MANAGEMENT OF MEDICATION-REFRACTORY OVERACTIVE BLADDER (OAB)

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- Potential for conflict(s) of interest:
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LEARNING OBJECTIVES

By participating in this educational session, health care providers can expect to:

- Review the treatment options for medication-refractory idiopathic overactive bladder (OAB)
- Discuss best practices in managing OAB in urologic practices
- Identify strategies to overcome barriers to the various treatment options for medication-refractory idiopathic OAB

OAB – THE NEED FOR OPTIONS BEYOND PHARMACOTHERAPY

TREATMENT OPTIONS FOR ADULT OAB – CUA GUIDELINES

FIRST LINE

Behavioural therapies, lifestyle changes, education
Fluid/caffeine/dietary modification, weight control, management of bowel regularity, optimization of comorbidities, exercise, smoking cessation, bladder training, pelvic floor muscle training

SECOND LINE

Pharmacological management:
- Antimuscarinics (oxybutynin, tolterodine, darifenacin, trospium, solifenacin, propiverine, fesoterodine)
- β-3 adrenoceptor agonist (mirabegron)

THIRD LINE

Onabotulinumtoxin A (BoNT-A)

Posterior tibial nerve stimulation (PTNS)

Sacral neuromodulation (SNM)

Indwelling catheters, augmentation cystoplasty, urinary diversion

Corcos J, et al. Can Urol Assoc J 2017;11:E142-73

DISCUSSION

Which of the following options for the treatment of OAB are offered where you practice?

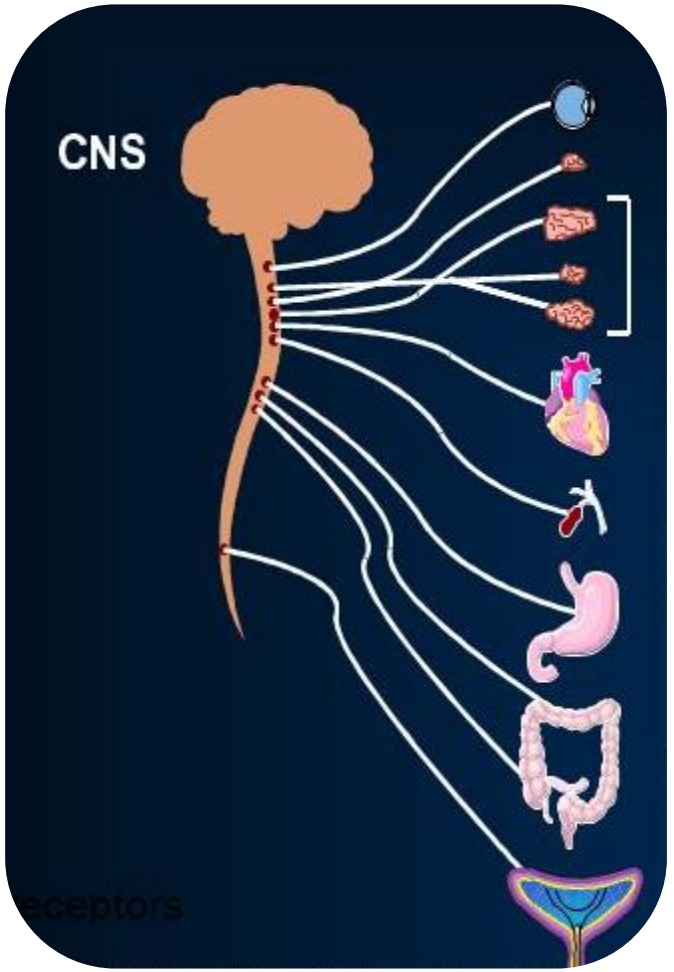
- ***BoNT-A treatment***
- ***PTNS***
- ***SNM***

BEYOND SECOND-LINE?

- Patients struggle with OAB medication therapy for a variety of reasons:
  - Lack of efficacy
  - Side effects
    - Dry mouth
    - Constipation
    - Cognitive concerns
  - Polypharmacy
  - Cost

COGNITIVE SIDE EFFECTS OF ANTIMUSCARINICS IN THE ELDERLY

- Antimuscarinics block muscarinic receptors throughout the body, including in the brain
- Elderly are more susceptible to increased antimuscarinic load
  - ↑ permeability of the blood brain barrier
  - Linked to cognitive impairment



CNS Central nervous system

Araklitis G, et al. Clin Interv Aging 2020;15:1493-503

PERSISTANCE TO PHARMACOLOGICAL TREATMENTS TO OAB

- Persistence to pharmacological therapies after 1 year:
  - Antimuscarinics: 12% to 25%
  - Mirabegron: 32% to 38%
- Median time to discontinuation:
  - Antimuscarinics: < 5 months
  - Mirabegron: 5.6 to 7.4 months

Yeowell G, et al. BMJ Open 2018;8:e021889

PREDICTORS OF DISCONTINUING OAB MEDICATIONS

- Smoking
- Uncertainty about the need for multiple daily doses of medication
- Questions around severity of AEs
- More severe/persistent symptoms
- Not used to taking multiple medications

AE Adverse events

Brubaker L, et al. BJU Int 2010;105:1283-90

CLINICAL VIGNETTE

- 73-y.o. female
- Gravida 3 Para 2
- Bothered by frequency 14x/day, nocturia 3x/night, urgency with most voids, worsening urgency incontinence
- Current Rx: solifenacin 10 mg qd without optimal response
- Exam normal
- Urinalysis normal

What treatment options are available for this patient?

