UCA

UROLOGY CENTERS OF ALABAMA

When You Gotta Go, You Gotta Go: Overactive Bladder

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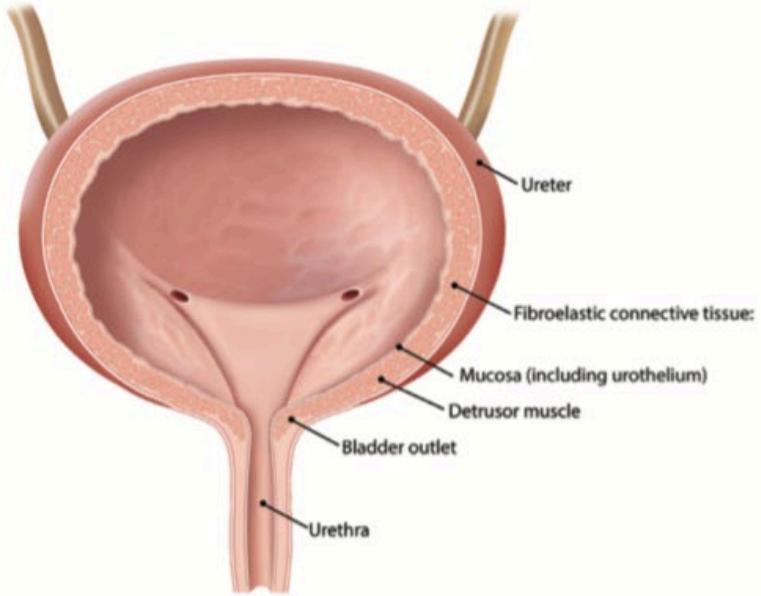
In My Practice…

- 100% of my patients are female
- Urinary incontinence, pelvic prolapse, pelvic pain, UTIs, hematuria, kidney stones

BLADDER ANATOMY: A REFRESHER

The bladder wall has 3 layers[1]

- Internal layer (*mucosa*)—the epithelium, which appears smooth when the bladder is full, but contracts into folds when the bladder empties
- Middle layer (*detrusor muscle*)—the detrusor muscle, which is responsible for emptying the bladder
- External layer (*fibroelastic connective tissue*)—this layer expands with the distention of the bladder



The detrusor is the muscular layer of the bladder[1,2]

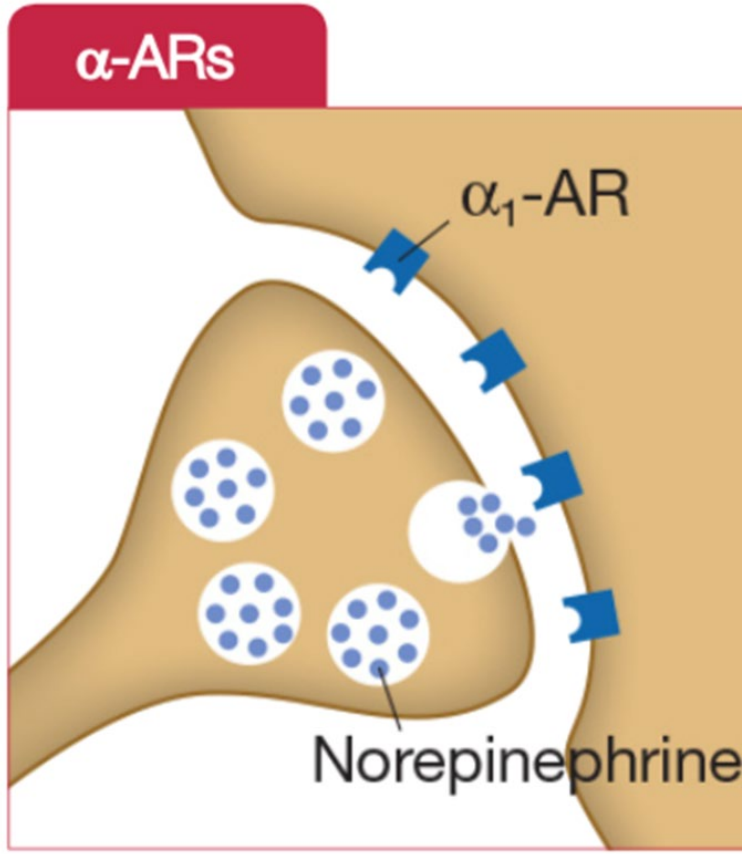
- It also has 3 layers, with intermingled smooth muscle fibers arranged into inner and outer longitudinal layers and a middle circular layer
- The changes in the thickness and organization of the detrusor layer may contribute to the bladder's ability to accommodate increasing volumes of urine
- Micturition depends on the contraction of the neurally mediated detrusor

Adequate **storage** depends on a relaxed bladder and a closed outlet, while efficient **voiding** depends on an adequate bladder contraction coordinated with relaxation of the bladder outlet[3]

References: 1. Chung BI, Sommer G, Brooks JD. Anatomy of the lower urinary tract and male genitalia. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, eds. *Campbell-Walsh Urology.* 10th ed. Philadelphia, PA: Elsevier Saunders; 2012:33-70. **2.** Yoshimura N, Chancellor MB. Physiology and pharmacology of the bladder and urethra. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, eds. *Campbell-Walsh Urology.* 10th ed. Philadelphia, PA: Elsevier Saunders; 2012:1786-1833. **3.** Wein AJ. Pathophysiology and classification of lower urinary tract dysfunction: overview. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, eds. *Campbell-Walsh Urology.* 10th ed. Philadelphia, PA: Elsevier Saunders; 2012:1834-1846.

