Upon completion, participants should be able to:

• Recognize signs and symptoms of urinary incontinence (UI)
• Describe nerve-stimulation techniques used in the treatment of UI
• Identify patients for whom nerve stimulation may be an effective treatment for UI
Introduction to Urinary Incontinence

• Definition: the involuntary loss of urine
• Three types of UI
  – UUI: sudden and compelling urge to void
  – SI: release of urine when pressure is placed on the abdomen (ie, laughing, coughing, jumping, sneezing)
  – Mixed UI: a combination of UUI and SI

Terminology of Urge Urinary Incontinence

• Overactive Bladder (OAB):
  – Urinary urgency: sudden, compelling desire to pass urine
    • Frequency
      – Voiding more frequently than previously
    • Nocturia
      – Interruption of sleep 1 or more times to void
    • No urinary tract infection or other obvious pathology
    • With or without UUI
Prevalence of UI in Women Increases With Age

Prevalence, %


Anatomy of the Bladder

Ureter

Peritoneum

Detrusor muscle

Internal urethral sphincter

Ureteral openings
Multiple Pathways Involved in Storage

- Bladder filling stretches muscle fibers and activates **A-delta fiber afferent activity**
- **Sympathetic efferent activity** is stimulated
- **Somatic efferent activity** increases, resulting in increased tone of the urethral sphincter
- Spinal reflex pathways promote continence
- The parasympathetic system is **inhibited** due to sympathetic activity

UUI May Have Several Pathophysiologic Causes

- Changes in neurotransmitter signaling
- Detrusor muscle alterations
- C-fiber afferent upregulation


de Groat WC. Urology. 2004;64:7-11;
Brading AF. Urology. 1997;50:97-73;
Symptoms of UUI May Present as a Spectrum

**DRY**
- Urgency/frequency
- Good pelvic floor muscles

**WET**
- Urgency/frequency
- ± good pelvic floor muscles
- Small volume, intermittent leakage
- Urgency/frequency
- Decompensated pelvic floor muscles
- Poorly coordinated pelvic floor muscles
- Leaks regularly
- Large volume leakage


Current Treatment Options for UUI

- **First-line therapy**
  - Treat reversible causes of UUI
  - Behavioral therapy
    - Fluid management
    - Bladder retraining
  - Pelvic floor muscles exercises
    - Biofeedback

- **Second-line therapy**
  - Medications
    - Anticholinergics
    - B3 adrenergic agonists

Nerve Stimulation for UUI

- Third-line therapy; If refractory OAB symptoms, then referral to a specialist is recommended:
  - Posterior tibial nerve stimulation
  - Sacral nerve stimulation
  - Intradetrusor injection of onabotulinumtoxinA

Posterior Tibial Nerve Stimulation (PTNS)

- FDA approved in 2000
- Direct electrical stimulation of posterior tibial nerve to the sacral plexus, which regulates the control of pelvic floor muscles and the bladder
- Mechanism still unclear; studies report 65% to 80% improvement in patient symptoms
- Adverse events are uncommon (1% to 2%) and include bruising or bleeding at needle site, tingling, mild pain


PTNS Is Effective in Treating OAB Symptoms

- **SUmiT Study:** 54.5% of patients reported moderate or marked improvement after 13 weeks of PTNS treatment compared with 20.9% improvement in patients receiving sham ($P < 0.001$)
- Significant improvement in overall bladder symptoms and urinary frequency in the PTNS-treated group compared with the sham-treated group

### Intent-to-treat analysis comparing PTNS and sham GRA at week-13 assessment.

<table>
<thead>
<tr>
<th>Percent Subjects Indicating Moderately or Markedly Improved</th>
<th>PTNS, n = 110</th>
<th>Sham, n = 110</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall bladder symptoms (intent to treat)</td>
<td>60/110 (54.5)</td>
<td>23/110 (20.9)</td>
</tr>
<tr>
<td>Overall bladder symptoms</td>
<td>60/103 (58.3)</td>
<td>23/105 (21.9)</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>44/103 (42.7)</td>
<td>24/105 (22.9)</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>49/103 (47.6)</td>
<td>23/105 (21.9)</td>
</tr>
<tr>
<td>UI</td>
<td>39/103 (37.9)</td>
<td>23/104 (22.1)</td>
</tr>
</tbody>
</table>


