Overactive Bladder: Evaluation and Treatment

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Last Updated:

Wednesday, January 11, 2023

1. Introduction

Overactive bladder (**OAB**) **is defined as urinary urgency, with or without urgency urinary incontinence** (**involuntary loss of urine**), **in the absen of urinary tract infection or other obvious pathology** .[1] OAB is a clinical diagnosis and characterized by the presence of bothersome symptoms such a urinary urgency, urinary frequency, nocturia, and urgency urinary incontinence.[2]

Urinary urgency is the complaint of a sudden, compelling desire to pass urine which is difficult to defer and replaces the normal physiologic urge.[1] **Increased urinary frequency** is the complaint of micturition occurring more frequently than previously deemed normal and is characterized according to daytime and nocturnal voids. [1] **Nocturia** is the complaint of interruption of sleep one or more times because of the need to micturate.[1] **Urgency urinary incontinence** is involuntary loss of urine associated with urgency.[1-3]

Keywords

Bladder outlet obstruction; BTX-A; onabotulinumtoxinA; ICS; International Continence Society; LUTS; Lower urinary tract symptoms; OAB; Overactive bladder; PFMT; Pelvic floor muscle training; PTNS; posterior tibial nerve stimulation; SNS; sacral neuromodulation system; SUFU; Society of Urodynamic Female Pelvic Medicine, and Urogenital Reconstruction; UUI; urgency urinary incontinence

2. Risk Factors and Pathophysiology

OAB is a symptom complex and thus often idiopathic. **Underlying urologic conditions resulting in lower urinary tract symptoms (LUTS) must be considered before making a diagnosis of OAB. Common causes of LUTS may include urinary tract infection, malignancy, urinary calculi, pelvi floor muscle dysfunction, diabetes, polydipsia, neurogenic bladder, and interstitial cystitis/bladder pain syndrome (IC/BPS)**. Nocturia must be precisely characterized, as each void needs to be preceded and followed by sleep.[1,4] Nocturnal polyuria (typically defined as the production of more than one-third of 24 hour total urine volume during the sleep cycle) should be excluded. [5] In the setting of nocturnal polyuria, modifiable etiologies (e.g. obstruc sleep apnea, congestive heart failure, renal disease, excessive salt intake, diabetes, and daytime edema with resorption and kidney filtration at night) sho be identified. Adults with OAB are more likely to have had enuresis as a child. [6] Longstanding bladder outlet obstruction (BOO, potentially related to kinkir the bladder neck from prolapse,[7] urethral sling procedures[8] or prostate enlargement) can lead to pathologic changes in the bladder associated with OAB symptoms. De-novo OAB symptoms may be unmasked after treatment of BOO; therefore it is prudent to assess urgency symptoms before management BOO. [9]

3. Epidemiology

LUTS, OAB, urinary incontinence, and BOO are common, with an estimated worldwide prevalence of 45%, 11%, 8%, and 22%, respectively.[10,11] I the United States, the overall prevalence of OAB is similar between men (16.0%) and women (16.9%).[12] **The definition of OAB does not include a both measure and the majority of epidemiologic surveys only assess the presence or absence of symptoms**.

In other population-based studies[12,13,14,15,16,17] OAB prevalence rates range from 7% to 27% in men, and 9% to 43% in women. No clear differences exist betv studies conducted in North America versus other populations. Some studies report higher prevalence rates in women than men, while others found simila rates across genders. [12,13,14,15,16,17]

Several studies have suggested an increased risk of urinary symptoms in persons with female family members who also have the disorder.[6] Data from th Swedish Twin registry (60% response rate from nearly 42,000 persons) indicate that LUTS are more common in women than in men. **The strongest ger effects on urinary symptoms were noted for urinary incontinence, frequency and nocturia. Urinary urgency, defined in this study as a compelli urge to urinate that is difficult to postpone [3] showed the weakest genetic link and was predominantly effected by environmental factors**.[18] Gene mapping in a large 4-generation Danish family confirmed a high prevalence of urgency incontinence and nocturnal enuresis and suggested a genetic bas for these concerns.[19] Several candidate biomarkers in OAB have been identified,[20] however the precise genetic bases of OAB, if they exist, are still poorly understood.

4. Diagnosis and Evaluation

The most contemporary **Guideline for management of OAB** in adult patients was published in 2019 by the American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU). [2] This has led to the development of the **AUA/SUFU Clinical C Pathway**.[2]

In evaluation of OAB, the clinician should engage in a diagnostic process to document symptoms and signs that characterize OAB and exclud other disorders. The minimum requirements for this process include a careful history, physical examination and urinalysis .[2] The 2019 AUA/SU guidelines detail indications for more in-depth work up and diagnostic testing.[2]

History should investigate the exact nature of each component of OAB and elucidate any underlying medical problems which may masquerade or contril

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to the symptom complex. **Examples of common comorbid conditions include neurogenic bladder (frequently seen in patients with other neurolo disorders such as spinal cord injury or neurodegenerative conditions), constipation, pelvic floor muscle dysfunction, recurrent urinary tract infection, pelvic organ prolapse, prostate obstruction, bladder cancer, hematuria, limited mobility, and excessive intake of fluid[11] and/or caffein**

A complete **physical exam** should be performed with particular attention directed towards any neurological findings, cognitive function, scars from prior abdominal surgery, and lower extremity edema. **A pelvic examination is critical and should include assessment for pelvic floor muscle hypertoni** (increased **levator and sphincter tone**), **perineal reflexes, and skin breakdown**. In women, assessment for genitourinary symptoms of menopause an pelvic organ prolapse are essential; a speculum and/or bimanual exam should be considered to rule out pelvic pathology. In men, genitourinary exam including digital rectal exam is recommended to assess for enlargement or nodularity.

