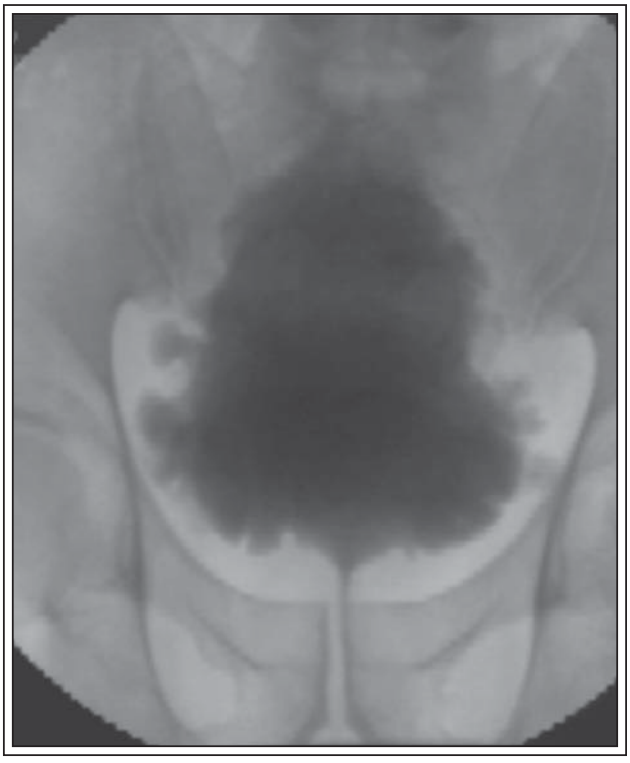

**Figure 2.** Bladder trabeculation in longstanding obstruction.

This can be present in both men and women, has an early age of onset, and can present with a combination of emptying symptoms (weak stream, hesitancy, intermittency, incomplete emptying) or storage symptoms (frequency, urgency, urge incontinence, or nocturia). Pain (46% of men and 15% of women) and elevated post void residual are common.[14] The bladder neck fails to open during voiding due to either persistent mesenchyme,[15] increased sympathetic tone,[16] or functional extension of the striated sphincter to the bladder neck.[17] Data is scant and skewed as it is comprised of retrospective reviews of referral populations. In the referral centers, PNBO is present in 33%-54% of men under 55 with LUTS.[18-20] In one large urodynamic series of women with LUTS, PNBO was present in 4.6%.[14] Cystoscopic evaluation should always include specific comment on the bladder neck in patients with voiding dysfunction. Trabeculation is not an uncommon finding. However, diagnosis is truly made by fluoroscopic urodynamic testing. The exact criteria for obstruction have not been standardized, but diagnosis is suggested by a relatively high pressure, low flow void with isolated bladder neck obstruction on fluoroscopic urodynamics.[14] Diagnosis is more difficult in patients with "shy bladder" as a history and during testing, who can have PNBO. There is no literature to guide diagnosis without a successful void on pressure flow study. Since the risks of treatment are permanent, the diagnosis should be made carefully. Treatment of PNBO is based on retrospective data. An initial attempt can be undertaken with alpha blockade, which is successful in a small proportion of patients.[21] Bilateral bladder neck incision led to an 87% improvement in symptoms but a 27% retrograde ejaculation rate in 18 men studied retrospectively.[21] Unilateral bladder neck incision in another study of 31 men allowed for preservation of antegrade ejaculation.[22] Bladder neck incision is also successful in women with PNBO. De novo stress urinary incontinence should be counseled as a definite risk.[23]

### *Pelvic organ prolapse*

Pelvic organ prolapse can lead to bladder outlet obstruction by kinking the urethra. Evaluation of urinary and defecatory symptoms preoperatively is essential to creating appropriate expectations postoperatively. Urodynamic testing with and without vaginal packing can characterize improvement in urgency or emptying ability with reduction of the cystocele and can identify occult stress urinary incontinence. A pessary trial can prognosticate response to surgery in real time, and can serve as a long term intervention in the elderly. Kinking of a cystocele over a prior sling should be specifically sought in

patients with relevant surgical history as the prolapse may be more subtle. Obstruction should be suspected and sought on urodynamics in prolapse.