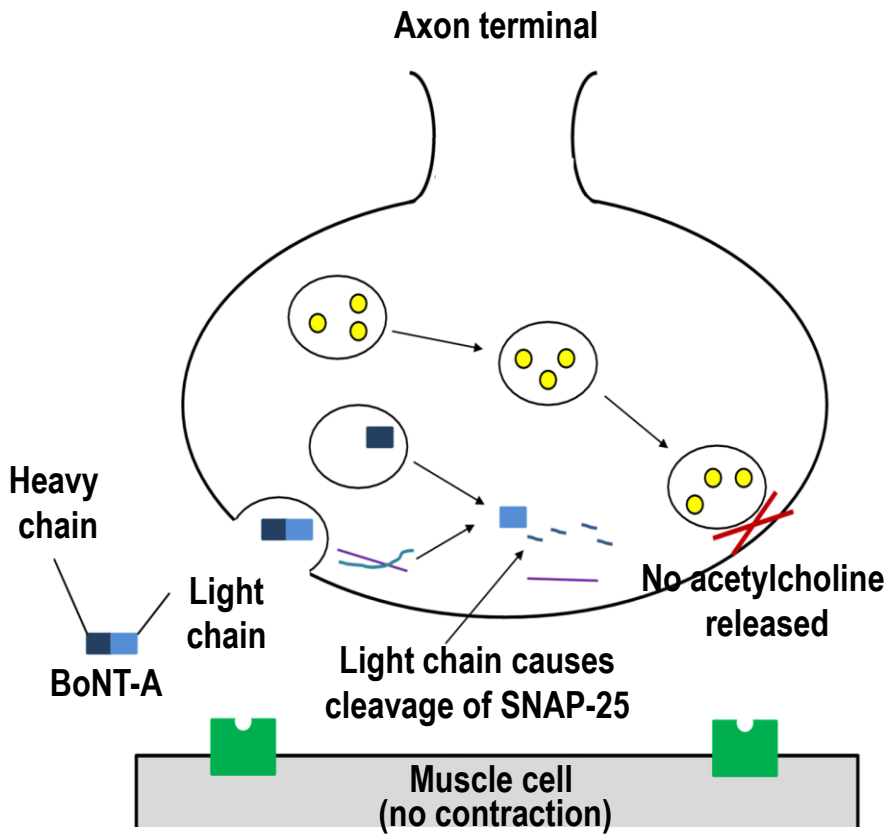
What are the options for medication-refractory OAB?

- OnabotulinumtoxinA (BoNT-A)
- Posterior Tibial Nerve Stimulation (PTNS)
- Sacral Neuromodulation Therapy (SNM)

OnabotulinumtoxinA (BoNT-A)