Urinalysis is performed to rule out urinary tract infection and hematuria. Microscopic hematuria is defined in the **2020 AUA/SUFU Guideline Microhematuria**[23] as the presence of 3 or more red blood cells on microscopic examination of a properly collected specimen in the absence of infection. prior guidelines had recommended upper tract imaging and cystoscopy for all adults above age 35, now a risk stratified approach is recommended based age and risk factors.

Additional procedures and measures may be necessary to evaluate and diagnose[24,25] a patient with OAB. Additional tests may include urine culture, post- residual (by ultrasound or catheterization), intake-voiding diaries, and psychometrically validated symptom questionnaires. [2] **Urine culture** is only necessa there are symptoms of an infection such as dysuria (burning with urination), and signs of infection are present on urinalysis, which may include: positive leukocyte esterase, positive nitrate, pyuria, or bacteria. A **post-void residual** should be considered if there is concern for incomplete bladder emptying, s as obstructive symptoms, prior incontinence surgery, neurologic disorders, or renal failure. An intake-voiding diary is typically collected for three days to document time, fluid intake, voided volume, associated symptoms, and assess for nocturnal polyuria. **Symptom questionnaires** related to OAB may inc but are not limited to the **AUA Symptom Score (AUA SS)**[25] ICIQ FLUTS[24,26] (female), ICIQ MLUTS (male), and OAB-q SF.[27] Symptom questionnaires are useful for initial screening and for tracking change in symptoms and response to therapy over time.

Cystoscopy, urodynamics and ultrasound are not indicated in the initial workup of the uncomplicated OAB patient.[2] Cystoscopy is reserved for cases presenting with hematuria or when there are potential confounding causes of symptoms such as malignancy, foreign body, and anatomic anomalie (e.g. bladder neck obstruction). Urodynamics should be reserved for patients in whom the diagnosis is unclear, initial medical therapy fails, and when invasive, potentially morbid or irreversible treatments are being considered. Urodynamics may also be indicated before empiric therapy in patients preser with OAB in whom there is suspicion for a poorly compliant bladder, weak detrusor contractility, bladder outlet obstruction, intrinsic sphincter deficiency, o other condition where delay in definitive treatment may lead to deterioration in health (e.g. renal function). For example, a patient with a history of transve myelitis who presents with OAB symptoms would be an appropriate candidate for urodynamics to identify a neurogenic bladder (poor compliance, detrus overactivity, detrusor sphincter dyssynergia) and institute appropriate treatment before renal dysfunction from inadequate emptying and elevated bladder pressures occurs. Urodynamics may also be useful to guide additional treatment based on pathophysiology identified prior to invasive, potentially morbid irreversible treatments.[28] More information on urodynamics is detailed in the **AUA Core Curriculum urodynamics** chapter and in the **2012 AUA/SUFU Guideline on Adult Urodynamics**.[28]

5. Treatment

Idiopathic OAB is a symptom complex. After excluding potentially morbid underlying pathology, OAB should be treated as a means of improvi quality of life. If treatment does not improve quality of life, then no treatment is an acceptable option.[2] Patients may be seeking an evaluation of their symptoms in order to rule out a life-threatening condition. Once the appropriate evaluation is complete and comorbid conditions are excluded, then it is reasonable for patients to opt out of treatment.

5.1 First Line Treatments

First line treatments for OAB are behavioral therapies that should be offered to all patients alone or in combination with other modalities as they can be h effective with limited or no adverse side effects. [29] **Behavioral therapies include**; **fluid management, bladder training, bladder control strategies, urgency suppression and pelvic floor muscle training. All of these approaches can be supplemented with biofeedback techniques**.[2]

Fluid management includes modification (**typically reduction**) **of fluid intake with respect to the type of fluid, the volume ingested and the timir fluid consumption**. Elimination of carbonated and caffeinated beverages along with other known bladder irritants can result in significant improvement ir OAB symptoms. [21,22] **Bladder training** is the process of using behavior modification to delay urinary urgency for progressively greater periods of time, and this technique is nicely outlined in The SUFU Foundation OAB Clinical Care Pathway (CCP) educational handout titled "***Controlling Your Bladder Urges*** **Pelvic floor muscle training (PFMT)** is the process of learning to perform pelvic floor muscle exercises. When there is an urgency to void, the patient is instructed to contract the pelvic floor muscles in 3 to 5 quick flips in order to inhibit a bladder contraction. It is essential that this technique is performed without a concurrent abdominal contraction and rise in intra-abdominal pressure. A patient's ability to perform an isolated pelvic floor contraction is critical the success of this technique, and is also outlined in the SUFU OAB CCP education handout titled ***Guide to Pelvic Floor Muscle Training***". Bladder trai alone or in combination with pelvic floor muscle training may help patients control OAB symptoms; however the evidence for efficacy of these approaches alone is limited, with only two randomized controlled trials showing improvement in urgency urinary incontinence. [29] **Alternative bladder control strategi include timed voiding, and the use of a voiding diary** to determine the mean daytime interval between voids. Using the **timed voiding** approach, pati are instructed to set a goal voiding interval shorter than their average interval between urgency incontinence episodes. The intent of this technique is to v more frequently in order to prevent the bladder from reaching the filling state associated with urgency symptoms. As bladder control is improved, the inter may then be gradually increased in order to improve functional bladder capacity.