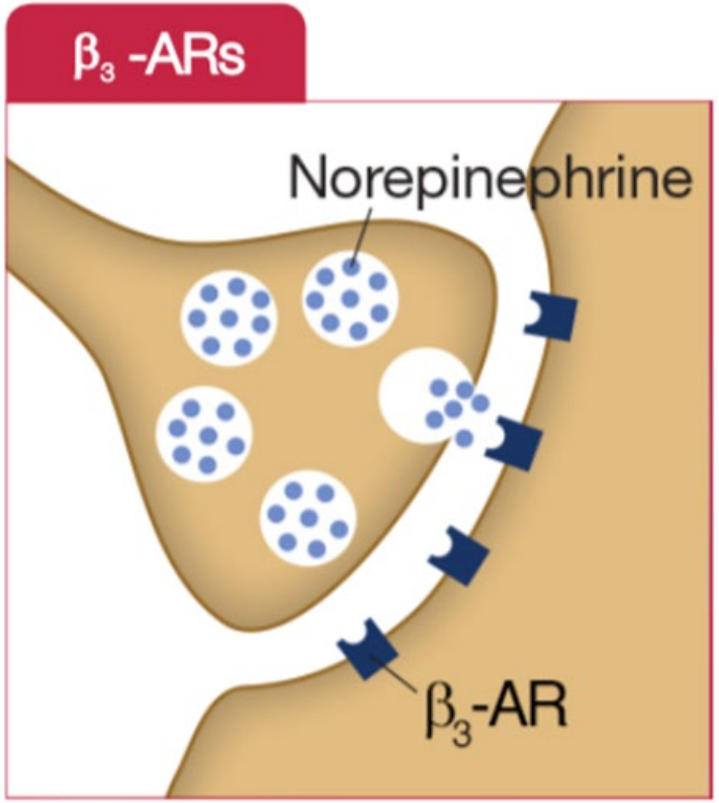
Sympathetic nervous system: neurotransmitters

- Expression of α-Ars in the bladder
  - Both α_{-1} -ARs and α_{-2}-ARs are expressed in the lower urinary tract in humans
    - Activation of noradrenergic pathways contracts the urethra to maintain continence during the storage phase of micturition
    - α_{-1} predominates in the bladder neck
  - Norepinephrine binds to α_{-1}-ARs, which are expressed in the urethra, resulting in the closing of the internal sphincter and an increase in urine volume
    - Contraction of the internal sphincter is mediated by both the sympathetic and pudendal nerves