BoNT-A: MECHANISM OF ACTION

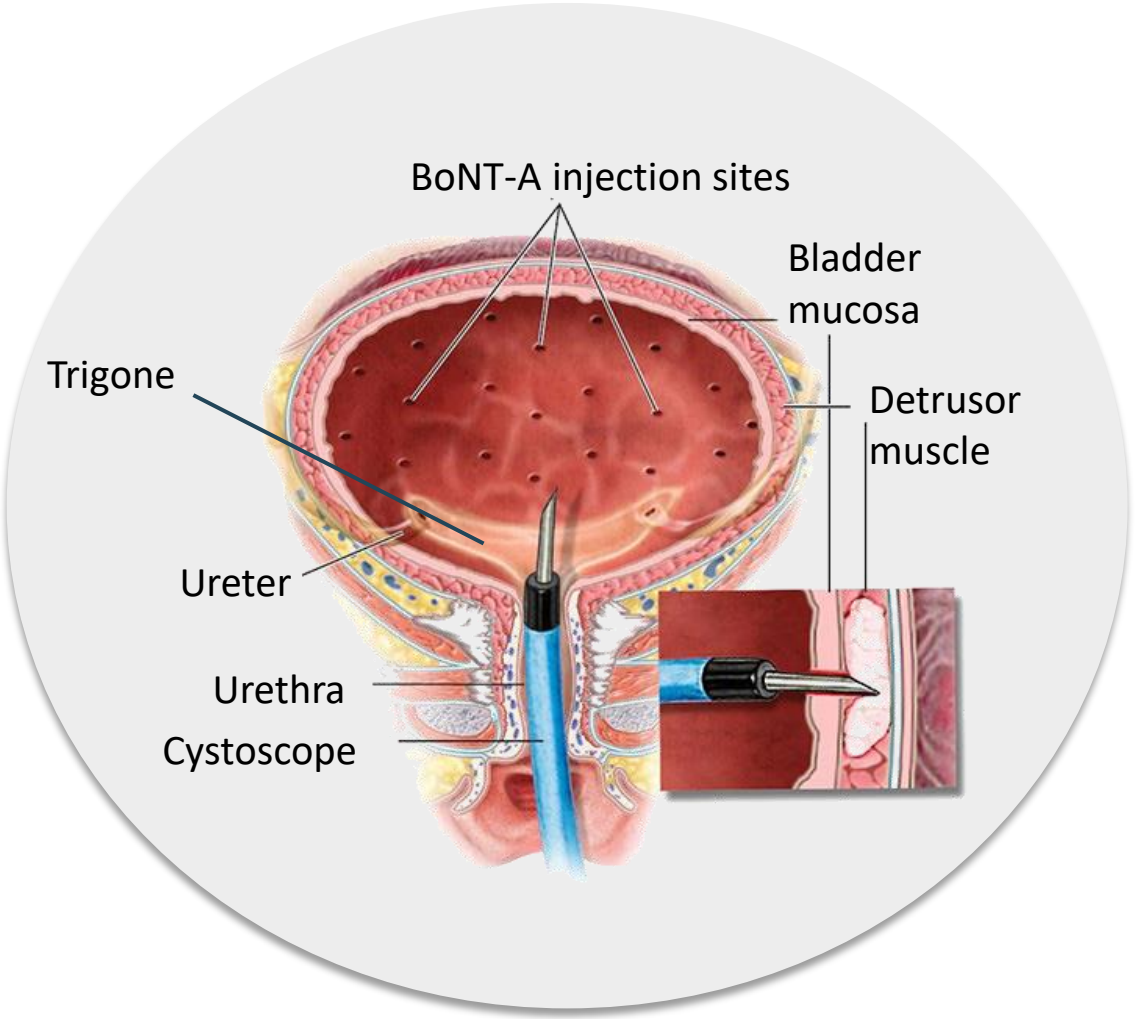
- Light chain + heavy chain linked by a disulfide bond
- Cleavage of the disulfide bond results in binding of the light-chain to SNAP-25
  - Inhibits exocytosis of neurotransmitters from the vesicles
    - Affects bladder neck contracture and detrusor relaxation
    - Reduces the urge and frequency of urination



Lin YH, et al. Toxins (Basel) 2020;12:129

BoNT-A ADMINISTRATION

- Reconstituted BoNT-A injected into detrusor muscle via cystoscope
  - Avoid the trigone
- Local anesthetic may be used
- Needle inserted ~2 mm into detrusor
- Injections spaced ~1-2 cm apart



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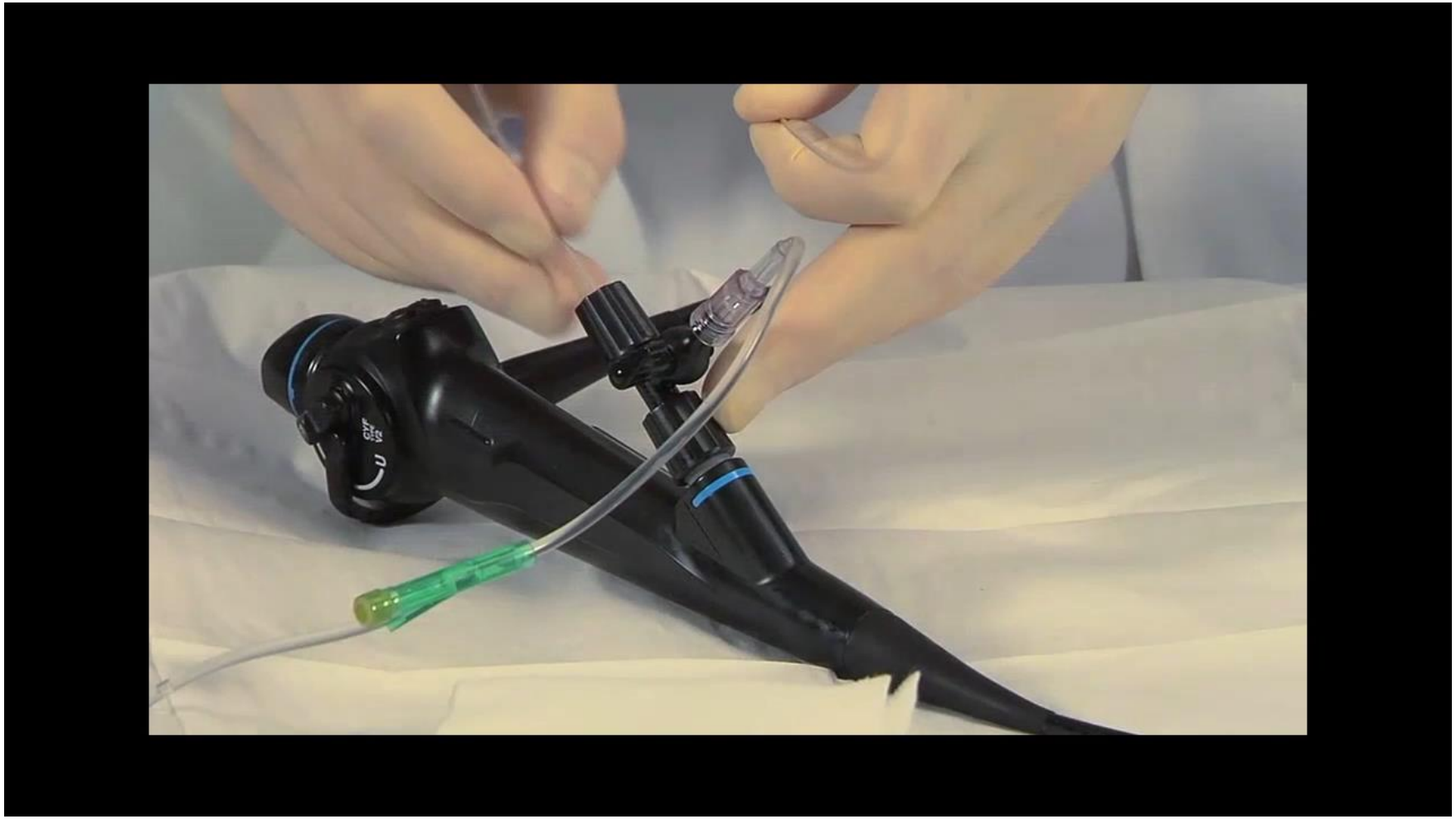
BoNT-A ADMINISTRATION VIDEO