Biofeedback refers to the use of electronic monitoring of a normally automatic bodily function in order to train a patient to acquire voluntary control of tha function. In the context of pelvic floor disorders, biofeedback typically refers to placement of external or internal voltage or pressure sensors to assess pel floor muscular activity. Visual or verbal feedback is then provided to the patient by a graphic representation or pelvic floor physiotherapist, and is useful to

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guide treatment planning.[30] Biofeedback is often combined with **pelvic floor physical therapy**, a range of musculoskeletal treatments designed to help manage pelvic floor dysfunction. In treatment of pelvic floor disorders, in addition to educational handouts, a pelvic floor physiotherapist may also provide **PFMT** to help patients identify and isolate the pelvic floor muscles. Under the supervision of a physiotherapist, this approach may involve either up-trainin down-training of the pelvic floor muscles to help reach their optimum function, and can also include deep tissue massage or stretching of the muscles if a high tone pelvic floor is identified as a contributing factor to OAB. If intrinsic sphincter deficiency or dysfunctional pelvic floor contraction with concomitant abdominal straining is identified, then a process of up-training may be instructed by the pelvic floor physiotherapist.[31] Pelvic floor physical therapy can be employed in patients with concurrent pelvic pain of musculoskeletal etiology. Adjuvant electrical stimulation of the pelvic floor muscles (transvaginal or transanal) may also be used to treat pelvic floor muscle dysfunction and has shown benefit for management of OAB. [32,33]

5.2 Second Line Treatments

Second line treatments for OAB (**Podcast**) are pharmacological therapies and are considered for patients not meeting their goals with first line behavior therapies. Second line pharmacotherapy may be used concurrently with first line behavioral therapies. Oral pharmacotherapies include anti-muscarinics/anticholinergics (**Table 1**[34] and **Table 2**[35]) and the β3-adrenoceptor agonists mirabegron and vibegron. When nocturnal polyuria is identif then DDAVP (1-deamino-8-D-arginine vasopressin) analogs are considered to decrease nocturnal urine production.[36,37]

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Table 1: Pharmacological characteristics of commonly used drugs for OAB

Medication	T1/2 (hr)	Food Bioavail-ability	Adverse Effects
Oxybutynin (Desethyl-oxybutynin)	2-3	25% increase	Dry mouth (71.4%), dizziness (16.6%), constipation (15.1%), somnolence (14%), nausea (11.6%), urinary hesitancy (9.5%), urinary retention (6%)
Darifenacin	13-19	None	Dry mouth (35%), constipation (21%), dyspepsia (9%), UTI (5%), abdominal pain (4%)
Solifenacin	45-68	3% increase	Dry mouth (28%), constipation (13%), UTI (5%), blurry vision (5%)
Tolterodine*	3	53% increase	Dry mouth (39.5%), dysuria (1-10%), blurred vision (5%), urinary retention (1.7%)
Fesoterodine*	5	None	4 and 8 mg: Dry Mouth (18.8-34.6%) constipation (4.2-6.0%), nausea (0.7-1.9%), UTI (3.2-4.2%), dry eyes (1.4-3.7%), urinary retention (1.1-1.4%), peripheral edema (0.7-1.2%), Insomnia (1.3-0.4%)
Trospium	20	80% decrease	Dry mouth (20%), constipation (10%), headache (4%)
Mirabegron	50	29% decrease	Hypertension (7.5-11.3%), nasopharyngitis (3.5-3.9%), UTI (2.9-4.2%)
Vibegron	31	20-47% decrease	Urinary tract infection (6.6%), headache (4%), nasopharyngitis (2.8%), diarrhea (2.2%), nausea (2.2%)

Table adapted from *Cognitive Burden of Anticholinergics in the Elderly*[34] with bioavailability and adverse effect data sourced from drugs.com. (*) Fesoterodine and Tolterodine are both rapidly hydrolysed to 5-hydroxymethyl tolterodine (5-HMT)