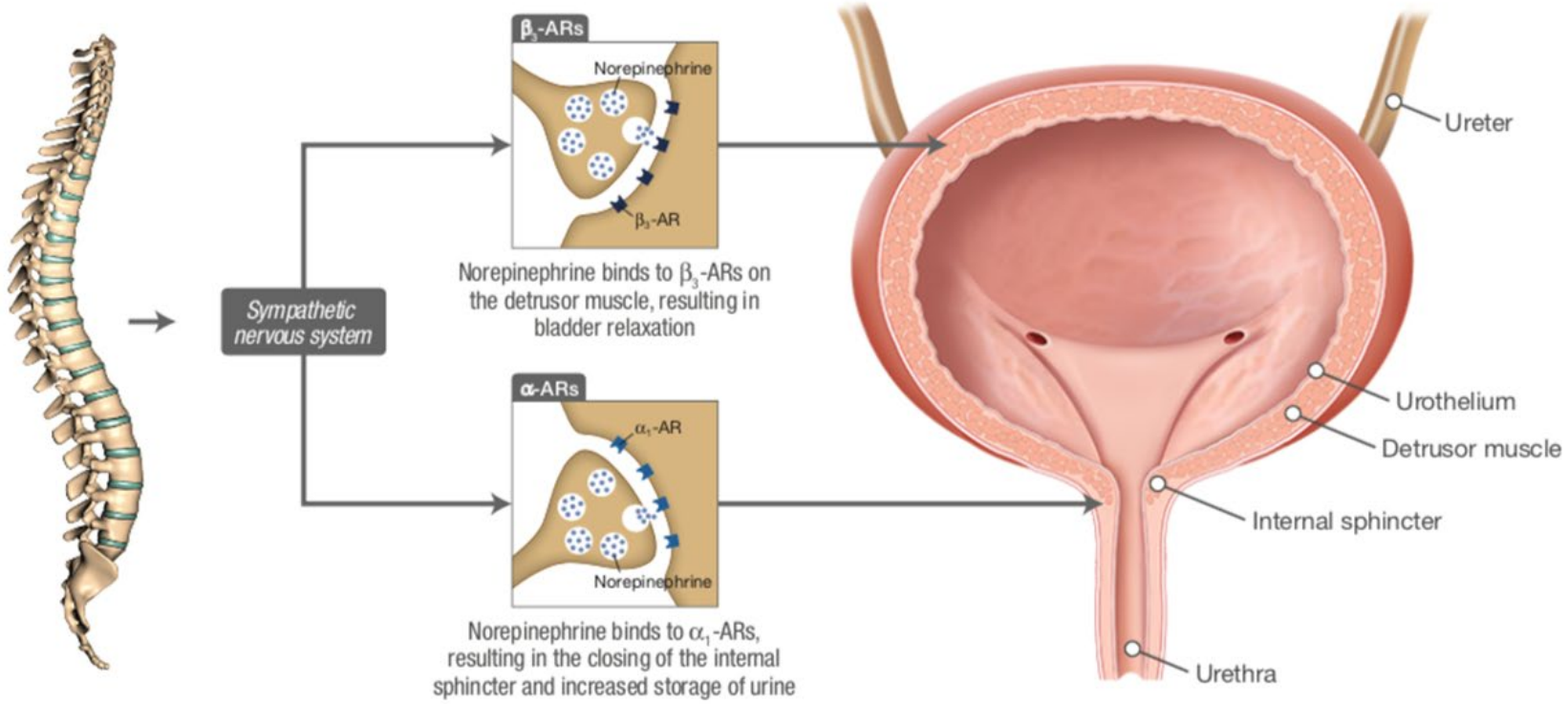


Sympathetic nervous system: neurotransmitters

- Expression of β-ARs in the bladder
  - Sympathetic nerves determine the duration of the urine storage phase during the micturition cycle
    - Norepinephrine released from sympathetic nerves activates β_3-AR in the human detrusor muscle to relax the bladder
  - All 3 β_3-ARs are expressed in the human bladder, but β_3-messenger RNA (mRNA) predominates
    - The β_1-AR subtypes make up 1.5% and 1.4% of the total β-AR mRNA, respectively
  - While β-ARs are expressed in the detrusor muscle, they are also found in the urothelium, which contributes to the regulation of bladder function
    - During the storage phase, the urothelium stretches in tandem with the bladder wall when the bladder starts filling with urine



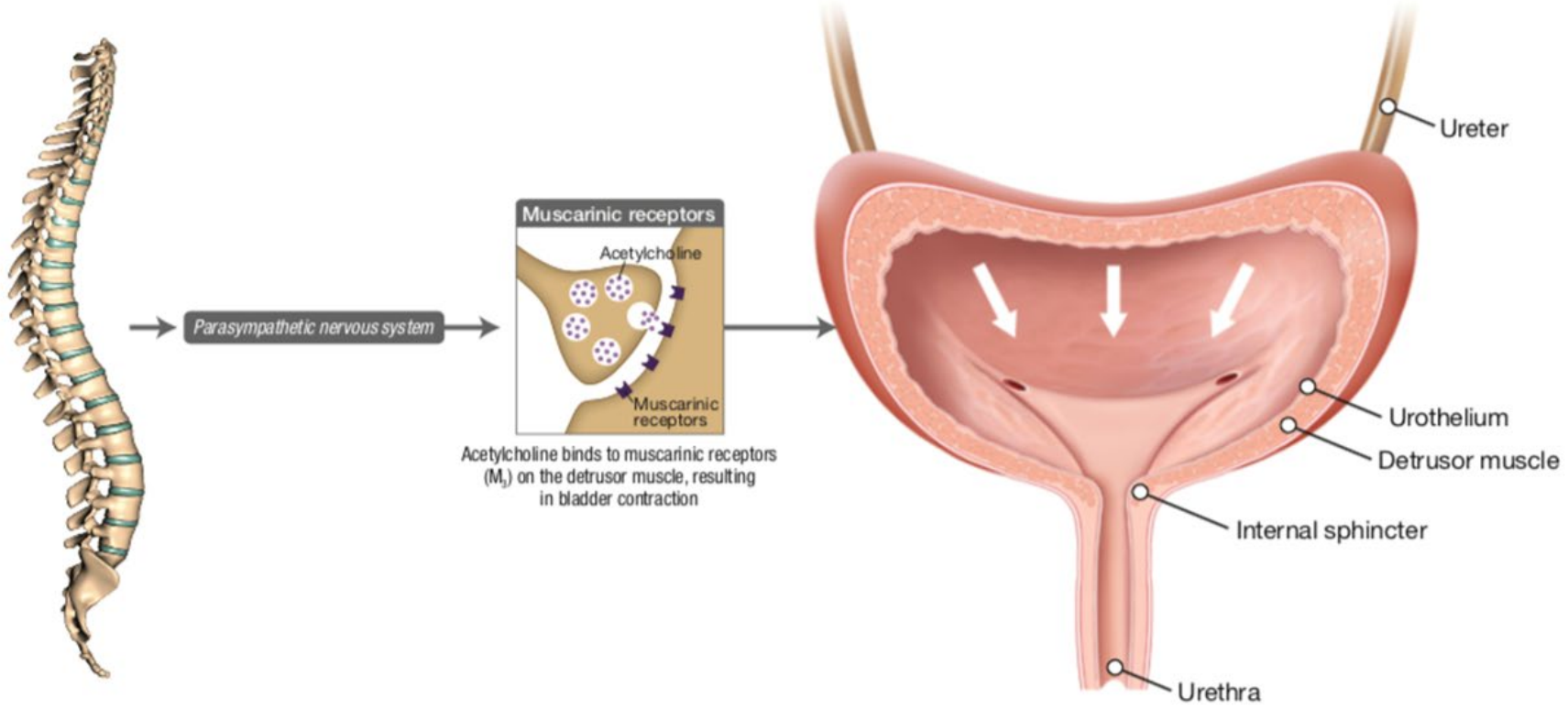
Sympathetic nervous system: neurotransmitters