PTNS Is Effective in Treating OAB Symptoms

- **OrBiT Study:** PTNS is as effective as pharmacotherapy with anticholinergic in improving patient assessment of OAB symptoms
  - Mean number of voids not different
  - Noninferiority, unblinded
- **STEP study:** Viable long-term therapy: significant improvements still seen after 3 years with once-monthly maintenance treatments

Statistically significant reduction at 12 months compared with both 3 month and 6 month ($P = 0.0001$ and $0.0002$, respectively)

Intradetrusor Botulinum Toxin Injection

- Approved by FDA for OAB in 2013
- Telescopic camera (cystoscopy) used to inject onabotulinumtoxinA into the bladder in the office
  - Neurotoxin inhibits presynaptic release of acetylcholine from neuromuscular junction
  - Improves storage of bladder and reduces contractions

![Diagram of bladder and injection sites]

- Possible side effects: hypersensitivity, dysphagia
- Efficacy:
  - RCT 100 U onabotulinumtoxinA vs placebo in patients with OAB and UI
    - Statistically significant improvement over placebo demonstrated in two large phase 3 trials: 60.8% ($P < 0.001$) and 62.8% ($P < 0.001$)
  - ABC trial: 100 U onabotulinumtoxinA vs daily solifenacin*
    - Complete resolution 27% vs 13%, $P = 0.003$
    - Catheter use at 2 months 5% vs 0%, $P = 0.01$

*Side effects include dry mouth, constipation, and blurred vision

- FDA. www.fda.gov/newsevents/newsroom/pressannouncements/ucm336101.htm;
- OnabotulinumtoxinA (package insert). Irvine, CA; 2015;
Intradetrusor Botulinum Toxin Injection

- Adverse events:
  - Postprocedure urinary retention requiring clean intermittent self catheterization (5% in ABC study)
  - Urinary tract infections (33% in ABC study)
  - Transient hematuria
  - Pain
  - Recurrence in symptoms
    - Average of 9 months; range 6 to 15 months

Sacral Nerve Stimulation (SNS)

- Sacral nerves regulate the bladder and muscles related to bladder function
- Small implanted device sends electrical signals to the sacral nerve roots
  - Mechanism: suspected inhibition of abnormal C-fiber signaling or micturition reflex


Fowler CJ. Urology. 2002;59(Suppl 1):37-42;
SNS Procedure

- Procedure
- Stage 1: test stage
  - Only the lead is placed internally
  - If > 50% improvement, then implanted
- Stage 2: implantable generator
- Alternative:
  - Percutaneous nerve evaluation test in office
  - Implant of both lead and generator


SNS Reduces the Number of Incontinence Episodes in Patients With UUI

- In patients with urgency frequency symptoms, SNS significantly reduced the number of voids daily from 16.9 ± 9.7 to 9.3 ± 5.1 (P < 0.0001) at 6 months
  - Number of voids daily did not clinically change for control group (baseline 15.2 ± 6.6, 6 months 15.7 ± 7.6)
- At 6 mo, SNS group had significant increases in voiding volume (SNS: 226 ± 124 mL, control: 123 ± 75 mL; P = 0.001) and average degree of urgency before voiding (SNS: 1.6 ± 0.9, control: 2.3 ± 0.5; P = 0.01)
- Efficacy
  - Trials range: 64% to 88%
  - Persistent improvement in ~60% over 5 years

SNS Has Low Complication Rates

- Complications
  - Surgical site infection (10%), with reoperation (~15%)
  - Pain (~3%)
  - Lead migration (~12%)
  - Lack of response
  - Need for new battery
- Limitation: cannot have body MRI
  - Not recommended in patients with multiple sclerosis

Identifying Patients for Whom Nerve Stimulation May Be an Effective Therapy

- Nerve therapy is recommended as a third-line treatment for OAB
- In the treatment of UUI, nerve therapy is typically recommended for patients with severe refractory UUI who do not respond to behavioral therapy or medications
- The specific treatment option selected should take patient comorbidities and risk tolerance into account

References:
Zbar AP. Gastroenterol Rep (Oxf). 2014;2:126-33;
Nerve Stimulation for the Treatment of UUI

- Clinical data have shown intradetrusor onabotulinumtoxinA therapy, PTNS, and SNS to be effective in the treatment of OAB and UI
  - Reduce UUI episodes, reduce severity of symptoms, improve quality of life
- These third-tier treatments are safe and effective in correctly selected patients


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