Table 2: Compilation of Data

Medications Compared	QOL	Leaks within 24 h	Voids within 24 h	Urgency Within 24 h	Reported Cure or Improvement	Withdrawals due to adverse events	Side Effects
Tolterodine vs Oxybutynin	No Difference	No Difference	No Difference		No Difference	Lower with Tolterodine RR 0.52 (95% CI 0.40-0.66)	Dry Mouth lower with Tolterodine RR 0.65, 95% CI 0.60-0.71)
Solifenacin vs Tolterodine	Solifenacin SMD 0.12 (95% CI -0.23 to -0.01)	WMD favor Solifenacin -0.30, 95% CI -0.53 to -0.08		WMD -0.43, 95% CI -0.74 to -0.13	Solifenacin superior RR 1.25, 95% CI 1.13 to 1.39		Dry mouth rates lower in Solifenacin versus IR Tolterodine (RR 0.69, 95% CI 0.51 to 0.94
Fesoterodine vs Tolterodine ER	Fesoterodine Superior SMD -0.20, 95% CI -0.27 to -0.14	Fesoterodine Superior WMD -0.19, 95% CI -0.30 to -0.09	Fesoterodine Superior WMD -0.27, 95% CI -0.47 to -0.06	Fesoterodine Superior WMD-0.44, 95%CI -0.72 to -0.16	Fesoterodine Superior RR 1.11, 95% CI 1.06 to 1.16	Tolterodine Superior RR 1.45, 95% CI 1.07 to 1.98	Tolterodine Superior RR 1.80, 95% CI 1.58 to 2.05
Tolterodine IR (2mg BID vs 0.5, 1, and 4mg BID)		No difference	No difference				Dry mouth higher in the 2 and 4mg doses at 2-12 wks
Solifenacin (5 vs 10mg)			Better with 10 mg	Better with 10 mg			More dry mouth at 10 mg dose at 4-12 weeks
Fesoterodine (4, 8, and 12mg)		8mg (but not 12mg) superior to 4mg	8 mg (but not 12mg) superior to 4mg		8mg (but not 12mg) superior to 4mg		More dry mouth with 8mg and 12mg vs 4 mg
Oxybutynin (IR vs ER)		No difference	No difference		No difference		ER less dry mouth at 2-12 weeks

Tolterodine (IR vs ER)		No difference	No difference	No difference		ER less dry mouth at 2-12 weeks
Tolterodine ER vs Oxybutynin ER	No difference	No difference	No difference		No difference	Less dry mouth with tolterodine ER: RR 0.75, 95% CI 0.59 to 0.95
Oxybutynin (Transdermal vs ER)		No difference	No difference			No difference in dry mouth, but withdrawal occurred due to skin reaction with the transdermal patch

Taken from Cochrane Review[35] *Which anticholinergic drug for overactive bladder symptoms in adults*

An extensive review of randomized trials that evaluate anti-muscarinic pharmacologic therapies for OAB reveal no compelling evidence for difference in efficacy between medications.[35,38,39,40,41,42] On qualitative analysis, baseline OAB symptom level was closely related to degree of symptom reduction across medications (i.e. the worse the symptoms of urgency incontinence and frequency, the more effective the medication).[2,43] Potential side effects from the anticholinergic class of drugs are primarily related to inhibition of other cholinergic actions in the body and include constipation, dry eyes, dry mouth (xerostomia), and mental status changes.

Although there is no clear difference in pharmacotherapy efficacy, there are several considerations for optimizing pharmacotherapy, as outlin the 2019 AUA/SUFU guideline statements for the second line treatment of non-neurogenic OAB .[43]

The most recent Cochrane Review was undertaken to evaluate comparative effects of antimuscarinics for OAB.[35] The analysis included randomized comparisons between drugs or doses, but had to exclude crossover trials in the meta-analyses and is therefore not fully comprehensive. Although the lo incidence of dry mouth associated with transdermal oxybutynin was not captured in the Cochrane review, many studies have suggested this. Of the trials referenced in the AUA/SUFU guideline statement on OAB, [2] the rate of dry mouth (4.1 to 14.9%)[44,45,46,47] for transdermal oxybutynin appears to be less tha meta-analyzed rates of 40% and 68% for ER and IR oral oxybutynin respectively.

Long term adherence to anticholinergic medications is low. Reasons for this have been explored, including lack of efficacy, intolerance, cost, and lack of follow up on the part of the prescribing physician.[48,49] **The AUA guideline recommends that the clinician arrange follow up after initiation of anticholinergic medications to assess compliance, obstacles to acceptance, efficacy, side effects, and possible alternative treatments**.[2]

Recent epidemiologic studies[50,51,52] have shown an association between dementia and anticholinergic use in patients over the age of 55. In a recent 2019 JAMA Internal Medicine article, the use of bladder antimuscarinic therapy was found to have an adjusted odds ratio of 1.65 (95% CI 1.56-1.75) associate with dementia, compared to patients in whom no anticholinergic medications was given in the 1-11 years prior. [50] These associations were stronger in pat diagnosed prior to 80 years of age. This was consistent with data found in other, smaller series. While these population based epidemiologic studies demonstrate an association between anticholinergic prescribing and the dementia diagnosis, and not a direct cause and effect relationship, caution is still warranted when prescribing anticholinergics to patients with pre-existing risk factors for dementia.

Mirabegron is a novel beta-3 adrenoceptor agonist and alternative treatment for OAB.[53] Since it is not an anti-muscarinic, it can be used in patients with contraindications or poor tolerance of the antimuscarinic class. The efficacy of mirabegron for OAB is similar to antimuscarinic therapy, with low rates of d mouth and a low risk of QT prolongation. [54] Mirabegron has not been studied in patients with uncontrolled hypertension and is therefore not recommende those patients. [55] Due to the fact that it is a moderate inhibitor of CYP2D6 (weak effect on CYP3A) it can potentiate other medications such as digoxin, amitriptyline, and metoprolol.[56]

Vibegron is the newest medication indicated for the treatment of overactive bladder. It comes in a single dose of 75 mg. Like mirabegron, it is also a beta- agonist, but does not inhibit the CYP2D6 pathway. In the EMPOWUR study, it was not found to cause hypertension at a higher rate than placebo or wher compared to tolterodine. **Vibegron may also be crushed, unlike mirabegron**. Most common side effects included hypertension, nasopharyngitis, diarrh nausea, headache, and upper respiratory tract infection.[57] Vibegron also interacts with digoxin and may increase digoxin levels.