Role of Parasympathetic Nerves

- The *parasympathetic* division primarily mediates bladder contraction1
- Bladder *voiding* is primarily regulated by this division
- *Muscarinic receptors*, a component of the parasympathetic nervous system, are activated by acetylcholine[2–7]
- There are 5 subclasses of muscarinic receptors: M_1, M_2, M_3, M_4, and M_5
- The muscarinic receptors can be found in urothelial cells
  - M_2 and M_3 are the predominant muscarinic receptors found in the bladder
  - M_3 receptors are important for normal bladder contraction, while M_2 receptors may play a more prominent role in certain disease states (demonstrated *in vitro*)
  - Binding of acetylcholine to M_3 receptors on the detrusor muscle activates a signaling pathway that leads to bladder contraction and voiding

Role of Parasympathetic Nerves



Types of Incontinence

URGE INCONTINENCE (OAB)

STRESS INCONTINENCE

MIXED INCONTINENCE

OVERFLOW INCONTINENCE

OAB Definition: Syndrome Not Disease

- The 4 key OAB symptoms are:
  1. URGENCY:
     - Hallmark symptom of OAB, described as a sudden, compelling desire to pass urine that is difficult to defer
  2. FREQUENCY:
     - voiding too often during waking hours
  3. NOCTURIA:
     - voiding >1 during the night
  4. URGE INCONTINENCE:
     - involuntary leakage or loss of urine accompanied by, or immediately preceded by, urgency

Diagnosis

- AUA guidelines:
  - Physical Exam
    - Neurologic
    - Mental status
    - Weight/Body mass index (BMI)
    - Abdomen
    - Genitalia
  - Urinalysis
    - R/ O UTIs, glucosuria, hematuria, proteinuria, etc.
  - Post-void residual (PVR) measurement
    - ultrasound bladder scanner or a catheter immediately after the patient voids
    - PVR is not necessary for patients who are receiving first-line behavioral interventions or for uncomplicated patients