### *Pelvic floor spasm*

Many patients with pelvic floor muscle spasm have seen multiple physicians and have been refractory to other interventions. The office interaction is long and sometimes difficult due to anxiety over prior negative experiences. The importance of identifying the hypertonic levator ani complex on physical exam at the initial visit cannot be emphasized enough, as it can save time, effort, and failed interventions. Pelvic floor spasm can be satisfactorily treated with biofeedback, electrical stimulation and pelvic floor physical therapy and ultimately self directed exercises. In addition, treatment of pelvic floor dysfunction identified preoperatively can be helpful in preventing perioperative crises. For example, pelvic floor spasm can lead to retention and excessive pain perioperatively. Sacral nerve stimulation or intramuscular botox injections can be employed for patients with refractory levator spasm when rehabilitative therapies fail.

### *Nocturia*

Nocturnal polyuria (actual increased production of urine at night) can be easily diagnosed based on the history and the voiding diary. This is defined as > 35% of the 24 hour volume being produced during the sleep cycle.[2] Causes of nocturnal polyuria include: increased evening fluid intake, nocturnal diuretic use, excessive resorption (congestive heart failure, venous stasis peripheral edema, hyperalbuminemia, nephritic syndrome, increased salt intake), osmotic diuresis (diabetes mellitus, sleep apnea), abnormal renal regulation (diabetes insipidus, reversal of circadian arginine vasopressin). Treatment for nocturnal polyuria usually includes treatment of the underlying condition in collaboration with the primary care physician and lifestyle changes such as evening fluid modification.

### *Diabetes*

Voiding dysfunction is present in 5%-59% of patients with diabetes.[24] Classic diabetic cystopathy is characterized as an end stage bladder due to years of sensory (and motor) neuropathy. The bladder suffers from impaired sensation, contractility, and emptying. It should be suspected in infrequent voiders (< 5x per 24h). High post void residual heralds the diagnosis and urodynamic testing can confirm it. The classic picture may not be the most common finding seen in diabetic bladders. One group of referral practices reviewed 182 consecutive patients with diabetes and persistent voiding symptoms. Fifty-five percent had involuntary bladder contractions, 23% impaired detrusor contractility, 10% had detrusor areflexia, and 11% "indeterminate findings".[24] Another group found that diabetics have a 50% increased risk of urge incontinence. Microvascular complications affect the innervation of the sphincter and detrusor, the detrusor function, and the overall vascular supply. Damage is related to the duration and severity of diabetes, the glycemic control, and the presence of peripheral neuropathy.[25] Serum glucose should be checked in patients with refractory voiding dysfunction, especially if the urinalysis is suggestive.

### *Neurogenic bladder*

Neurogenic bladder is often already known by the time the patient presents for evaluation. However, approximately 10% of all patients with multiple sclerosis (MS) present with lower urinary tract symptoms as the only complaint. 505-90% of patients with MS complain of voiding symptoms at some time during their neurological illness. This includes frequency/urgency (31%-85%), incontinence (37%-72%), and obstruction/ retention (2% to 52%).[26] Other occult neurological diseases must be kept in mind. Metastatic disease to the spine, spinal stenosis or spinal disc disease, and Parkinson's disease can all present with refractory overactive bladder.

One very challenging diagnosis is Myesthenia Gravis. Not only can myogenic bladder dysfunction be present, but this disorder is treated with procholinergics. Anticholinergics and botulinum toxin are contraindicated due to the effect on the neuromuscular junction. There is no data on sacral neuromodulation in these patients.

The treatment of neurogenic bladder is outside the scope of this paper but low pressure storage and complete emptying (facilitated by intermittent catheterization or diversion if necessary) are the mainstays of therapy. Periodic renal ultrasound, creatinine, and urodynamic testing are performed every 6 months to 2 years depending on stability. Surveillance cystoscopy seeking squamous cell carcinoma of the bladder is controversial, as annual cystoscopy often misses the rapidly progressive cancer.