While not an official part of the AUA OAB guidelines, **the diagnosis of nocturnal polyuria should be considered in any patient with significant bothersome or refractory nocturia**. In 2019, the International Continence Society (ICS) updated their terminology report for nocturia and nocturnal lowe urinary tract function.[5] In this report, nocturnal polyuria is defined as “Excessive production of urine during the individual's main sleep period. This should quantified using a bladder diary.” The **nocturnal polyuria index** is the most commonly used definition for nocturnal polyuria (nocturnal urine volume / 24 hour voided volume). The ICS working group recognizes that this index varies with age, and recommends age dependent cutpoints (>20% in younger ag 20-33% in “middle age”; >33% in elderly over 65 years of age) for making the diagnosis of nocturnal polyuria. In 2018, the FDA approved the use of the DDAVP analog desmopressin acetate in the formulation sublingual tablet (Nocdurna® 27.7 to 55.3 mcg). Indications for use include the treatment of “nocturnal polyuria in adults who awaken at least 2 times per night to void”, with nocturnal polyuria defined as night-time urine production exceeding one- of the 24-hour urine production. These agents are typically administered 30-60 minutes prior to bedtime. Contraindications include hyponatremia or histo hyponatremia, polydipsia, loop diuretics, glucocorticoids, eGFR <50 mL/min/1.73m^2, syndrome of inappropriate antidiuretic hormone (SIADH) secretion, electrolyte imbalance illnesses, congestive heart failure and uncontrolled hypertension. Following initiation of treatment, serum sodium should be checke monitor for hyponatremia within 1 week, at 1 month and periodically thereafter.

Table 3: Drugs with pharmacologic effect on OAB, assessments according to the Oxford system

Drug	Level of Evidence	Grade of Recommendation
Antimuscarinic drugs		
Atropine, hyoscyamine	3	C
Darifenacin	1	A
Fesoterodine	1	A
Oxybutynin	1	A
Solifenacin	1	A
Tolterodine	1	A
Trospium	1	A
Antidepressants		
Imipramine, Nortriptyline, Amitriptyline	3	C
Duloxetine	2	C
Beta Adrenergic Receptor Antagonists		
Terbutaline (beta 2)	3	C
Salbutamol (beta 2)	3	C
Beta Adrenergic Receptor Agonists		
Mirabegron / Vibegron (beta 3)	1	B
Toxins		
Botulinum toxin A (neurogenic)***	1	A
Botulinum toxin A (idiopathic)***	1	B
Capsaicin (neurogenic)**	2	C
Resiniferatoxin (neurogenic)**	2	C
Other drugs		
Baclofen*	3	C
Hormones		
Vaginal Estrogen	2	C
Desmopressin#	1	A

Table adapted from textbook courtesy of Paul Abrams.[58] (+) male LUTS/OAB, (*) intrathecal, (**) intravesical, (***) bladder wall, (#) nocturia (nocturnal polyuria), caution hyponatremia, especially in the elderly.

5.3 Third Line Treatments

Third line treatments for OAB (Podcast) include: intradetrusor onabotulinumtoxinA chemodenervation, peripheral tibial nerve stimulation, and sacral neuromodulation. The efficacy for these treatments are summarized in Figures 1 through 3 above and their use is outlined in the 2019 AUA/SUFU guideline statements for the third line treatment of non-neurogenic OAB .[2-43]

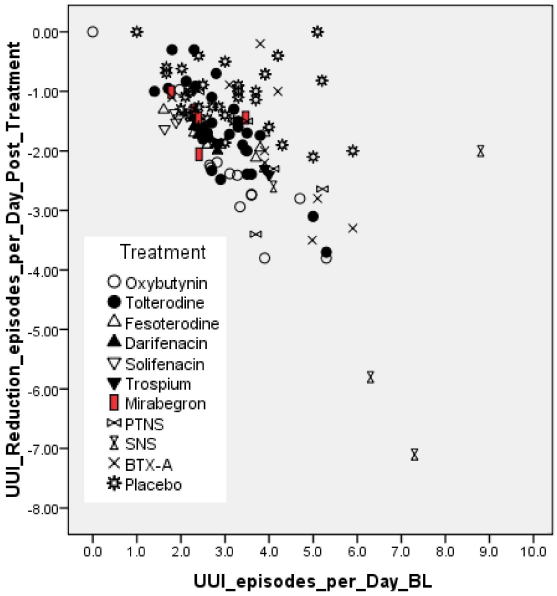

Figure 1: Baseline urgency urinary incontinence (x-axis; #episodes/day) versus reduction in urgency urinary incontinence (y-axis; #episodes/day) for randomized trials by treatment. *BL* baseline, *UUI* urgency urinary incontinence, *PTNS* posterior tibial nerve stimulation, *SNS* sacral neuromodulation system, *BTX-A* onabotulinumtoxinA[43]