CANDIDATES FOR BoNT-A

INDICATIONS

- OAB inadequately controlled with behavioural therapy, antimuscarinic medication, or beta-3 agonist

CONTRAINDICATIONS

- Hypersensitivity to BoNT-A or any ingredient in the formulation
- Active UTI or recent history of frequent UTIs
- Unwilling/unable to initiate CIC

SPECIAL POPULATIONS

Pregnancy

- Potential risk unknown

Breastfeeding

- Exercise caution

Anticoagulated patients

- Consider discontinuing anti-coagulation/anti-platelet agents and/or take measures to minimize risk of post-injection bleeding

CIC Clean intermittent catheterization **UTI** Urinary tract infection

Adapted from Rovner E. Neurourol Urodyn 2014 Jul;33 Suppl 3:S32-7
Botox Product Monograph. March 2021

BoNT-A: WHAT CAN PATIENTS EXPECT?

Symptom improvement takes 1-2 weeks

- ~80% of patients experience treatment benefit*
- Reduction in urgency, urinary incontinence, frequency, nocturia

Potential AEs: UTI, transient dysuria, hematuria, CIC

Describe ease of use of CIC and that it's transient

Re-injection needed after ~6–10 mos (no sooner than 3 mos)

Counsel patients on concomitant use of oral OAB medications:

- When to discontinue them
- When to introduce them

AE Adverse event

Adapted from Rovner E. 2014;33 Suppl 3:S32-7
*Niti VW, et al. J Urol 2016;196:791-800

BONT-A INJECTIONS AND UTI RISK

- In a phase 3 trial, 15.5% of patients experienced UTI following injection (vs. 5.9% in placebo group) [1]
  - Lab vs. clinical definition of "UTI"
- Antibiotic prophylaxis is recommended
- May consider offering Rx for self-start therapy
- Consider pre-treatment culture
- What to do if cystitis observed at cystoscopy?

1. Nitti VW, et al. J Urol 2013;189:2186-93

IS THERE A PREFERRED ANTIBIOTIC PROPHYLAXIS REGIMEN TO PREVENT UTIs FOLLOWING BONT-A FOR OAB?

Antibiotic regimen	Risk of post-procedural UTI vs. no antibiotic prophylaxis	
	RR (95% CI)	p
Oral only		
Cephalexin	1.97 (0.47–8.27)	0.36
Ciprofloxacin	2.07 (0.41–10.36)	0.38
Nitrofurantoin	1.23 (0.35–4.35)	0.75
SMZ-TMP	1.72 (0.36–8.30)	0.50
IV only		
Cefazolin	1.35 (0.60–3.05)	0.47
Ciprofloxacin	1.72 (0.56–5.32)	0.34
Clindamycin	0.69 (0.13–3.73)	0.67
Gentamicin*	2.18 (0.78–6.13)	0.14
IV and Oral		
Cefazolin + cephalexin	1.91 (0.72–5.07)	0.19
Cefazolin + Ciprofloxacin	1.43 (0.56–3.63)	0.45
Cefazolin + Nitrofurantoin	1.55 (0.53–4.57)	0.43
Cefazolin + SMZ-TMP	1.44 (0.50–4.09)	0.50
Ciprofloxain + Ciprofloxacin	2.30 (0.53–9.96))	0.27

In this cohort, no route of antibiotic administration was superior in the prevention of UTI. In fact, antibiotic prophylaxis did not lower the rate of post-procedural UTI when compared to no antibiotics.

