Refractory Overactive Bladder

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Disclosures

- **Advisory Board and/or Speaker**
  - Allergan
  - Medtronic
  - Astellas

- **AUA Guidelines**
  - Urodynamics, Member 2011-2014
  - Stress incontinence, Chair, 2015-current

All honoraria go to Virginia Mason
Prevalence

- Up to 100 million worldwide
- 16.6% of adult population in US
  - OAB dry: 13.6% men, 7.6% women
  - OAB wet: 2.4% men, 9.3% women
- <40% seek treatment

Wein AJ. *Urology*. 2002;60(Suppl 5A):7-12.
Terminology

- **Overactive bladder (OAB)**
  - A symptomatic diagnosis defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia

- **Detrusor overactivity (DO)**
  - A urodynamic observation characterized by involuntary detrusor contractions (IDC) during the filling phase

AUA/SUFU OAB Guidelines

- Based on 151 articles
- Based on evidence strength
- AUA nomenclature linked to LOE
- Statements divided into three tiers
  - First line treatments
  - Second line treatments
  - Third line treatments

OAB Guidelines Statements

Treatment

- First line
  - Behavioral therapies (Standard)
  - Above may be combined with pharmacotherapy (Recommendation)

OAB Guidelines Statements

Treatment

- Second line
  - Oral antimuscarinics (Standard)
  - B-3 agonist (Standard)
  - Extended release should be preferentially offered (Recommendation)
  - Transdermal oxybutynin (Recommendation)
  - Change dose or agent as necessary (Clinical principle)

OAB Guidelines Statements

Treatment

- Third line
  - Sacral neuromodulation (Recommendation)
  - Percutaneous Tibial Nerve Stimulation (PTNS) (Recommendation)
  - OnabotulinumtoxinA (Standard option)

OAB Guidelines Statements

Treatment

- Additional treatments
  - Indwelling catheters as last resort (Expert opinion)
  - Augmentation cystoplasty/diversion (Expert opinion)
    - Severe, refractory complicated cases only
- Follow up recommended to assess compliance, efficacy, side effects, to offer alternatives
  - No data available

Treatment Options for Urinary Incontinence

**Stress Incontinence**
Leakage with laughing, coughing, physical activity

**Non-Surgical**
- Pelvic floor muscle training
- Pelvic floor physical therapy
- Incontinence pessary
- Urethral inserts

**Surgical**
- Urethral bulking
- Sling
  - Autologous fascia (your own tissue)
  - Mesh (retropubic or transobturator approach)
- Retropubic suspension (Burch)

**Mixed Incontinence**
- Bladder squeezes more than expected
- Urethra is weaker than expected

**Overactive Bladder**
Urinary frequency, urgency, and/or incontinence associated with urgency

1. **1st line:** Behavioral Therapy
   - Bladder control strategies & bladder training

2. **2nd line:** Non-Surgical
   - Fluid management & avoidance of bladder irritants
   - Pelvic floor physical therapy

3. **3rd line:** Minor Procedure or Surgical
   - Overactive bladder medications
   - Vaginal estrogen
   - Botox® injections into the bladder
   - Peripheral tibial nerve stimulation
   - Sacral neuromodulation (Interstim®)

**Clinical Trials**

*If you are not improving and still experiencing bothersome symptoms, please call your physician and schedule a follow up appointment*
Options

- "Conservative measures"
- Pharmacotherapy
- Neuromodulation
  - Electrical or biological
- Reconstruction
  - Augmentation cystoplasty
  - Urinary diversion
  - Sling-lysis/urethralysis
Conservative measures

- Dietary modification
- Bladder drills and retraining
- Pharmacotherapy
  - Antimuscarinics
  - Beta-3 adrenergics
  - Combination therapy
- Local hormone replacement therapy
WHEN DOES IT BECOME “REFRACTORY”?
Beta-3 adrenergic agonist MOA

- Increase bladder capacity
- *Without* effect on voiding parameters
  - Qmax
  - PdetQmax
  - Residual volume