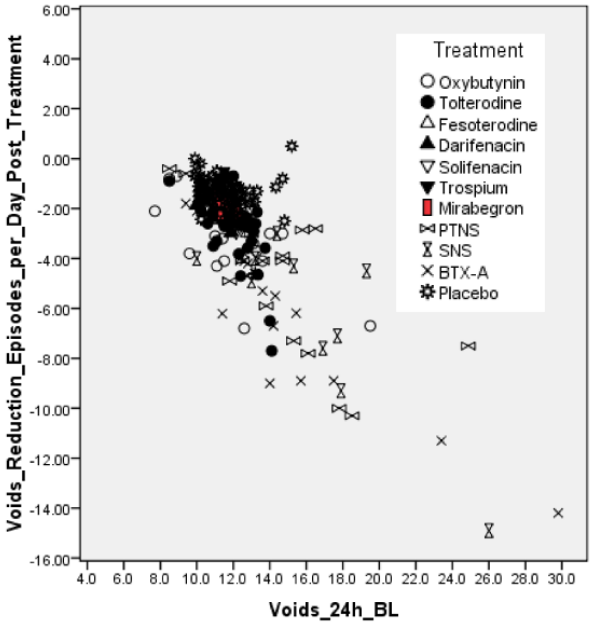

Figure 2: Baseline urinary frequency (x-axis; #voids/day) and reduction in urinary frequency (y-axis; #voids/day) for randomized trials by treatment.[43] *BL* baseline, *PTNS* posterior tibial nerve stimulation, *SNS* sacral neuromodulation system, *BTX-A* onabotulinumtoxinA

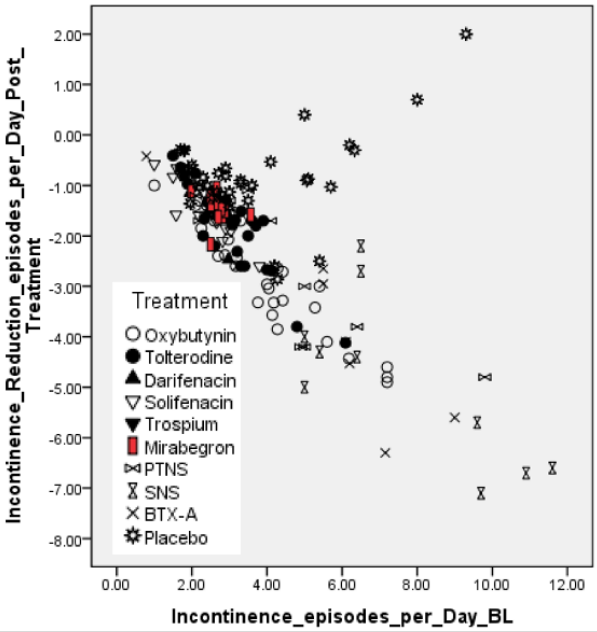

Figure 3: Baseline incontinence (x-axis; #episodes/day) versus reduction in incontinence (y-axis; #episodes/day) for randomized trials by treatment.[43] *BL* baseline, *PTNS* posterior tibial nerve stimulation, *SNS* sacral neuromodulation system, *BTX-A* onabotulinumtoxinA

Intradetrusor OnabotulinumtoxinA (BTX-A) Chemodenervation: OnabotulinumtoxinA was FDA approved for the management of idiopathic OAB in 2013.[59] BTX-A is administered using either a flexible or rigid cystoscope, with aliquots of BTX-A injected directly into the detrusor muscle using a cystosco injection needle. Following injection, BTX-A binds to the synaptic vesicle proteins and is then internalized into the neuron endplate, the heavy and light chains separate, and synaptosome-associated protein 25 kDa (SNAP-25) is then cleaved by the BTX-A light chain. Following cleavage of SNAP-25, the pre-synaptic vesicles containing acetylcholine are unable to fuse with the motor neuron endplate[60], preventing parasympathetic release of acetylcholine. In addition to this primary mechanism of action, additional neurotransmitters have been implicated, including sympathetic with inhibition of norepinephrine a sensory fibers with inhibition of glutamate.[60]

Prior to FDA approval, the dose of 100 units for idiopathic OAB was selected following a multi-national phase 2 double-blind placebo controlled randomiz dose-ranging trial, with results published in 2010 by Dmochowski et al.[61] In this trial, doses of 50, 100, 150, 200 and 300 units were assessed at the prima time point of 12 weeks after injection for the change in number of urgency urinary incontinence episodes. From this study BTX-A at the dose of 100 units found to balance symptom benefits with post-void residual safety profile. Leading up to FDA approval in 2013, two large regulatory phase 3 randomized controlled trials were published by Nitti[59] and Chapple,[62] which showed three to four-fold greater reductions from baseline in the mean daily frequency of urinary incontinence episodes with BTX-A 100 units versus placebo (–2.65 vs -0.87; P < 0.001, Nitti) and a significant improvement of the number of incontinence episodes in a 3-day bladder diary (-2.95 vs 1.03, P < 0.001, Chapple). The urinary tract infection rate after BTX-A was 15.5 to 20.4% and ra initiating self-catheterization was 6.1 to 6.9% versus 0 to 0.7% in the BTX-A versus placebo arms respectively. Patients receiving BTX-A should be willing return to the office for a follow up post-void residual and counseled on the risk of incomplete bladder emptying and requirement to perform clean intermitt catheterization for a temporary period of time after the procedure[2].