## Treatment of refractory OAB

### *Lifestyle and behavioral interventions*

These interventions should be offered as first line therapy, but often patients arrive at an initial visit already on anticholinergics. Behavioral interventions can augment virtually any other form of therapy.

Reduction or cessation of caffeine, tobacco, and artificial sweeteners should be encouraged. Fluid intake should be quantified with a voiding diary and reduced. Often simply informing patients that "eight glasses of water per day" has never been shown to be healthy can help reduce fluids and symptoms. Weight loss has been shown to reduce incontinence.[27] Treatment of constipation can improve OAB in both idiopathic and neurogenic patients, most likely due to decreased afferent input along S 2,3,4.

### *Pelvic floor muscle training, biofeedback and electrical stimulation*

These interventions can be presented to the patient as teaching the "on-off" switch for the detrusor muscle. Many urologists are not familiar with these therapies, and the literature is sparse regarding the application to overactive bladder. It is best conceptualized by reviewing neural control of the lower urinary tract. Voluntary contraction of the external urethral sphincter via S 2,3,4 somatics (the pudendal nerve) leads to inhibition of the parasympathetics to the detrusor. A 50%-80% reduction in urge and/or stress incontinence episodes and 15%-50% dry rates have been demonstrated in randomized controlled trials.[28,29] Combination therapy with anticholinergic medication shows improvement beyond either intervention alone.[30] In pelvic floor muscle spasm, the purpose of relaxing the levators is to decrease afferent input along the S 2,3,4 pathways and consequent "cross talk" with the bladder (innervated by S 2,3,4 as well[7]). Biofeedback and electrical stimulation are effective in about 70% of women with pelvic floor spasm.[31] In men with chronic nonbacterial prostatitis and chronic pelvic pain syndrome, pelvic floor biofeedback reeducation led to a highly significant decrease in the Chronic Prostatitis Symptom Index (NIH-CPSI) (23.6 to 11.4, $p < 0.0001$).[32] Pelvic floor physical therapy led to moderate to marked improvement in 70% of female patients with interstitial cystitis in one study.[33] These therapies are indispensable in managing a voiding dysfunction referral practice but unfortunately the literature is not yet strong enough to instill confidence in the general urologist. As in any case of refractory overactive bladder, treatment failure should lead to consideration of diagnostic testing.

### *Anticholinergic failure*

When the pathology discussed above has been ruled out, addressed or optimized, anticholinergic medications form the mainstay of therapy. They are not always an option, as in patients with gastric retention, uncontrolled narrow-angle glaucoma, and severe renal or hepatic failure. At the time of presentation, many patients have already tried medications within the class with suboptimal outcome or prohibitive side effects. It is important to determine the dose and name of the prior medication. Increasing a dose or simply changing to another option may improve the response. Whereas some comparison trials exist among anticholinergics,[34] most comparisons are to the immediate release forms of oxybutynin and tolterodine. The change of anticholinergic choice is often empiric. Some basic differences among the medications can help. For example, those who had prohibitive dry mouth on immediate release oxybutynin may be able to tolerate transdermal delivery. Those with hepatic impairment may be permitted to take trospium chloride, which has primarily renal clearance. Lastly, the effect of imipramine hydrochloride may be synergistic with anticholinergics[35] and despite its narrow safety profile is often employed to improve storage pressures in neurogenic bladder. Patients who have previously failed anticholinergic medications may have success after other interventions, e.g. transurethral resection of the prostate.

With the advent of other treatment options for OAB, the central nervous system side effects of anticholinergic medications gain more importance. Klausner and Steers[36] recently reviewed the central nervous system (CNS) side effects, most importantly indicating that data is not available in the most at risk elderly populations. Additionally, CNS side effects are often self-reported and potentially inaccurate. In a 3 week randomized study of healthy subjects greater than age 50, 15 mg or more daily of oxybutynin ER led to impaired moderate and delayed recall, equivalent to 10 years of normal aging. The effect was not seen in darifenacin. The affected subjects were not aware of their deficit.[37] A separate prospective cohort study found mild cognitive impairment in 80% of people taking antimuscarinics for overactive bladder versus 35% of age-matched controls.[38] Another longitudinal cohort study abstract presented at the American Academy of Neurology this year demonstrated that initiation of medications with anticholinergic activity was associated with a more rapid decline in the cognitive performance of normal individuals.[39] Information regarding cognition receives a great deal of attention in the lay press and studies are lacking to answer these concerns.

