University of South Florida
GERIATRIC WORKFORCE ENHANCEMENT PROGRAM (GWEP)
Learn@Lunch
Geriatric Education Series

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Principal Investigator

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Making Life Better®
UNIVERSITY OF SOUTH FLORIDA
Stemming the Flood: Treatment for Urinary Incontinence

Jan Busby-Whitehead, MD
Mary & Thomas Hudson Distinguished Professor of Medicine
Chief, Division of Geriatric Medicine
Director, Center for Aging & Health
Director, Hartford Center of Excellence in Geriatric Medicine
University of North Carolina Chapel Hill
Objectives

• Describe the pathophysiology of UI.
• Discuss the evaluation and referral criteria for UI.
• Describe behavioral and pharmacologic treatments for UI.
• Discuss neuromodulation and sphincter replacement therapies for UI.
Prevalence of Urinary Incontinence: Women & Men

Impact of Urinary Incontinence

Symptom distress

Decreased quality of life

Financial impact

Social isolation

Emotional impact

Major indication for nursing home placement

Adapted from Markland.
Involuntary detrusor contractions
Urethral pressure

Sudden increase in abdominal pressure
Urethral pressure

Urethral pressure

Involuntary detrusor contractions
Urethral pressure

Involuntary detrusor contractions
Urethral pressure

• Human bladder smooth muscle contains primarily M2 (66%) and M3 (33%) subtypes.

• Activation of M3 receptors is primary stimulus for bladder contraction.

• $\beta_3$ adrenoceptor mediates detrusor muscle relaxation.
Screening for UI

During the last 3 months did you leak urine:

- When you were performing some physical activity such as: coughing, sneezing, lifting or exercising? **STRESS INCONTINENCE**

- When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough? **URGE INCONTINENCE**

- Without any physical activity or without a sense of urgency? **OTHER INCONTINENCE**

Which one most often?
Evaluation of UI

- History: Bladder diary
- Physical examination, especially Genitourinary and Neurological
- Bladder stress test
- Postvoid residual volume
- Urinalysis, urine culture if indicated
- BUN, creatinine, fasting glucose

<table>
<thead>
<tr>
<th>Time</th>
<th>Drinks</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amount (ml)</td>
<td>Type</td>
</tr>
<tr>
<td>6am</td>
<td>WOKE</td>
<td></td>
</tr>
<tr>
<td>7am</td>
<td>300</td>
<td>Water</td>
</tr>
<tr>
<td>8am</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9am</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10am</td>
<td>Cup</td>
<td>Tea</td>
</tr>
<tr>
<td>11am</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midday</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Potentially Reversible Factors

Delirium/Drugs

Infection – UTI vs. asymptomatic bacteriuria

Atrophic Urethritis

Psychological - Depression, Dementia

Endocrine – Diabetes

Restricted Mobility

Stool Impaction (Constipation)

Neil M. Resnick, M.D., and Subbarao V. Yalla, M.D.
Drugs Potentially Contributing to UI

ACE inhibitors
Antipsychotics
Alcohol
Alpha Blockers
Anticholinergics

Caffeine
Calcium Channel Blockers
Diuretics
Narcotics
Sedatives
78 y/o with worsening UI. Symptoms of urgency and large volume loss, also loss with laughing and sneezing. HTN, Diabetes Type 2, Insomnia and worsening UI Symptoms, no Dysuria or Hematuria.

Habits: 3 cups coffee daily
2 glasses of wine at dinner

Meds: HCTZ
Metoprolol
Glipizide
Benadryl

Case 1: Mrs. G
Exam:
  mild atrophy
  mild cystocele
  weak pelvic squeeze

Urinalysis:
  1+ glucose
  4 WBC
  8 epithelial cells

Glucose: 185
PVR: 90 mL

Case 1: Mrs. G
Treatment Options for UI

- Behavioral
- Pharmacological
- Neuromodulation
- Surgery
What should you prescribe first?