Concurrent with the above trials, The Anticholinergic versus Botulinum Toxin Comparison (ABC) double-blind, double-placebo-controlled, randomized-tria was published in 2012 comparing anticholinergic pharmacotherapy (solifenacin 5-10 mg, possible switch to trospium XR 60mg) to 100 units BTX-A.[63] Fro this trial, a similar mean reduction in episodes of incontinence were noted in both treatment groups, with BTX-A having less dry mouth, and more likely to have complete resolution of urgency incontinence, with BTX-A chemodenervation associated with higher rates of transient incomplete bladder emptying a urinary tract infection following injection.[63]

Additional studies have been performed comparing use of BTX-A and sacral neuromodulation (SNS) in the Refractory Overactive Bladder Sacral NEuromodulation versus BoTulinum Toxin Assessment (ROSETTA) trial. A multicenter, open label study performed by Amundsen et al compared reducti in urgency incontinence episodes over a 24 month period in patients who received either BTX-A or SNS. Adverse events and patient satisfaction were lis as secondary outcomes. Patients undergoing BTX-A were found to have higher patient satisfaction, although no difference was seen between the two gr in reduction of urgency incontinence episodes per day at 2 years for sacral neuromodulation versus BTX-A (-3.00 [95% CI -3.38 to -2.62] vs -3.12 [95% C -3.48 to -2.76], p=0.66]). Following a within-trial cost analysis and secondary decision analysis, two-year costs were found to be higher for sacral neuromodulation than for BTX-A ($35,680 [95% CI 33,920 to 37,440] vs $7,460 [95% CI 5,780 to 9,150], p <0.01), and cost persisted through to 5 years ($36,550 [95% CI 34,787 to 38,309] vs $12,020 [95% CI 10,330 to 13,700], p <0.01).[64] UTI rates were higher in those patients receiving BTX-A. SNS was removed in 9% of study patients.[65] The ROSETTA group used a dose of 200 units which is higher than the AUA Guidelines suggested dose for idiopathic OAB. In the 2018 International Continence Society Best Practice Statement on Use of Sacral Neuromodulation, no recommendations could be made in deciding between BTX-A and SNS for a preferred third line therapy in the absence of a head to head trial.[66]

Neuromodulation is based on implantation of permanent electrodes adjacent to the sacral nerve roots (sacral nerve stimulation) or placement of tempor percutaneous electrodes next to the tibial nerve (peripheral tibial nerve stimulation). Use of electrical current in order to improve incontinence has been suggested since the 1960s. Stimulation of the S3 and S4 nerve roots was suggested by Tanagho et al in 1989 in treatment of patients with neuropathic voiding disorders. [67] In 1983, McGuire reported improvement in detrusor dysfunction with electrical stimulation of the posterior tibial nerve with acupuncture. [68] **The evidence is strongest for use of neuromodulation in patients with idiopathic (non-neurogenic) OAB refractory to medical management**.

Peripheral Tibial Nerve Stimulation (PTNS): PTNS is also known as Percutaneous or Posterior Tibial Nerve Stimulation. The posterior tibial nerve cont fibers from spinal roots L4 through S3 and therefore parallels and cross-talks with sacral fibers of the pelvic floor and bladder.[69-70] PTNS uses a fine needle inserted alongside the posterior tibial nerve to create feedback.[71] The exact mechanism of action is not known. PTNS has been shown in short term studie be efficacious for frequency and urgency urinary incontinence. It has been compared to medications with mixed results.[72] There is evidence to suggest th 12 week course of PTNS may have more lasting effects than the same trial of anticholinergic, however patients must have the ability to return to the office treatment visits (typically once to twice weekly) followed by maintenance visits.[2] This has historically prevented the patient from choosing this option giver burden of travelling to the office. However, new options including implantable leads for PTNS are currently in FDA trials. These either are self-contained o use antennae to allow the patient to perform this at their discretion. [73-74]

Recently, the FDA approved an implantable posterior tibial nerve device, allowing the patient to receive therapy at home. eCoin may be implanted in the o and will deliver 30 minute therapies every three days for 18 weeks and every four days thereafter automatically without the need for patient manipulation. percent of patients reported at least a 50% reduction in their symptoms during the single-arm trial, with 20 percent reporting at least complete continence the end of a 52 week period. Other companies such as BlueWind and StimGuard are also in development of implantable devices.

Sacral Neuromodulation (SNS): Sacral neuromodulation involves placement of a stimulating lead alongside the S3 nerve root. Feedback alters efferent afferent signaling although the mechanism is incompletely understood. Patients will typically undergo a trial period to determine potential response to SNS This is either done with a percutaneous lead placement in the office, called a percutaneous nerve evaluation (PNE), or surgical implant of the permanent tined lead connected to an external generator. Motor and sensory responses are confirmed. Motor response includes contraction of the pelvic floor leadin to a bellows response as well as plantar flexion of the great toe. This confirms placement in the S3 foramina. After external testing confirms at least 50% improvement in patient symptoms, a permanent pulse generator may be implanted surgically. The 2012 AUA Guidelines on overactive bladder summariz the 13 studies in the literature on efficacy and adverse events of SNS in patients with severe OAB (baseline incontinence episodes 5-11.6 times per day, frequency 13 times per day, and/or > 4 pads per day). Greater than 50% improvement was observed at five years for in 68% of patients with urgency incontinence and in 56% of those with frequency-urgency in those who initially had success with the external testing and went on to generator implantation. [75-76-77] These numbers are corroborated in other studies. The InSite trial also included patients with less severe urgency/frequency and foun that 80% of patients went to generator implantation and at 24 months had a success rate of 81% for incontinence and 78% for decrease in frequency. [78] When compared to medical therapy, patients undergoing sacral neuromodulation reported an improvement of 61% versus 44% for those patients continu on standard medical therapy.[79]