### *Sacral neuromodulation*

Sacral neuromodulation (SNS, Interstim) is approved by the Food and Drug Administration (FDA) for urgency/frequency, urge incontinence, and idiopathic

urinary retention. Well over 25,000 patients have had the procedure since approval.[40]

SNS is thought to "reset" somato-visceral interactions within the sacral spinal cord by modulating sensory processing and micturition reflex pathways in the spinal cord.[40-42] Inhibition of guarding reflexes can allow for correction of idiopathic urinary retention. Inhibition of afferent interneuronal transmission as well as direct inhibition of bladder preganglionic nerves are theorized to impact detrusor overactivity.[40,42]

*Technique:* Peripheral nerve evaluation (PNE) is test stimulation with a temporary lead, placed percutaneously. Lead migration can occur and it is difficult to know whether failure is due to technical factors or the patient's potential for responding. PNE has largely been replaced by the two stage technique which involves the initial percutaneous minimally invasive tined lead[43] and, if successful, the subsequent implantation of the generator. The cross-hair technique for fluoroscopic localization is extremely simple. In the AP view, the inferior margin of the sacroiliac joint forms a horizontal line and the midline processes the vertical.[44] It is also helpful to mark the diagonal lines along the medial side of the foramen, and to insert the spinal needle into the skin along this line 2 cm above the intersection with the horizontal line, Figure 3. Lateral imaging is useful, the goal being to place lead 0 and 1 anterior to the sacral cortex and leads 2 and 3 within. A > 50% improvement on a carefully collected voiding diary is considered a successful trial.

Most surgeons perform unilateral testing. Bilateral SNS was investigated in a randomized crossover clinical trial of unilateral versus bilateral temporary lead testing of SNS in 33 patients.[45] Eight patients had lead migration. Of the remaining 12 patients with urge incontinence and 13 patients with idiopathic urinary retention, there was no statistically significant difference in success. Other non-randomized studies have shown benefit to bilateral stimulation. More research is necessary.

Sacral nerve stimulation, in its initial multicenter randomized controlled trial, is reported as curing urge incontinence in 47% of refractory patients with benefit in an additional 29%.[46] Fifty-six percent of patients with refractory urgency–frequency returned to normal voiding (4-7 times per day) or were at least 50% improved.[47] Sixty-nine percent of patients with idiopathic retention were able to discontinue CIC.[48] Many of these data should be interpreted for patients as including only those who did well with the percutaneous test trial and who went on to implantation of the permanent lead and generator. Therefore the true denominator of non-responders is much greater. Five year data is now published for the initial FDA approval trials. Only those who passed the test trial were enrolled. For urge incontinence, mean number of leaks per day decreased from 9.6 to 3.9. For those with urgency frequency, voids per day decreased from 19.3 to 14.8. For those with retention, number of catheterizations per day decreased from 5.3 to 1.9.[49] Unfortunately the dry rates and the catheter free rates were not reported. Surgical revision rates are reported as high, but have been decreasing over time with better technology to avoid lead migration, errant stimulation, and pain. Battery life is 7-10 years for the Interstim I generator and 4-5 years for the newer, smaller Interstim II generator with more programming options.