*Note: The effect of BoNT-A may be increased by aminoglycoside antibiotics, including gentamicin (Botox Product Monograph. March 2021)

SMZ-TMP Sulfamethoxazole and trimethoprim

Eckhardt SE, et al. Int Urogynecol J 2021 Epub ahead of print

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- Gravida 3 Para 2
- Bothered by frequency 14x/day, nocturia 3x/night, urgency with most voids, worsening urgency incontinence
- Current Rx: solifenacin 10 mg qd without optimal response
- Exam normal
- Urinalysis normal

Our patient is interested in pursuing BoNT-A injections, but she is currently taking apixaban for afibrillation.

What considerations are necessary before treating this patient?

Rx Prescription medication

IS IT NECESSARY TO STOP ANTIPLATELETS OR ANTICOAGULANTS BEFORE BONT-A?

- Multicentre retrospective review
- 532 patients – 63 on AC or AP (mean age 69 years)
    - 114 individual episodes of BoNT-A injections
        - Aspirin (n = 44)
        - Clopidogrel (n = 37)
        - Warfarin (n = 19)
        - NOAC (n =14)
- Significant hemorrhagic event in 1 patient (0.88%)
    - Patient on rivaroxaban, previous prostate RT, self-catheterization
    - Post-injection hematuria – resolved spontaneously

AC Anticoagulant **AP** Antiplatelet **NOAC** non-vitamin K oral anticoagulant
RT Radiation therapy

Mensah EE, et al. Neurourol Urodyn 2021 (Epub ahead of print)

BoNT-A: DOES THE NUMBER OF INJECTIONS MATTER?

- RCT, n = 72 [1]
  - BoNT-A 100 U in 10 mL at 10, 20, or 40 sites
  - 1° endpoint GRA ≥ 1 after treatment
  - Similar therapeutic outcomes and AEs in all groups
- Prospective pilot study, n = 45 [2]
  - BoNT-A 100–300 U at 1–3 sites
  - 73% achieved ICIQ-SF score improvement > 5 points
  - 69% Subjective success rate

1 mL BoNT-A injections (10 U) at 10 sites was adequate to achieving optimal therapeutic effect in patients with OAB.

Administering BoNT-A via 1–3 intradetrusor injection sites has similar clinical efficacy and rates of AEs vs. the established technique.

GRA Global response assessment **ICIQ-SF** International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form
RCT Randomized controlled trial

1. Liao CH, et al. Neurourol Urodyn 2016;35:717-23 **2.** Avallone MA, et al. Neurourol Urodyn 2017;36:1104-7

DISCUSSION

Discuss the different approaches to BoNT-A injection for OAB:

- *Is urodynamic assessment (UDS) necessary prior to starting BoNT-A? On whom might you do UDS?*
- *What options for local anesthetic would you consider?*
- *Is the number and location of injection sites important?*
- *Is antibiotic prophylaxis necessary?*
- *Do you teach self-catheterization prior to injection or deal with it as the need arises?*

BoNT-A: POST-INJECTION CARE

Monitor for infection, hematuria, pain, and other AEs

1- to 4-week follow-up visit:

- Measure PVR volume
- Question for signs or symptoms of UTI, dysuria, hematuria, retention, other AEs

3- to 4-month follow-up visit:

- Virtual or in-person
- Determine need for repeat injections
- Could include PVR/flow scan/PROs
- Determine need to adjust dose (depending on retention, duration, efficacy)
- Counsel patient about concomitant use of oral medications

PRO Patient reported outcome **PVR** Post-void residual

Adapted from Rovner E. Neurourol Urodyn 2014;33 Suppl 3:S32-7

DISCUSSION

How do you manage the timing of repeat injections in your practice?

- *Wait for the patient to call?*
- *Automatically book injections at 6-mo intervals?*
- *Book 2nd injection at 6 mos and adjust timing of subsequent injections as needed?*

BoNT-A: WHEN TO REINJECT?

- Consider reinjection when clinical effect of previous injection diminished
- Median duration of response in clinical trials ~24 to 30 weeks
- Determine what symptom(s) trigger a repeat injection
  - Patient specific
- No sooner than 3 mos from prior injection

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POTENTIAL REASONS FOR LACK OR DIMINISHED RESPONSE TO BoNT-A (REAL OR PERCEIVED)

- Inadequate dose selection
- Patient perception of benefit vs. initial results
  - Use of PROs pre- and post-injection helpful
- Inappropriate storage or reconstitution
- UTI
- Unrecognized or untreated urinary retention
- Discontinuation of oral OAB medication
- Received BoNT-A for another reason

Botox Product Monograph. March 2021

WHAT TO DO IF THE PATIENT SAYS “THAT DIDN’T WORK”

- Check PVR
  - Did it work too well? (High PVR)
- Try again with different dose (after appropriate interval) or different technique (in OR vs. local)
- Add a medication
- Try to understand "why didn't it work?
  - What were they expecting?“
  - Does the patient have mixed incontinence?
  - Why or when do they leak?