Symphony: Combination therapy

- Monotherapy
  - Mirabegron, solifenacin, placebo
- 6 combinations mirabegron + solifenacin
  - 25 or 50mg AND 2.5, 5, or 10mg
- Combo therapy efficacy greater than solifenacin 5mg
  - Mean volume voided/micturition, frequency/24 hours, urgency
- All combos tolerated well

MILAI: Combination therapy

- Multicentre, open-label phase IV study
- Patients on solifenacin (2.5 or 5mg)
- Add mirabegron 25mg x16 weeks
- Measures
  - Safety
  - Efficacy

Outcomes

- **Safety**
  - Adverse events
  - Labs
  - Vital signs
  - Electrocardiogram
  - QT interval
  - Post void residual

- **Efficacy**
  - OAB-SS, OAB-q-SF
  - Micturitions
  - Urgency
  - Urgency incontinence
  - Mean voided volume
  - Nocturia

Results/Conclusions

- Add on therapy well-tolerated
- AE 23% - mostly mild-moderate
  - Constipation most common
  - No retention
  - QT, heart rate, blood pressure, PVR changes NOT clinically significant
- Significant improvements all groups

But what if meds don't work?
What Treatment Should We Use If Drugs Fail for OAB; and, What Really Works After Drugs?

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Alternative Options

- "Conservative measures"
- Pharmacotherapy
- Neuromodulation
  - Electrical or biological
- Reconstruction
  - Augmentation cystoplasty
  - Urinary diversion
  - Sling-lysis/urethrolysis
PERCUTANEOUS TIBIAL NERVE STIMULATION (PTNS)
Percutaneous tibial nerve stimulation

- 34-gauge needle
- 3-5 cm cephalad to medial malleolus
- Placement confirmed
  - Great toe plantar flexion
  - Sensation on plantar aspect of foot
- 6-12 weekly treatments
- Maintenance (?)
PTNS: SUmiT Trial

- Study of Urgent PC vs Sham
  Effectiveness of Treatment of Overactive Bladder Symptoms
- Improvement in global response assessment (GRA)
  - PTNS vs sham: 58.3 vs 21.9%
- Response at 12 weeks, not at 6 weeks
- Improved QOL, frequency, urgency, UUI, nocturia

OrBIT trial

- **Overactive Bladder Innovative Therapy**
- PTNS versus tolterodine\(^1\)
- Improvement per GRA:
  - 79.5% vs 54.8%
- PTNS vs solifenacin with cross over\(^2\)
  - Bladder specific assessment
  - Both groups showed improvement

STEP Study

- Carryover effect of PTNS
- Patients who had effect at 12 weeks
- 14 week tapering
  - 2 treatments over 14 days
  - 2 treatments over 21 days
  - q 28 days

STEP Study results

- At 36 months 77% had sustained moderate/marked improvement\(^1\)
  - All domains tested
- Over 36 months, average 1.1 treatments/month
- OrBIT phase 2 similar carryover noted\(^2\)

Normal ACh release

1. SNARE proteins form complex
2. Vesicle and terminal membranes fuse
3. ACh released
Botox inhibits Ach release

1. Botulinum toxin binds to receptor
2. Botulinum toxin endocytosed
3. Light chain cleaves specific SNARE proteins
   - Types A, C, E: SNAP-25
   - Types B, D, F, G: VAMP
4. SNARE complex does not form: ACh not released

Same MOA for Other Neurotransmitters
A recent meta-analysis on BoNTA

- n=1320 in 8 publications
  - 6 RCTs
- Incontinence episodes/day: -2.77 vs -1.01
- Voids per day: -1.61 vs -0.87
- MCC 91.39 vs 32.32
- Incontinence-free: 29.20% vs 7.95%

Cui Y, et al., Neurourol UDS 2014
Jury still out...

- Dose
- Injection technique
  - Location
  - Depth
  - Number of injections
- Retreatment interval
- Long term efficacy and safety
Safety

- Systemic effects – unlikely for bladder
- Urinary retention
  - 11-40% depending on study
  - 9-fold higher risk than placebo in meta-analyses
  - 2015 AUA study showed 30%
    - Again definition of AUR was unclear

Milhouse and Siegel, AUA 2015
Challenges in literature

- Lack of uniformity in:
  - Definitions
    - Success
    - Retention
  - Follow up
  - Management
    - Recurrent symptoms
    - Retention
Repeat injections OK?