A. Stop Caffeine
B. Stop HCTZ
C. Stop Wine
D. Stop Benadryl
E. All of the Above
What should you prescribe next?

A. Pelvic floor exercises
B. Scheduled voiding
C. Anticholinergic drug
D. Botox Injection
Bladder Control
Behavioral Therapies

SELF MANAGEMENT
Fluid management
Weight loss
Dietary modifications

TREATMENT
Voiding schedules
Pelvic floor muscle training
Biofeedback
Weight Loss

- Randomized trial of 338 women, mean BMI 36 kg/m²
- 6 month weight loss vs. education
- Weight loss 8% vs. 1.6%
- 47% vs. 28% in stress but not urge UI
Pelvic Muscle Exercises (Kegels)

- Isolation of the pelvic muscles during pelvic exam using biofeedback

- Avoidance of abdominal, buttock or thigh muscle contractions

- Ability to hold contraction 2 seconds, increase up to 10 seconds
  - repeat in groups of 10-30 TID

- 3 sets of 8 to 12 slow velocity contractions sustained for up to 10 seconds
  - 3-4 times weekly for at least 4 to 6 months
Suppressing the Urge with Quick Kegels

Stop and Relax Body

Walk normally to the bathroom

Wait until the urge subsides

Squeeze Pelvic Floor Muscles

Behavioral strategies and PFMF are effective:

• Outcomes are similar to anticholinergic medication therapy.

• Clinical guidelines support as first line treatment

• Minimal adverse effects
Randomized Trials of Behavioral Treatment for Stress UI

- 24 RCTs, but only 11 of high quality
- Pelvic floor exercises were effective (up to 75%) in reducing symptoms of stress UI
- Limited evidence for high vs low intensity
- Benefits of adding biofeedback (BFB) unclear

Cochrane Collaboration 2011
Behavioral vs. Drug Rx for Urge UI in Older Women

- Randomized, controlled trial of 197 women aged 55-92
- 8 weeks of BFB, 8 weeks of oxybutynin
- 2.5 to 5 mg qd to tid, or placebo control
- All 3 groups reduced UI frequency
- Effectiveness: BFB>drug>placebo

Oxybutynin vs Behavioral Treatment for Urge UI

Leaks per week

Pre
Post

Behavioral
Control

Pharmacotherapy of Urge Incontinence

**Anticholinergics**
- Oxybutynin
- Tolterodine
- Fesoterodine
- Darifenacin
- Solifenacin
- Trospium

**β3 Receptor agonist**
- Mirabegron

**α Blocker**
- Tamsulosin
- Doxazosin

**5α Reductase Inhibitor**
- Finasteride
- Dutasteride
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Distribution</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Brain (cortex, hippocampus), Salivary gland</td>
<td>Cognitive function, memory; saliva secretion</td>
</tr>
<tr>
<td>M2</td>
<td>Heart, brain, smooth muscle</td>
<td>Regulation of heart rate &amp; HR variability; behavioral flexibility</td>
</tr>
<tr>
<td>M3</td>
<td>Smooth muscle, glands, eye</td>
<td>Smooth muscle contraction, iris contraction, gland secretion</td>
</tr>
<tr>
<td>M4</td>
<td>Brain (forebrain, striatum)</td>
<td>Dopamine dependent behaviors</td>
</tr>
<tr>
<td>M5</td>
<td>Brain (substantia nigra), eye</td>
<td>Regulation of striatal dopamine release</td>
</tr>
</tbody>
</table>
## Anticholinergics

