OBJECTIVES - At the end of this activity, participants will be able to:

1. Assess the clinical severity of symptoms and context in which symptoms determine type of urinary incontinence and appropriate management
2. Discuss treatment strategies with the patient and design a patient-specific treatment plan to achieve optimal outcomes

CLC:

Women and men can become incontinent from obesity, neurologic injury, birth defects, stroke, multiple sclerosis, and physical problems associated with aging. Patients seeking treatment is low across all ethnic groups.

I do not have any relevant financial interests to disclose.

Epidemiology

- OAB: 17% Men, 30% Women
- UUI: 7% Men, 15% Women
- Cost of managing OAB in the USA: 6 billion dollars

IUGA/ICS: Urgency

- Urgency Urinary Incontinence:
  - Complaint of involuntary loss of urine associated with urgency
- Urgency:
  - Complaint of a sudden, compelling desire to pass urine which is difficult to defer
- Overactive Bladder:
  - Urinary urgency, usually accompanied by frequency and nocturia. +/- urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology

Haylen 2010

AUA Treatment Guidelines

- First-line therapies
  - Behavioral therapies (e.g., bladder training, pelvic floor muscle training, fluid management)
- Second-line therapies
  - Anti-muscarinics including darifenacin, fesoterodine, oxybutynin, solifenacin, toterodine or trospium
  - Transdermal formulations
- Third-line therapies
  - Sacral Neuromodulation
  - Posterior Tibial Nerve Stimulation (PTNS)
  - Intradetrusor onabotulinumtoxin A

Coyne 2013
Shamiyan 2009
Risk Factors for OAB

+ Age
+ Obesity
+ Recurrent UTI
+ Neurologic disease
+ Radiation
+ Parity
+ Diabetes

Obesity

+ BMI ≥30
+ Increases abdominal pressure
+ Association with neurogenic diseases
+ Correlation with insulin resistance and diabetes
+ Abdominal adiposity independent risk factor for UI
+ Decrease in Ghrelin levels adverse effect on detrusor

Obesity Prevalence USA

- Percent of adults age 20 years and over who are obese: 35.1% (2011-2012)
- Percent of adults age 20 years and over who are overweight, including obesity: 69.0% (2011-2012)

Worldwide Prevalence

- Lancet 2014
- 3.4 million deaths worldwide
- 38% woman worldwide
- 23% children worldwide
- 8.4 to 13.4% in developing countries
Factors Contributing to Obesity

- Genetic predisposition (Leptin, Neuropeptide Y)
- Food environment
- Decrease in physical activity
- Decreased energy expenditure for daily living
  - Not matched by a reduction in caloric intake

Melanson et al., Medicine and Science in Sports and Exercise

Losing Weight May Require Some Serious Fun

Obesity-Interventions

- Is it fun or exercise?
  - Werle et al., 2014
  - Hypothesis: Consumers eat more when they exercise.
  - Can framing exercise as fun reduce individuals tendency to indulge
  - 3 studies
    - Studies 1 and 2 participants performed a physical activity that was described as fun or as exercise, after, food consumption measured
    - Study 3 participants were asked to rate how much fun they had while running and then were offer a choice between two snacks.

Obesity-Interventions

- Study 1: 36 females at Northwestern.
  - Group A: 30 minute walk with labeled 1 mile map, lunch to follow. Purpose of the walk was to have fun and listen and rate music on an MP3 Player.
  - Group B: Same 30 minute walk, were instructed it was for exercise and to rate their energy levels. Lunch to be provided
  - Participants in the fun group found the activity more exciting.
  - Labeling exercise as fun reduced the consumption of a high caloric meals
  - Study 2: 46 females no MP3 player. Same results.

Obesity-Interventions

- Study 3: Observational field study
  - Participants of 5, 10K were asked to fill out questionnaires post run
  - As an incentive they could receive a chocolate or granola bar
  - 231 runners participated
  - Answered a set of questions about perception of the race (competitive, exercise or fun run)
  - Participants that rated the race as fun were more likely to choose the granola bar (P=0.05)
  - Framing physical activity as something fun reduces high caloric consumption- counseling tool for patients
Obesity and Incontinence

- Obesity is a risk factor for urinary incontinence
- There is a dose-response effect of weight gain on urinary incontinence
- Several studies demonstrate that weight loss can decrease episodes of urinary incontinence in obese women
- 4 RCT (Level 1)

Weight Loss

- Subak et al: RCT of overweight and obese women with at least 10 episodes of UI per week
- Six month weight loss program including diet, exercise, and behavior modification (treatment)
- Structured education program (control)
- 7-day voiding diaries (self-reported)
- Weight loss program
  - Mean weight loss of 8% (7.8 kg) in treatment group vs. 1.6% (1.5 kg) in control group
  - Decrease in mean weekly UI episodes
  - 47% reduction in treatment group vs. 28% in controls

Weight Loss in the Elderly

- 21 Korean women ages 69-72
- 52 week exercise program
  - 40 minutes cardio, 30 minutes resistance exercises 5x week
- Body composition, blood pressure, lipids, OAB score measured
- Significant reductions in frequency, nocturia and UUI episodes
- Reduction in body weight averaged 3Kg
- Significant improvement in SBP, cholesterol
- QOL parameters improved except “impact on life” domain