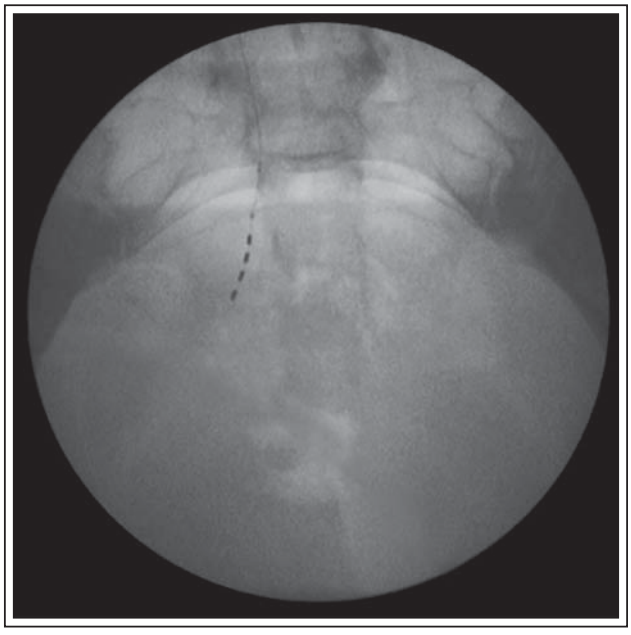

**Figure 3.** Cross-hair technique and outline of sacral foramen for localization of third sacral neural foramen.

SNS is not approved for neurogenic bladder, interstitial cystitis, pelvic pain, bowel dysfunction, or orgasmic dysfunction, although research continues for these indications.[40] In nine patients with neurogenic urge incontinence, five patients were completely dry at 43.6 months follow-up, with the average number of leaks per day decreasing from 7.3 to 0.3, frequency from 16.1 to 8 voids per day, and mean volume improving from 115 ml to 249 ml.[50] However, other larger studies contradict these results. A prospective randomized trial of 42 children with neurogenic dysfunction noted no significant improvement.[51] Seventeen of 25 patients with interstitial cystitis who went on to implantation had positive results in a prospective non randomized study. Frequency decreased from 17.1 to 8.7 and

nocturia from 4.5 to 1.1. Voided volume increased from 111 cc to 264 cc. Perhaps most surprisingly, pain decreased from 5.8 to 1.6 on a scale of 1-10, and significant decreases were seen in the IC Symptom and Problem Index scores. All results were significant to $p < 0.01$. Six of ten patients with isolated pelvic pain had improvement at 19 months.[52] A recent review details more studies regarding pelvic pain.[53] A review of heterogeneous literature on faecal incontinence found total continence in 41%-75% and improvement in 75%-100% of patients, with only limited data available for constipation.[54] A more rigorous review from 2008 identifies the need for better quality studies.[55] Small studies have investigated SNS in female sexual dysfunction with report of benefit.[56,57]

Neuromodulation can be performed in the form of percutaneous tibial neurostimulation (PTNS). Treatment involves percutaneous access to the posterior tibial nerve and once a week treatments for 12 weeks. Literature is limited, but generally a 20%-35% reduction in frequency, nocturia and UUI can be seen at 12 weeks while still undergoing treatment. Long term data and randomized placebo-controlled trials are not available. Pudendal nerve stimulation is another technology on the horizon holding promise. A summary of this literature is provided by Toby Chai.[58]

### *Chemodenervation of the bladder using botulinum toxin*

Botulinum toxin (BTX) prevents acetylcholine release at the neuromuscular junction by inhibiting exocytic neurotransmitter vesicle fusion[59] or formation[60] in peripheral motor neurons. It is reversible, easy to inject, and can be employed for idiopathic or neurogenic detrusor overactivity. BTX – Type A is most commonly used in the United States (Botox, Allergan, Inc. Irvine, California) and will be referred to as BoNT-A. Botox Type B is available in the United States and two other formulations of type A are marketed in Europe. BoNT-A has been used for less than 5 years but level-one evidence is in support of its efficacy.