### Antimuscarinics & M3 Receptor Selectivity

<table>
<thead>
<tr>
<th>Ratio of affinity</th>
<th>Muscarinic receptor subtype</th>
<th>M&lt;sub&gt;3&lt;/sub&gt; vs. M&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M&lt;sub&gt;3&lt;/sub&gt; vs. M&lt;sub&gt;2&lt;/sub&gt;</th>
<th>M&lt;sub&gt;3&lt;/sub&gt; vs. M&lt;sub&gt;4&lt;/sub&gt;</th>
<th>M&lt;sub&gt;3&lt;/sub&gt; vs. M&lt;sub&gt;5&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td></td>
<td>16.0</td>
<td>53.0</td>
<td>26.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td></td>
<td>0.2</td>
<td>0.5</td>
<td>1.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td></td>
<td>1.8</td>
<td>6.2</td>
<td>1.9</td>
<td>5.3</td>
</tr>
<tr>
<td>Solifenacin</td>
<td></td>
<td>2.2</td>
<td>15.0</td>
<td>9.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Tolterodine</td>
<td></td>
<td>0.6</td>
<td>0.95</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Trospium</td>
<td></td>
<td>1.5</td>
<td>1.3</td>
<td>2.0</td>
<td>4.6</td>
</tr>
</tbody>
</table>

<sup>a</sup>Relative mean affiliates calculated as the ration of K<sub>a</sub> values as reported by [16]

<sup>b</sup>Relative mean affiliates calculated as the ration of K<sub>a</sub> values determined from the antilog of pK<sub>a</sub> values as reported by [17]

<sup>c</sup>Relative mean affiliates calculated as the ration of K<sub>a</sub> values as reported by [18]

# Doses and Side Effects

**Table 1: Common Pharmacologic Therapies: Doses and Side Effect Rates**

<table>
<thead>
<tr>
<th>Antimuscarinics/Anticholinergics</th>
<th>Dry mouth</th>
<th>Constipation</th>
<th>Dry Eyes</th>
<th>Dyspepsia</th>
<th>Dizziness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin ER (5–30 mg o.d.)</td>
<td>60.8%</td>
<td>13.1%</td>
<td>6.1%</td>
<td>6.8%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Oxybutynin CR (5–20 mg o.d.)</td>
<td>64.0%</td>
<td>5.1%</td>
<td>2.5%</td>
<td>5.1%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Oxybutynin patch</td>
<td>4.1%</td>
<td>3.3%</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Tolterodine ER (4 mg o.d.)</td>
<td>23.4%</td>
<td>5.9%</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Solifenacin (5–10 mg o.d.)</td>
<td>10.9%</td>
<td>5.4%</td>
<td>0.3%</td>
<td>1.4%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Trosplum chloride (20 mg b.i.d.)</td>
<td>20.1%</td>
<td>9.6%</td>
<td>1.2%</td>
<td>1.2%</td>
<td>n/a</td>
</tr>
<tr>
<td>Darifenacin (7.5–15 mg)</td>
<td>20.2%</td>
<td>14.8%</td>
<td>2.1%</td>
<td>2.7%</td>
<td>0.9%</td>
</tr>
<tr>
<td><strong>β3-Adrenoreceptor Agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirabegron (25–50 mg o.d.)**</td>
<td>0.6%</td>
<td>0.9%</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

* Side effect rates taken from the products’ respective product monographs
** The side effect rates listed for mirabegron reflect the rates of adverse reactions leading to discontinuation reported by more than two patients and at a rate greater than active control in study 178-CL-049 (as reported by the mirabegron product monograph). These rates do not reflect overall side effect rates for this drug.
Contraindications for Anticholinergics

- Urinary retention
- Gastric retention
- Bladder outlet obstruction
- Cardiac arrhythmias
- Narrow angle glaucoma
Drug Treatment of UI in The Cognitively Impaired

- 4 RCT showed cognitive deficit with Oxybutynin treatment
- 3 RCT showed no cognitive deficit with Darifenacin

SENIOR: randomized, placebo controlled DB crossover multicenter trial in 26 MCI pt
- 3 TX periods x 21 days, washout between
  - Solefenicin 5 mg qd,
  - Oxybutynin 5 mg bid
  - Placebo
- No change from baseline in cog function

*Int J Clin Practice 2008*
*European Urology 2013*
Case 2: Mr. D

65 y/o man with mild BPH, COPD and Osteoarthritis of the knees. He has increasingly bothersome nocturia x3

Habits: Former smoker
4 cans of beer over the weekend

Meds: ASA
Metoprolol
Autaminophen
Albuterol inhaler
Case 2: Mr. D

Exam: slightly enlarged prostate gland
no nodules

Urinalysis: negative

PVR: 120 cc
What initial prescription is most appropriate?