- 3-year extension study
- Multiple injections on prn basis
- Assessments
  - Mean change in UI/day
  - Median time to request Rx
  - AEs

Nitti et al., AUA 2015
Repeat injections OK?

- n=543, 51% completed study
- Discontinuation
  - AEs: 5.3%
  - Lack of efficacy: 2.8%
- Mean baseline UI/day similar
- Mean reduction 2.9-4.5

Nitti et al., AUA 2015
Repeat injections OK?

- Median time to request retreatment
  - ≤6 months: 34.2%
  - 6-12 months: 37.2%
  - >12 months: 28.5%
- Median efficacy 7.6 months

Nitti et al., AUA 2015
Key considerations

- Safety
- Efficacy
- Ease of performance
- Duration of response
- Sequela
- Cost
Anticholinergic vs Botox™ comparison in women with urgency incontinence

n=242 randomized to two arms
- Botox™ and oral placebo
- Saline and trospium or solifenacin

### “ABC” trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Anticholinergic</th>
<th>OnabotulinumtoxinA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>UI episodes per day</td>
<td>-3.4</td>
<td>-3.3</td>
<td>0.81</td>
</tr>
<tr>
<td>Complete resolution of UI</td>
<td>13%</td>
<td>27%</td>
<td>0.003</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>46%</td>
<td>31%</td>
<td>0.02</td>
</tr>
<tr>
<td>Catheter use</td>
<td>0%</td>
<td>5%</td>
<td>0.01</td>
</tr>
<tr>
<td>UTIs</td>
<td>13%</td>
<td>33%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ROSETTA

- Refractory overactive bladder: Sacroeuromodulation vs Botulinum toxin Assessment
- 380-patient goal met last year
- Initial reports anticipated

Pelvic floor disorders network (PFDN)
SACRAL NEUROMODULATION
SNS vs standard medical therapy

- **Inclusion criteria**
  - ≥2 urgency leaks/72 hours OR
  - ≥8 voids/day
  - Failed at least one medication
  - At least one medication not tried

- **n= 147 randomized, 6 month f/u**
  - 70 SNM
  - 77 SMT

## SNS vs SMT

<table>
<thead>
<tr>
<th></th>
<th>SNS</th>
<th>SMT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success ITT</td>
<td>61%</td>
<td>42%</td>
<td>=0.02</td>
</tr>
<tr>
<td>As treated</td>
<td>76%</td>
<td>49%</td>
<td>=0.002</td>
</tr>
<tr>
<td>Improved urinary</td>
<td>86%</td>
<td>44%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>symptoms interference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete continence</td>
<td>39%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>30.5</td>
<td>27.3</td>
<td>-0.06</td>
</tr>
</tbody>
</table>

SNS: 12 month follow up

- n=341, 272 to implant
- 255 with 12 month follow up
- 220 with baseline and 12 month diary
- Baseline
  - UUI/day: 3.1 +/-2.7
  - Frequency: 12.6 +/-4.5

SNS: 12 month results

- Success: 85% at 12 months
- UUI/day $\downarrow$ 2.2 +/-2.7
- Frequency $\downarrow$ 5.1 +/-4.1
- All parameters of ICIQ-OABqol significantly improved (p<0.0001)
- 80% had improvement in urinary symptom interference

SNS: adverse events

- 16% (56/340) during test
  - 3 serious: Site infection, skin infection, respiratory arrest intra op
- 30% (82/272) post-implant
  - 1 serious: Implant site erosion

### SNS: Device-specific AEs

<table>
<thead>
<tr>
<th></th>
<th>0-3 m # events (#pts)</th>
<th>3-6m # events (#pts)</th>
<th>6-12m # events (#pts)</th>
<th>Events</th>
<th># pts % (n=272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undesireable change in stimulation</td>
<td>20(18)</td>
<td>10(10)</td>
<td>6(6)</td>
<td>36</td>
<td>32(12)</td>
</tr>
<tr>
<td>Implant site pain</td>
<td>11(9)</td>
<td>8(8)</td>
<td>7(4)</td>
<td>26</td>
<td>20(7)</td>
</tr>
<tr>
<td>Implant site infection</td>
<td>8(7)</td>
<td>1(1)</td>
<td>3(3)</td>
<td>12</td>
<td>9(3)</td>
</tr>
</tbody>
</table>

Other tidbits...