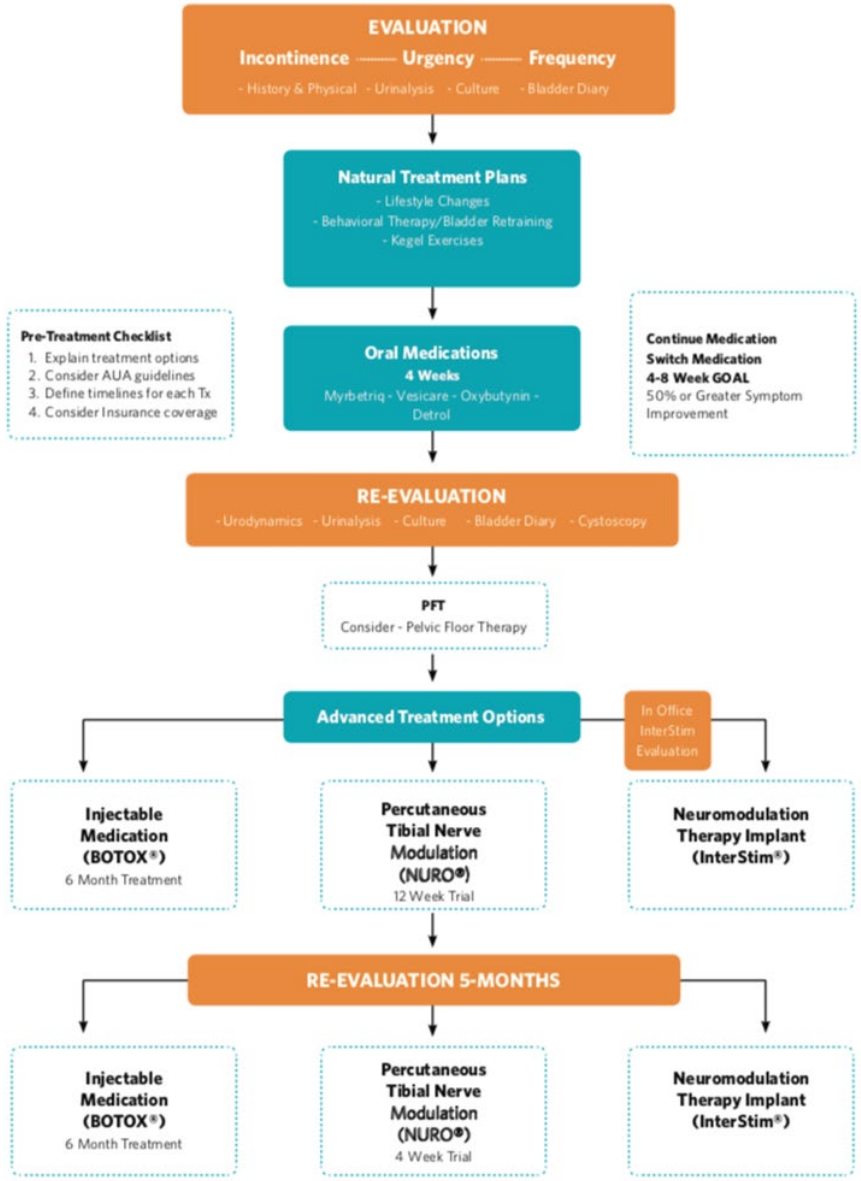
Additional Diagnostic Testing

- Urodynamic testing
- Cystoscopy
- Diagnostic renal ultrasound

Questions I Ask

- How many times do you void, get up to void?
- Do you wet on yourself, is your underwear or pad damp?
- What do you drink, what does your coffee cup look like?
- Do you work, where is the toilet?
- Have you tried medication?
- IS IT BOTHERSOME ENOUGH TO PURSUE TREATMENT??

Overactive Bladder (OAB) - Care Plan



Plan of Care

- First Line
  - Behavioral therapies for all patients
  - May be combined with oral agents
- Second Line
  - Oral agents and transdermal preparations
  - Dose modifications or switch to a different oral agent if inadequate efficacy or poor tolerability
- Third Line
  - IntradetrusorOnabotulinumtoxinA
  - Peripheral tibial nerve stimulation (PTNS)
  - Sacral neuromodulation (SNS)
  - Other surgical options

Cassidy Henningsen: OAB Navigator

Nonpharmacological Therapy

- Sometimes, no therapy chosen
- Behavioral Therapy
  - Timed voiding every 3-4 hours
  - Double voiding
  - Avoid bladder irritants
    - Caffeine, carbonation, citrus, cigarettes, alcohol, spicy food
  - No fluids 4 hours before bedtime
  - Kegel exercises or pelvic floor muscle therapy
  - Weight loss
  - Can be combined with or without pharmacotherapy

Second Line Therapy

Beta 3 agonists

- mirebegron (myrbetriq)

Anticholinergics

- oxybutynin, tolterodine, trospium, solfenacin,, darifenacin, fesoterodine, antispasmodics drugs

Combination

- mirebegron + anticholinergic

Vaginal estrogens

- important in post menopausal women

Dementia Risk and Anticholinergics

- Cumulative total anticholinergic consumption was associated with modified risk of dementia[1]
- Study to assess risks of dementia associated with meds with anticholinergic properties using prescription analysis up to 20 years before the diagnosis of dementia[2]
  - There is a clear and significant trend toward the development of the risk of dementia for higher exposure groups based on total daily dosing of meds
- There is a difference in anticholinergic meds compared to other classes of meds and cognitive risk[3]

1. JAMA intern Med 2015; 175: 401.
2. JAMA Intern Med 2019; 179: 1084
3. BMJ 2018; 361: k1315

Dementia Risk and Anticholinergics

Message to all practitioners:

provide patients with appropriate information re: long term risks especially those pts in the middle aged and older population

Beta 3 Agonists

Mimics the effect of norepinephrine, which binds to beta 3 receptors in the bladder, which stimulate detrusor relaxation and increase bladder storage and volume

Stimulates alpha 1 receptor in urethra which contracts sphincter muscle

When to Proceed with 3rd Line Therapy

- When medical therapy is not effective
- When medical therapy is costly
- When medical therapy causes intolerable side effects
- When patients do not want to be on medication

Third Line Treatment Options

- Intradetrusor onabotulinumtoxin a
- Peripheral tibial nerve modulation
- Sacral neuromodulation

Onobotulinum Toxin (Botox®)

- Inhibits ACh, which reduces bladder contraction, reduces leakage episodes and may increase capacity
- Can cause temporary muscle paralysis (dose dependent) and increase risk of UTIs (not dose dependent)
- Can last 3-10 ms (variable)

Is Botox® Better Than SNM?