OR Operating room

BoNT-A: TIPS FOR TROUBLESHOOTING COMMON PROBLEMS

PROBLEM	SUGGESTIONS
During procedure	
Failure of patient to tolerate the procedure	• Regional anesthetic gel applied to urethra • Taking a break • Finding more comfortable injection sites
Injection of blood vessel	• Complete the injection procedure, then come back to deal with the bleeding as needed • On rare occasion cautery may be required • Push needle or scope against the bleeding site and wait
Post-procedure	
PVR volume >200 but <350 mL with no symptoms of urinary retention and/or UTI	• Watch, wait, monitor for UTI or symptoms • Assess PVR at 2 to 4 weeks
PVR volume >200 mL with symptoms or PVR volume >350 mL with or without symptoms	• CIC preferred • Temporary indwelling catheter or suprapubic cystostomy tube • Compare PVR to prior to procedure
Urinary infection	• Culture (compare to any prior) • Assess PVR • Give culture appropriate antibiotics if clinically indicated

Adapted from Rovner E. Neurourol Urodyn 2014;33 Suppl 3:S32-7

DISCUSSION

What are some of the barriers/challenges to treating OAB with BoNT-A in your practice?

- *Patient-related challenges?*
- *Clinic/logistical challenges?*

Discuss potential ways of overcoming these challenges. What has worked/not worked in your practice?

- *Patient counselling tips?*
- *Tips for streamlining your practice?*

CONSIDERATIONS FOR SETTING UP YOUR BoNT-A INJECTION CLINIC

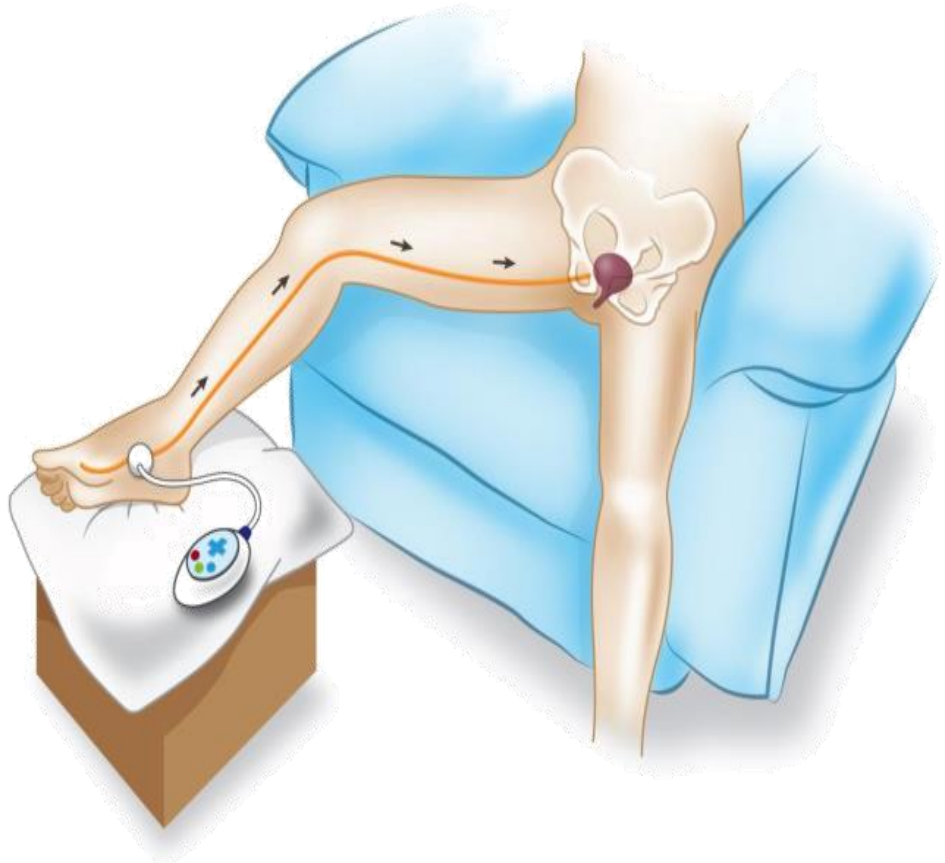
- Preop counselling and education
- Choice of cystoscopes - rigid vs. Flexible.
- Access to BoNT-A
- Local resources for CIC teaching and PVR
- Post-operative care in the office/ community
- Local anesthetic protocol versus none
- Available lift for wheelchair patients
- Choice of needle(s)
- Available electrocautery unit
- Expert nursing in the cystoscopy suite
- Patient support in the room

Other considerations?