The largest prospective studies in idiopathic OAB each had 100 patients and were not randomized. In Rapp's series, there was resolution of urgency in 82% and of incontinence in 86%. Frequency was reduced by half, nocturia by 2/3, and urodynamic capacity increased from 241 cc to 381 cc after 100 U.[61] In Schmid's series, 100 units of BoNT-A were injected at 30 detrusor sites in 100 patients. Urgency had resolved completely at 4 weeks in 72% and incontinence in 74%. Capacity increased by 56%. Benefits lasted 6 months. Poor response was noted in 8%.[62] Two randomized studies of idiopathic detrusor overactivity have shown benefit. Sahai et al randomized 16 patients to 200 U of BoNT-A and 18 to placebo. Impressive differences were observed in frequency, urgency and urge incontinence. Capacity increased by 145 cc at 3 weeks and 96 cc at 12 weeks. Benefit persisted at 24 weeks. Temporary but prolonged intermittent catheterization was necessary in 37.5% of patients.[63] In a study by the Pelvic Floor Disorders Network, 28 patients were randomized to 200 U BoNT-A in 15-20 injections and 15 patients were randomized to placebo. Sixty percent showed improvement based on the Patient Global Impression of Improvement scale. Seventy-two percent of the BoNT-A patients experienced a 75% or more decrease in the number of incontinence episodes. Perhaps most importantly, 43% experienced a PVR of 200 cc or greater.[64] Poor responders to 200 U in a small non-randomized prospective series were found to have high maximum detrusor pressures (> 110 cm $H_20$) preoperatively.[65] The potential for clean intermittent catheterization should be carefully counseled and taught preoperatively. Dosing of 100 U versus 200 U can be based on the patient's weighted concerns.

In neurogenic detrusor overactivity the best resource is an extensive review by Karsteny et al.[66] Two randomized controlled trials are included. In one study of placebo versus BoNT-A 200 U and 300 U, incontinence was reduced by 50% and capacity increased by 25%.[67] In a study of 75 patients randomized to 300 U BoNT-A versus resiniferatoxin, incontinence in the BoNT-A group decreased by 77%, versus 57% in the resiniferatoxin group. Seventy-three percent became completely continent.[68] Duration of effect in the Karsenty review is at least 12 to 39 weeks, with no outer limit characterized as of yet. In none of the studies reviewed by Karsenty were serious adverse events reported. UTI, hematuria, urinary retention, and injection site pain were the only complications.

Results can be impressive in individual patients, Figure 4a and 4b. Repeat injection of Botox is necessitated every 4-9 months or longer and insurance coverage can be a major issue depending on locality. Long term results are not available, but industry-sponsored randomized controlled trials are underway with an aim to FDA approval.

### *Open or laparoscopic surgery*

Bladder augmentation, autoaugmentation, and urinary diversion are options of last resort, and rarely necessary for idiopathic OAB given the newer options described above. These are primarily employed as the gold standard in patients with neurogenic detrusor overactivity who have failed medical management,