Adverse events include pain at the stimulator or lead site, lead migration, infection, electric shock, and need for surgical revision (greater than 30 % in the majority of studies). Despite this, 90% of patients report being satisfied with the treatment.[80] Due to the presence of the implanted lead and generator, patients need to be informed that special attention will be required at airport security. Additionally, the implanted device precludes magnetic resonance imaging below the head. A 1.5T MRI of the head is permissible with an older generation InterStim device in place. In 2019, the FDA approved an addition neuromodulation generator produced by Axonics. The ARTISAN-SNM trial consisted of 129 patients with refractory overactive bladder. At 1 year, 89% of participants were therapy responders. The average UUI episodes per day reduced from 5.6 ± 0.3 at baseline to 1.4 ± 0.2. [81-82-83] Another study showed tha this efficacy remains durable at 2 years. FDA Safety shows that the Axonics and InterStim can be in place if the patient requires an MRI of the head on ei 1.5 or 3T machines, and an MRI of the whole body in an 1.5T machine. In 2022, the FDA approved a non-rechargeable battery for the Axonics device wit battery life of 15 years. Medtronic also was approved for InterStim X, a battery with 10-15 years of battery life, whereas prior battery life had been betwee 5-7 years.

Relative contraindications for placement include rapidly progressing neurologic disease, established complete spinal cord injury, patients with abnormal sacral anatomy. It is unknown if this device is safe during the use of pregnancy and if this should remain activated if a patient becomes pregnant following SNS placement[86] Additionally, patients should be counseled that the device requires periodic generator battery replacement and the patient must have th cognitive ability to optimize the generator with the remote programmer. [2]

Both companies now offer both rechargeable and non-rechargeable options for their device. In 2022, the FDA approved the Axonics F15, which offered 1 years battery life and up to 20 years in energy-saving mode as well as the InterStim X which provides 10 years battery life, extending up to 15 years in energy-saving mode. In 2021, Medtronic had a rechargeable battery option also approved by the FDA, allowing more options for surgeons and their patie

5.4 Additional Treatments

Additional treatments, for the patient who fails first, second and third line OAB therapy, are outlined in the 2019 AUA/SUFU guideline statements for the treatment of non-neurogenic OAB. [2]

Augmentation Cystoplasty and Urinary Diversion: Although it is tempting to employ augmentation cystoplasty in the treatment of idiopathic OAB, the results are not as good as for neurogenic detrusor overactivity, and especially with the advent of onabotulinumtoxinA the use of augmentation cystoplasty treatment of OAB has decreased. Long-term symptomatic success was reported in as few as 53-58% of idiopathic patients,[84-85-86] versus 92% in neuropath patients.[87] Revision of the augmentation has been reported in 5-42% of patients.[88] Metabolic disturbances are to be expected, but 16% of patients will req bicarbonate for metabolic acidosis.[84] Urinary tract stones and incontinence may also occur.

Ileal conduit urinary diversion should be reserved for only the most extreme of situations, with a complication rate of 36% over time, and consideration mu

be given to concurrent cystectomy.[89] Bladder replacement with a continent reservoir is another extremely rare choice.

Indwelling Catheters: Indwelling catheters are viewed as an undesirable, although sometimes unavoidable, alternative for the management of OAB. Wh the emptying pattern is safe, spontaneous void into absorbent garments is considered superior due to the incidence of upper tract damage, vesicouretera reflux, urolithiasis, urinary tract infection, and possibly malignant transformation of the urothelium with indwelling catheters.[2] Suprapubic catheter has a lov incidence of urethral stricture and injury than urethral catheters.[90]

Most providers treating OAB offer a combination of the treatment options outlined above. There is some evidence that combination therapy is more effect than monotherapy.[72] **Follow up should be assessed for all patients**.

6. Clinical Care Pathway

See the 2019 AUA/SUFU diagnosis and treatment algorithm for the management of non-neurogenic overactive bladder in adults (see **Figure 4**).[2]

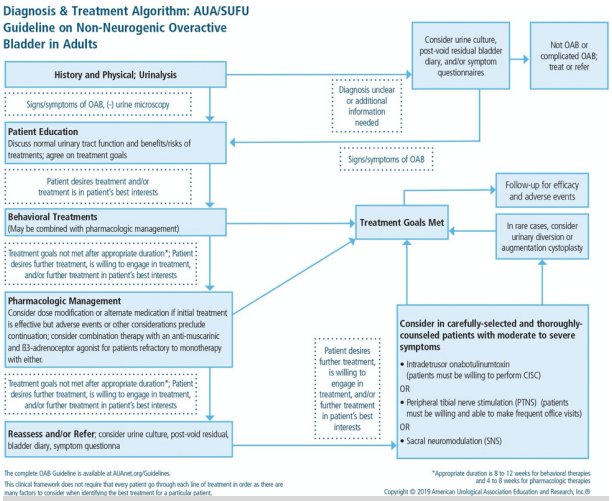

Figure 4: Diagnosis & Treatment Algorithm: AUA/SUFU Guideline on Non-Neurogenic Overactive Bladder in Adults[2]

Presentations

OVERACTIVE BLADDER: EVALUATION AND TREATMENT Presentation 1

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Data review regarding suprapubic catheterization and alternative forms of indwelling drainage