Posterior Tibial Nerve Stimulation (PTNS)

PTNS PROCEDURE

- Posterior tibial nerve stimulated with electrical current
  - Continuous square wave form
  - Duration 200 Us
  - Frequency 200 Hz
  - Intensity determined by the highest level tolerated by the patient
- 34-gauge needle inserted 4–5 cephalad to the medial malleolus
- Each session ~30 mins



Bhide AA, et al. Int Urogynecol J 2020;31:865-70

EFFECTIVENESS AND DURABILITY OF SOLIFENACIN VS. PTNS VS. SOLIFENACIN + PTNS IN WOMEN WITH OAB

- Prospective RCT of 105 women
- PTNS vs. solifenacin (SS)
  - No significant difference in daily or night-time micturition, urgency, urge incontinence, or QOL
  - PTNS > SS in 10-month OABSS and PGI-I scores
- SS + PTNS vs. SS or PTNS
  - PTNS+SS > SS in daily and night-time micturition, urgency, urge incontinence, and QOL parameters
  - PTNS+SS > PTNS in urgency, urge incontinence, and QOL parameters
  - PTNS+SS > SS or PTNS in 10-month OABSS and PGI-I scores

Combination PTNS + solifenacin showed greater effectiveness and durability than either PTNS or solifenacin alone

OABSS Overactive Bladder Symptom Score **PGI-I** Patient Global Impression of Improvement questionnaire **QOL** Quality of life

Vecchioli-Scaldazza C, et al. Int Braz J Urol 2018;44:102–8.

PTNS CONSIDERATIONS

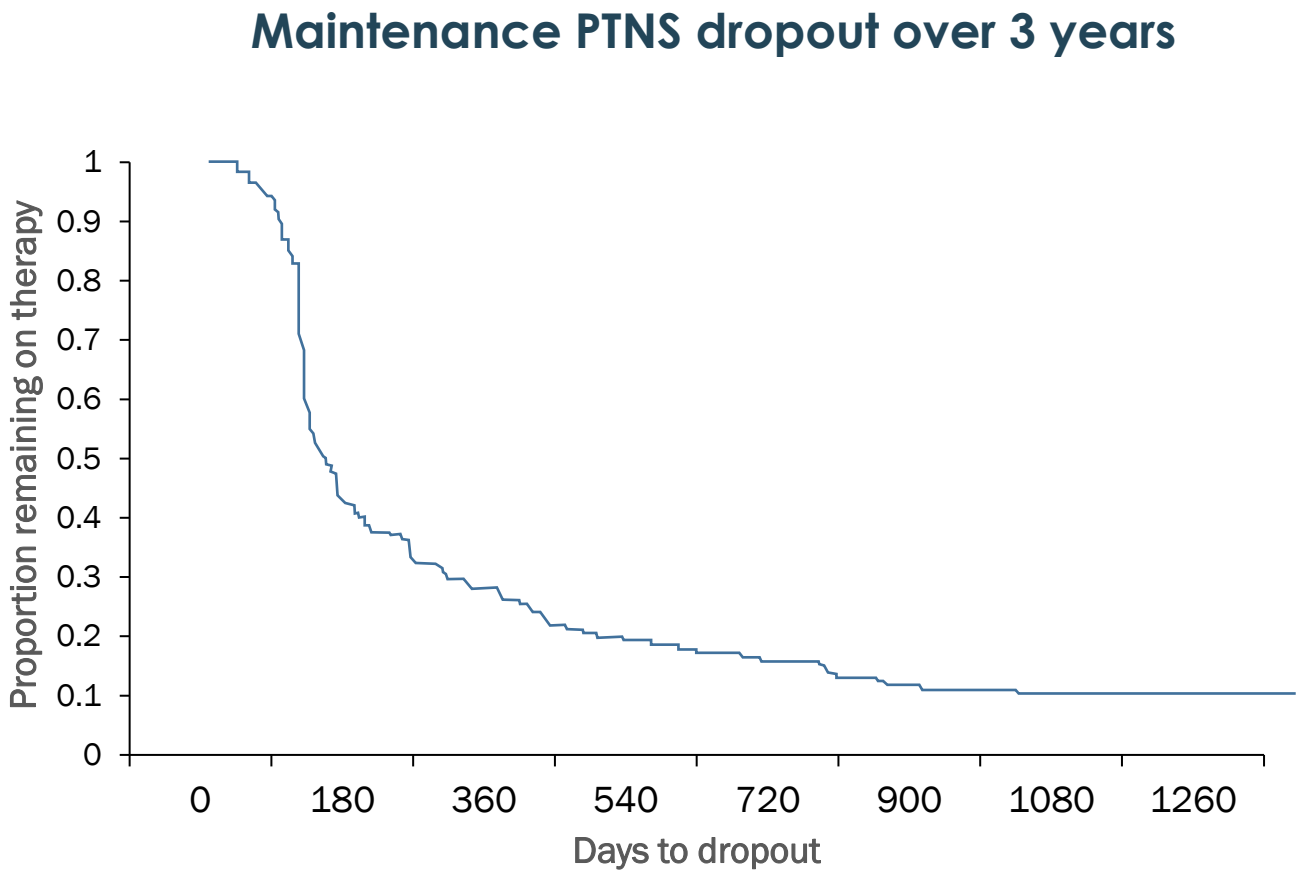
- Success rate ~70%*
- Frequent clinic appointments/follow-up (30 mins to 1 hour)
  - Motivation
  - Travel resources
- Cost considerations
- Contraindications:
  - Bleeding tendency
  - Peripheral neuropathy
  - Cardiac pacemaker
  - Pregnancy