- Rosetta study 2016
  - Multicenter RCT
  - 2012-2015
- 200 u Botox
- Evaluated # UUI episodes/6ms
  - Secondary: satisfaction, urinary symptom scores, adverse affects

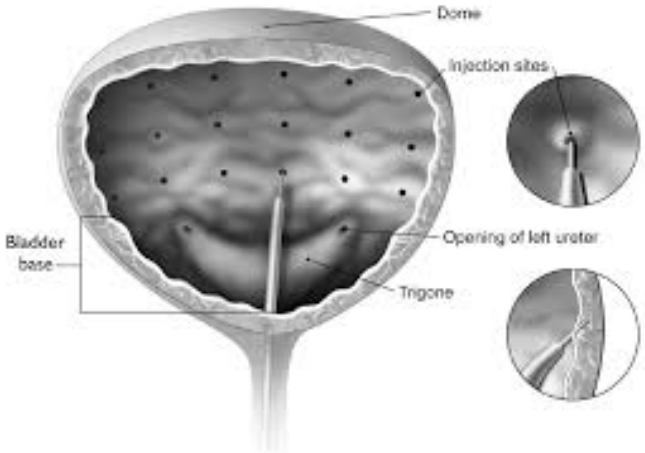
JAMA Intern Med 2016; 316(13): 1366-74.

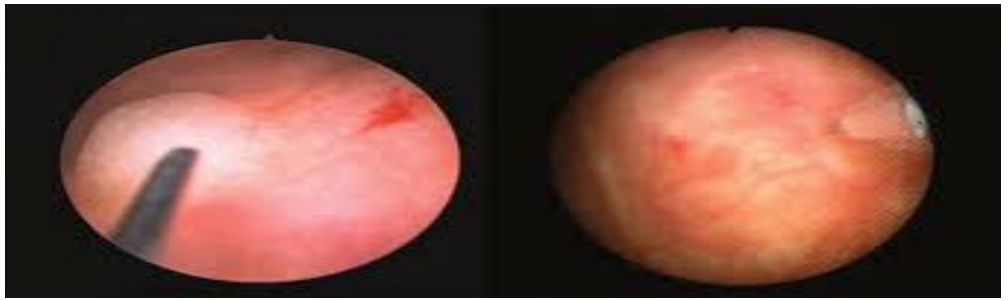
Is Botox® Better Than SNM?

- Findings: small statistical decrease in UUI (Botox®) –but does this translate into higher satisfaction
  - Increased side effects of Botox®: UTIs, intermittent caths (higher dose than office use)

JAMA Intern Med 2016; 316(13): 1366-74.

Administration of Intradetrusor Botox®

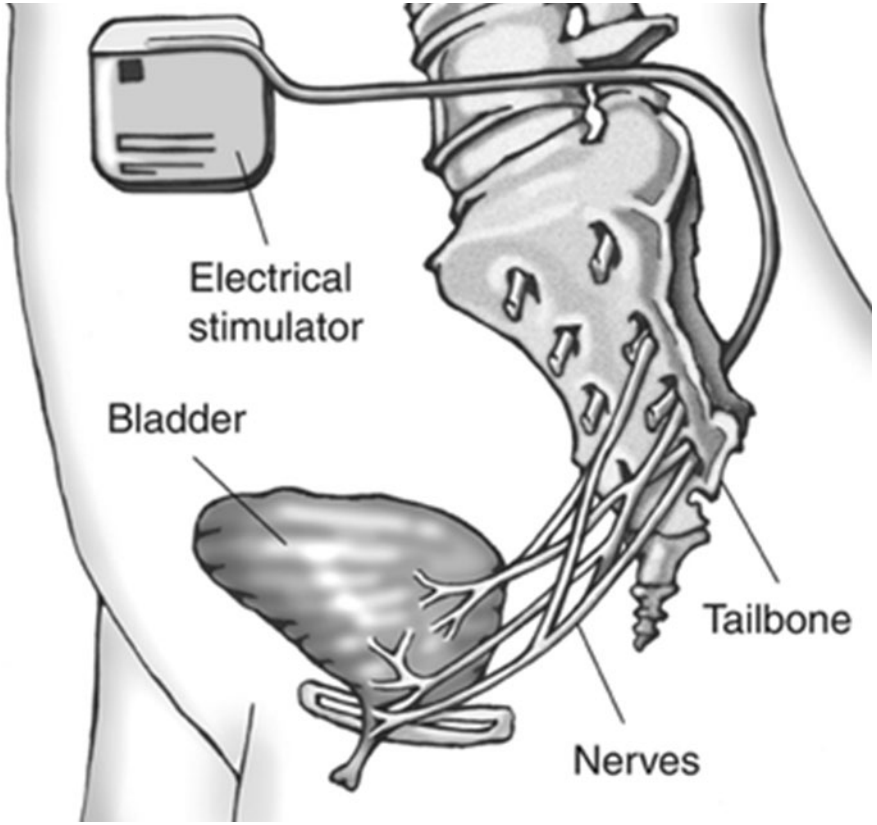




Efficacy of Botox®

- FDA approved, most insurances cover
- In office procedure
  - May need to check a urine cx few days before
  - Anesthesia: Only lidocaine jelly thru catheter
  - 10-30 injections (depending on dose, concentration)
- Complications (informed consent)
  - Temporary retention, UTI
- Follow up: 3weeks, 3ms, ...