- Sexual function improves
- Quality of life improves for FI
- Psychosocial outlook
  - Depression improves
  - Optimism is not a predictor of success
- Long-term safety in Medicare beneficiaries

Banakhar, 2014
Chungtai, 2014
Levin 2014
SNS success rates very good

- Pooled results from multiple publications\(^1\)
- \(n=234\) women
- 45% “cure” at minimum 6 months
- 46% maintained continence at 3 years
- 54% maintained self-reported improvement at 5 years
- Another pooled report: 56-69% at 2-3 years\(^2\)

Surgical revision low

- Rate: 3-16%
- Explantation
  - 6% due to lack of efficacy
  - 5-11% due to infection

And, though we can’t advocate for it...

- MRI may be feasible under controlled conditions
- n=9 underwent 15 MRIs
  - Both 0.6 and 1.5 Tesla machines used
  - IPGs off in all patients
  - IPG magnetic switch turned off in 8
- IPGs functioned in all 8 post MRI
- No complications
- Patients perceived no change

Overall…

- SNS has a good track record
- Easy, “test-drive” available
- SNS durability more stable than other Rxs
- SNS can also affect bowel and sexual function
- Long-term costs may be lower for SNS
From a practical standpoint...

<table>
<thead>
<tr>
<th>“Pros”</th>
<th>“Cons”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SNS</strong></td>
<td>Implanted device</td>
</tr>
<tr>
<td>Battery life 5-7 years</td>
<td>Potential complications</td>
</tr>
<tr>
<td>No retention</td>
<td>2-staged surgery</td>
</tr>
<tr>
<td>Global effects on pelvic floor</td>
<td>No MRIs</td>
</tr>
<tr>
<td></td>
<td>Not for neurogenic bladder</td>
</tr>
<tr>
<td><strong>BTX</strong></td>
<td>Risk of retention</td>
</tr>
<tr>
<td>Nothing implanted</td>
<td>Risk of UTI</td>
</tr>
<tr>
<td>Local anesthesia in office</td>
<td>Durability of response</td>
</tr>
<tr>
<td>Well-tolerated</td>
<td></td>
</tr>
</tbody>
</table>
## Cumulative 3-year costs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost (US $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTNS</td>
<td>7,565</td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td>11,748</td>
</tr>
<tr>
<td>Interstim®</td>
<td>24,681</td>
</tr>
<tr>
<td>Vaginal POP repair</td>
<td>6,353</td>
</tr>
</tbody>
</table>

Martinson et al.: J Urol 2013
Medicare, CMS
Cost effectiveness

- SNS more expensive ($15,743 vs. $4,392) and more effective (1.73 vs. 1.63 QALYs) than BoNTA
  - SNS was more effective
  - BTX was more cost-effective

- Cost per effectiveness (Incremental Cost Effectiveness Ratio = ICER) may change with longer follow up
  - (At 4 years, SNS becomes more cost effective)

Siddiqui NY et al, Neurourol Urodyn 2010; 29 Suppl 1: S18
Treatment Options

- “Conservative measures”
- Pharmacotherapy
- Neuromodulation
  - Electrical or biological
- Reconstruction
  - Augmentation cystoplasty
  - Urinary diversion
  - Sling-lysis/urethrolysis
The Last Resort...

ENLARGE THE BLADDER!

A big operation, but…it works!
Open a piece of bowel
Flatten it out
Sew it to the bladder...
Augmentation Cystoplasty

- Bowel segment to enlarge bladder
- Lowers intravesical pressure
- Increases capacity
- >80% must catheterize
Take Home Messages

- “OAB” multifactorial
- Conservative measures first
- Stepwise progression
- Successful options available
(Patients must be made aware)