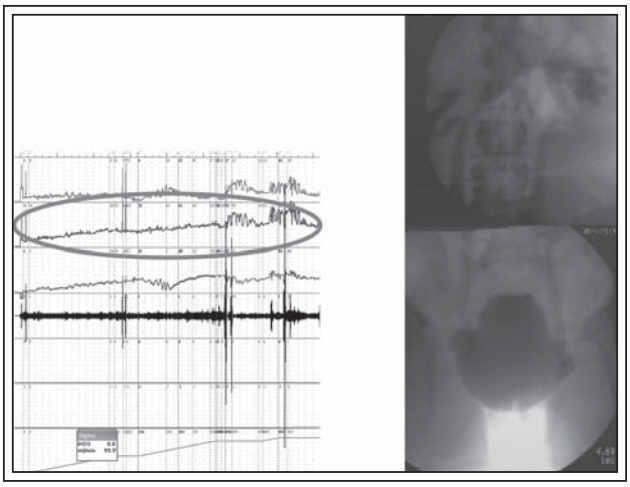

**Figure 4a.** Poor compliance, elevated creatinine, and reflux failing anticholinergics prior to botox.

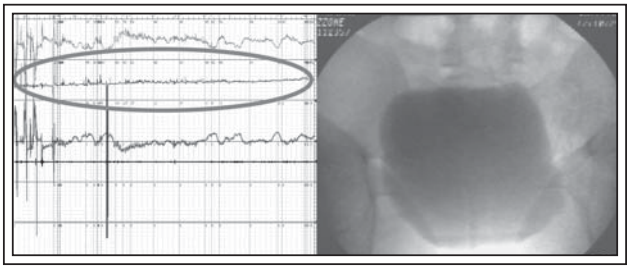

**Figure 4b.** Same patient as in 4a after Botox. Markedly improved compliance. Rectal contractions contribute artifact.

Figure 5. Randomized controlled trials of outcomes and complications do not exist, but benefits have been reported across the board. In one series of 59 neurogenic patients, improvements were seen in increased bladder capacity (220 cc to 531 cc), decreased end-filling pressures (48.9 cm to 15.8 $H_2O$), and better continence (67% dry and 29% with only mild incontinence). There was good patient satisfaction with 58/59 patients willing to repeat surgery and 59/59 >= mostly satisfied.[69] Detubularized ileum is considered superior to sigmoid.[70] In Greenwell's extensive review of the literature, neuropathic patients experienced a 92% success rate, defined as dry with stable renal function.[71] Another study reporting patient reported outcomes found 96% of patients with an improved quality of life.[72]

Complications include metabolic acidosis (alkalosis with stomach), mucus and stones, rupture (a fixed rate that does not decrease with time), cancer (11% with ureterosigmoidostomy, unknown for other segments), and incontinence. In Herschorn's study, complications occurred in 24 (40.6%): small bowel obstruction in 1, sling erosion in 1, a fluid collection in 1, deep venous thrombosis in 1, and late bladder perforation in 1, as well as need for reintervention in 21 (median time 10 years, e.g. laparotomy for rupture in 1, cystolitholopaxy in 6, stomal revision in 4, percutaneous nephrostolithotomy in 2, ureteral reimplant in 2, and further intervention for stress incontinence in 12). Greenwell reviewed complications in 1135 patients in 18 series including his own of 267. Early complications included small bowel obstruction in 3%-6%, wound infection in 5%-6%, ventriculo-peritoneal shunt infection in 0%-20%, and prolonged ileus in 5%. Late complications included failure to correct the lower urinary tract in 5%-42% largely due to the idiopathic patients in the series. Perforation occurred in 0%-9%.[70]

There is not a great deal of literature on augmentation in idiopathic detrusor overactivity. The literature that exists is heterogeneous. One report with 83% idiopathic patients reported that 78% of the group were "happy". Eleven of thirty used intermittent catheterization to empty. [70] In Greewell's review, symptomatic success was reported in only 53%-58% of patients with idiopathic detrusor instability.[70]

Autoaugmentation for idiopathic DO has had as much as a 70% reported success with some authors.[73] However, others have not reported the same results and the procedure is not used commonly.

Indwelling suprapubic tube is sometimes the option of compromise in elderly or debilitated patients. Surgical intervention is typically not reversible and should be approached with caution in non-neurogenic OAB.

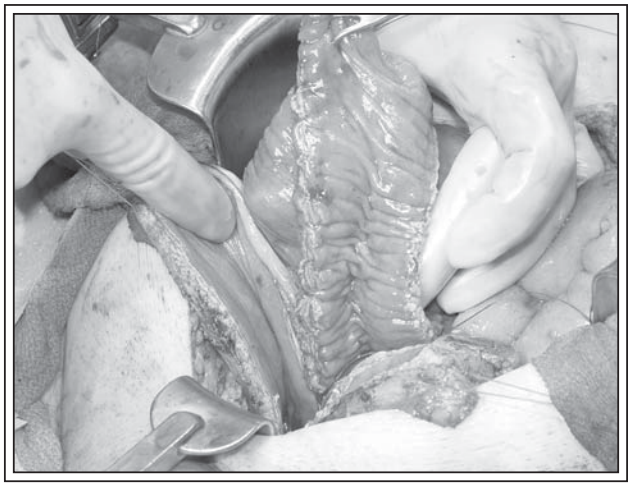

**Figure 5.** Augmentation Ileocystoplasty.

## Conclusion

The patient with refractory overactive bladder can be managed in a stepwise fashion. Careful consideration of each step above can lead to an ordered, safe, and successful approach in this difficult patient population. Due in part to availability of the newer interventions, outcomes can be highly satisfactory for patient and provider alike.

## Disclosure

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