Sacroneuromodulation



Sacroneuromodulation

Sacroneuromodulation

Stimulation of S3 nerve to reregulate bladder function

Electrically stimulates the sacral nerve which is thought to normalize neural communication between the bladder and brain and between the bowel and brain

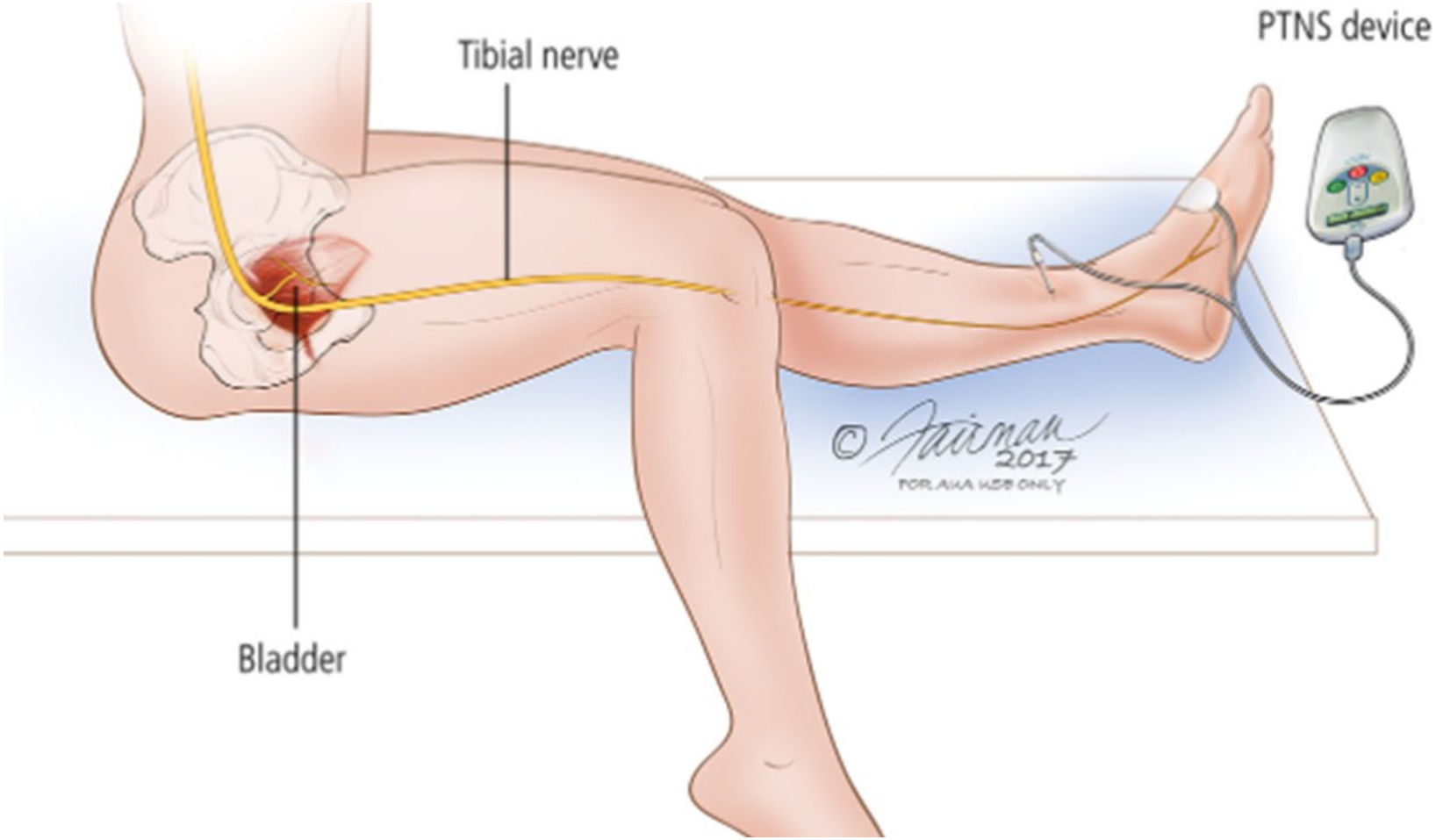
What is SNM?