A. Pelvic floor exercises
B. Tamsulosin (alpha-adrenergic blocker)
A. Oxybutynin (anticholinergic)
A. Finasteride (5 alpha reductase inhibitor)
Myrbetriq (Mirabegron)

Phase 3 randomized, double blind placebo controlled trial (Nitti)

• 1338 patients mean age 60 with OAB >8 voids/24 hr and >3 urgency episodes/72 hr

• Placebo vs 50 mg vs 100 mg x 12 weeks

• Mean # UI episodes/24 hr and voids/24 hr statistically significant improvement at week 4, no diff in adverse events

• Side effects: Hypertension (1.2 mm HG at 100 mg; 2.4 mm HG at 200 mg), increase in HR (1.6 BPM at 100mg, 4.1 BPM at 200 mg), headache, nasopharyngitis
Drug Treatment of Mild BPH

Alpha adrenergic antagonists

- Relaxes prostate smooth muscle of prostate and bladder neck
  - Tamsulosin (Flomax) 0.4 - 0.8mg daily
  - Doxazosin (Cardura) 1-2 mg then up to 8 mg daily IR, 4-8 mg ER

- Tamsulosin trials: 53 weeks, 31% and 36% improvement in maximal flow rate with 0.4 mg and 0.8 mg/day vs. 21% placebo

- Adverse effects: orthostatic hypotension and dizziness, floppy iris syndrome in cataract surgery patients
Drug Treatment of Mild BPH

• Dose:
  - Finasteride (Proscar) 5 mg daily
  - Dutasteride (Avodart) 0.5 mg daily

• Type II 5 alpha reductase inhibitor
  - Results in atrophy of the prostatic glandular epithelium due to decreased synthesis of dihydrotestosterone
  - Slow onset, 20% - 30% reduction in prostate volume and LUTS over time
  - Side effects: Ejaculatory dysfunction (8%), loss of libido (10%), erectile dysfunction (16%)
  - Trend for increased risk of more aggressive prostate cancer
  - Rare reports of breast cancer in men taking finasteride either 1 mg or 5 mg
Treatment of Urge UI in Men

- Start with alpha blocker
- May add low dose antimuscarinic
- One randomized trial of tamsulosin plus tolterodine more effective in reducing urge UI than placebo
Botulinum Toxin

• 100 U (US) injected directly into detrusor later and posterior bladder wall, trigone avoided

• 2005 first randomized placebo controlled study of 59 patients, 200 U, 300 U or placebo over 24 wks

• Mean decrease in UI 50% vs 0; p<.05

• RELAX RCT study: 8 UK centers enrolled 240 women, 200 U vs placebo; primary outcome voiding frequency/24 hr; at 6 mo, median leaks 1.67 vs 6.0; continence 31% vs 12%, daily urgency 3.83 vs 6.33; UTIs 16% vs 4%

• Major side effects: urinary retention, UTIs, pain, hematuria

doi:10.1016/S0302-2838(03)00250-1
http://www.skindivamedicalaesthetics.com/
• Identify and treat reversible causes of UI.

• Behavioral therapy is first-line treatment for stress and urge UI, and OAB.

• Anticholinergic medications are effective second-line treatment for urge UI and OAB.

• M3 selective drugs have fewer side effects.

• Mirabegron is a new $\beta_3$ agonist effective for urge UI and OAB.

Alpha adrenergic blockers are effective treatment for urge UI due to BPH.

• **Botulinum A** can be effective for refractory OAB.
Referral Criteria

- Recurrent urinary tract infections
- Hematuria not related to UTI
- Elevated postvoid residual or other evidence of possible obstruction
- Recent gynecological or urological surgery or pelvic radiation
- Failed treatment of stress or urge UI