*Defined as >50% reduction in urgency urinary incontinence episodes

Finazzi-Agrò E, et al. J Urol 2010;184:2001-6
Corcos J, et al. Can Urol Assoc J 2017;11:E142-73
Raju R, et al. Mayo Clin Proc 2020;95:370-7

LONG-TERM COMPLIANCE WITH MAINTENANCE PTNS IS LOW

- 146 patients in a single centre
- After 3 years, 11% (16/146) were still regularly undergoing PTNS
- Median duration of PTNS: 147 days
- Symptom improvement reported by 100% of patients who remained on PTNS vs. 60% of those who stopped



Du C, et al. AUA 2021. Abstr MP52-13

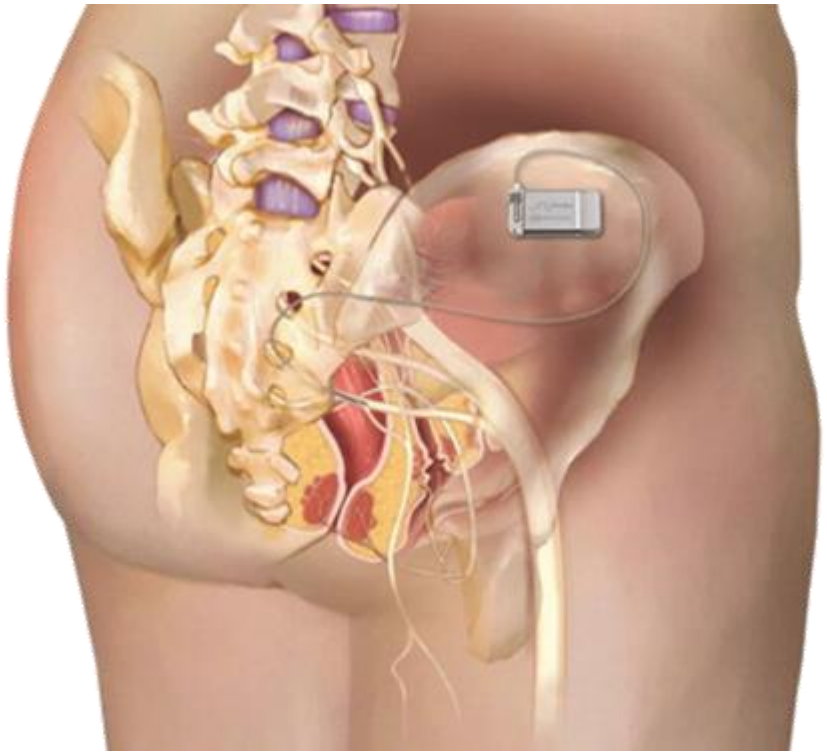
Sacral Neuromodulation Therapy (SNM)

SNM IS A MINIMALLY INVASIVE PROCEDURE PERFORMED IN 2 STAGES

- **Stage 1:** Lead is placed through the S2 foramen guided by fluoroscopic imaging
  - Tested for appropriate motor and sensory responses
  - Trial period, using an external generator

If ≥ 50% improvement

- **Stage 2:** A more permanent lead/pulse generator is placed



Raju R, et al. Mayo Clin Proc 2020;95:370-7

SNM CONSIDERATIONS

- Success rate*:
  - Stage 1 implant (testing phase) ~ 70% [1]
  - Stage 2 implant (treatment phase) 87% at 1 month, 62% at 5 years [2]
- Need for repeat treatments
- Risk of device infection
- Regional or general anesthesia
- Visits for reprogramming and battery replacement
- Cost

*Defined as at least a 50% decrease in the number of incontinence episodes or pads used daily

1. Davis T, et al. Can Urol Assoc J 2013;7:176-8
2. Groen J, et al. J Urol 2011;186:954-9
3. Raju R, et al. Mayo Clin Proc 2020;95:370-7

MOST COMMON SIDE EFFECTS OF SNM

- Rate of complications is about 30% – 40% within the first 5 years
  - High re-operation rate (33% – 41%)
- Regional pain at the implant site (3% – 42%)
- Impaired defecation (4% – 7%)
- Infection (4% – 10%)
- Electrode malposition (1% – 21%)

Sukhu T, et al. Res Rep Urol 2016;8:193-9
Hassouna MM, et al. J Urol 2000;163:1849–54
Hijaz A, et al. Urology 2006;68:533–7

DISCUSSION

How do you choose which third-line therapies to offer your patients?

- *Patient-related challenges?*
- *Clinic/logistical/reimbursement challenges?*

SUMMARY

- Treatment of medication-refractory OAB includes intravesical injection of BoNT-A, PTNS, and SNS
- All 3 treatment approaches are effective and generally well tolerated
- Treatment selection in the case of OAB refractory to pharmacological treatment relies on patient preference, availability/access to treatment, cost, and local expertise