- Stimulation of S3 nerve to re-regulate bladder function
- Electrically stimulates the sacral nerve which is thought to normalize neural communication between bladder/bowel and brain
- Can be tested in office with local sedation
- Can be done in OR with local anesthesia

Complications of SNS

- Wound infection
- Variable Battery life - requires changing battery
- Pain at pocket site
- Contraindications with MRI

Percutaneous Tibial Nerve Stimulation (modulation)



Percutaneous Tibial Nerve Modulation

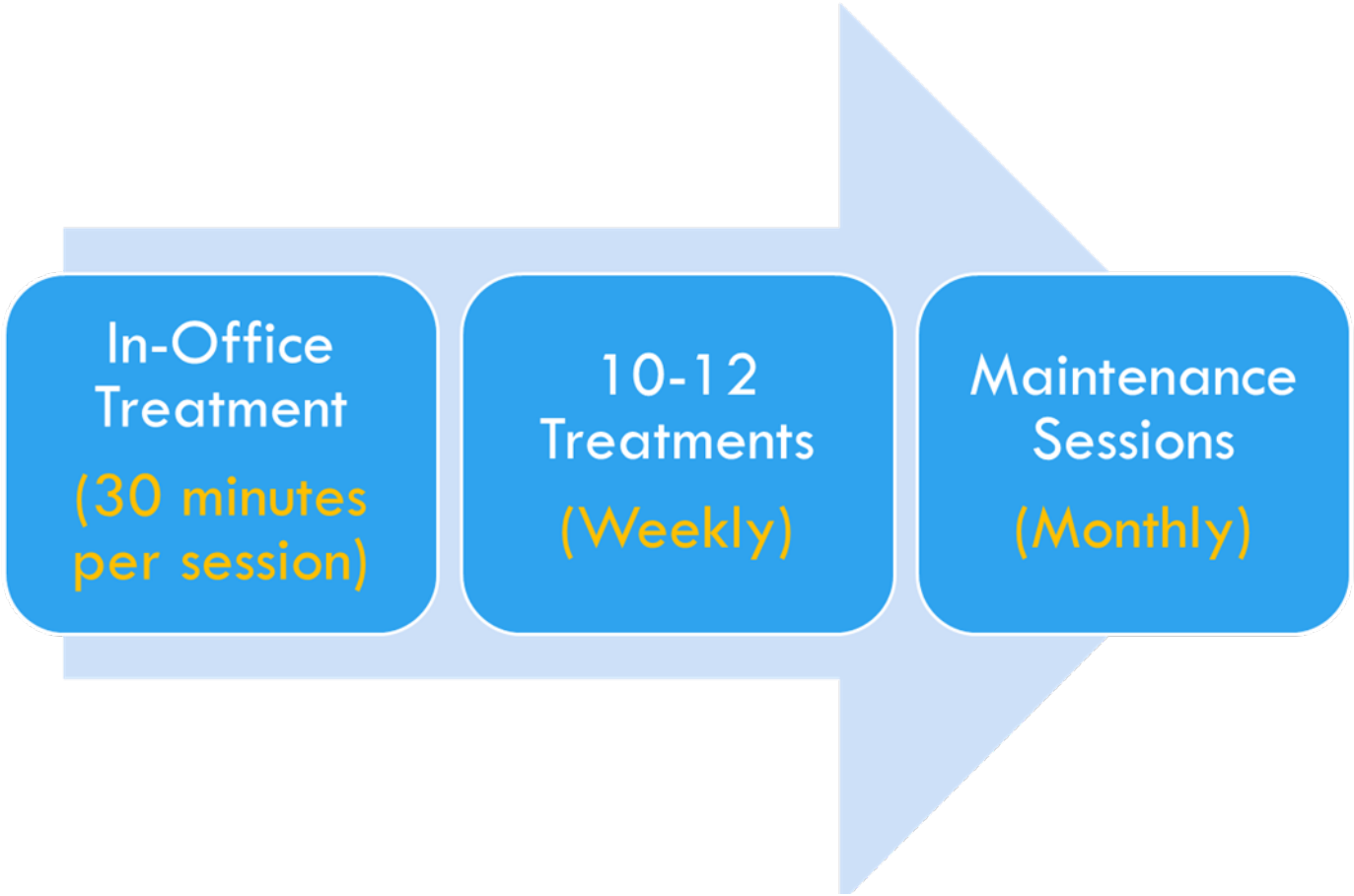
- PTNM delivers electrical pulses to stimulate the afferent fibers of the tibial nerve that extends to the sacral nerve plexus
- PTNM is thought to restore bladder function by modulating the bladder and the CNS pathway in a GRADUAL FASHION
- Weekly treatment for 12 weeks

Percutaneous Tibial Nerve Modulation

55% of patients reported “moderate” or marked improvement in symptoms

77% of responders had long-term, sustained efficacy at 3 years

Percutaneous Tibial Nerve Modulation



Complications of PTNM

- Adverse events are typically temporary
- Mild pain
- Minor inflammation
- Bleeding near treatment site

Final Thoughts

- Ask your patients
- Try to determine if it is bothersome to them
- Offer treatment, and inform that if they are a non responder that all is not lost

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THANK YOU

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