Weight Loss

- Weight loss after bariatric surgery
  - Examined the prevalence, bother, and QOL of pelvic floor disorders on women before and after weight loss surgery
  - Overall prevalence of UI decreased
  - Baseline: 32%
  - 6 months: 15%
  - 12 months: 20%
  - Resolution of UI occurred in 48% of women with symptoms at baseline

Weight Loss

- Surgical and non-surgical weight loss can significantly improve incontinence symptoms
- A 5% to 10% reduction in weight can provide similar improvements in incontinence compared to other non-surgical interventions
- Consider weight loss first line. Encourage fun activities daily over “exercise”
**AUA Second Line Therapy**

**Medications**
- **B3 Detrusor** = detrusor relaxation
- **ACh Detrusor** = detrusor contraction

**Antimuscarinic Therapy**
- Muscarinic ACh receptors in bladder
  - Oxybutynin (oral, patch, gel), Tolterodine, Solifenacin, Darifenacin, Trospium, Fesoterodine
- **OBJECT** trial
  - Overactive Bladder: Judging Effective Control and Treatment
  - Multicenter, randomized, double blind study
  - Oxybutynin ER vs. Tolterodine IR
  - ER was superior to IR
  - This trial opened the door for pharmacy coverage of ER preparations

**OBJECT trial**

**Solifenacin versus Tolterodine**
- **N=1,177 patients**
- Significantly less urgency and urgency incontinence in Solifenacin grp
- **Side effects**
  - Only ~25% still take at 1yr
  - Dry mouth and constipation
  - Contraindicated in narrow-angle glaucoma
  - Caution in impaired gastric emptying & cognitive issues
  - AUA guidelines do NOT endorse one anticholinergic over another

**B3 Agonist: Mirabegron**
- FDA approved June 2012
- Alternative to anticholinergic
- Initiate 25mg → 50 mg QD
- Max dose 100mg QD
- Contraindicated uncontrolled hypertension >180/110
- Adverse Events:
  - Increase pulse (max ~4bpm)
  - Headache
  - Nasopharyngitis
  - UTI

**B3: bladder** → promote relaxation
- Large Phase 3 Trials demonstrate efficacy vs. placebo (50mg, 100mg doses)
  - 1,328 Ps in US/Canada
  - 1,978 Ps Europe/Australia
  - -1.24 incontinence episodes/day
  - -1.41 fewer voids per day
AUA Third Line Therapy

Sacral Neuromodulation

- Sacral nerve modulation FDA approved in 1997
- Placement of wire via S3 nerve root
- Modulation of somatic afferents, increase inhibition
- Success Ranges
  - UUI & Urge-Frequency: 56-68% (up to 80%)
  - Urinary Retention: ~70%
  - Fecal Incontinence: 86-89% improvement; 36-40% continence

InSite Study

The purposes of the study are two fold:
1. To provide evidence from a randomized controlled trial that InterStim Therapy provides better relief of symptoms of OAB than standard medical treatments (SMT) in current use.
2. To fulfill the requirements of the FDA-mandated post-approval study of the safety of the tined lead using a minimally invasive approach

InSite Study

- 5-year prospective multi-center post-approval trial
- 38 centers
  - Phase 1 - randomized to SNM or SMT in 1:1 ratio
  - Enrollment from 2007 – 2010
  - N=147 (SNM=70; SMT=77)
- Quality of Life was measured using the validated disease-specific International Consultation on Incontinence Modular Questionnaire – Overactive Bladder Quality of Life (ICIQ-OABqol) instrument.
- No difference between SNM and SMT at baseline.
Primary Efficacy Objective

- OAB therapeutic success rate at 6 months is greater for the SNM group than for the SMT group.
  - >50% improvement in average voids/day from baseline or a return to normal voiding frequency (<8 voids/day) for subjects with UI at baseline
  - >50% improvement in average leaks/day from baseline for subjects with UI at baseline

Secondary Objectives
- Quality of Life measurements

Conclusions from InSite Study

- The OAB success rate was significantly greater with SNM vs. SMT in both the intent-to-treat as well as those evaluated. 61% vs. 42% (p<0.05)
- SNM showed significant improvements in validated QOL measures compared to SMT. 86% vs. 44% (p<0.001)
- SNM is a safe and effective treatment for OAB patients with mild to moderate symptoms.
- Limitations on MRI

Onabotulinum Toxin-A (BTX-A)

- Inhibits release of ACH pre-synaptic
- 2014 AUA Guidelines recommend as 3rd line therapy
- ABC Trial-
  - Anticholinergic vs. Botulinum Toxin Comparison Trial

Study Design

- Women with ≥5 UUI Episodes/3-Day Diary
- Randomization
  - Anticholinergic Meds
    - Placebo Injection
  - Botox 100U
    - Placebo Pills
- Bladder Diaries (Months 1-6)
- All Pills Stopped at 6 Months

ABC Outcomes

Primary Outcome:
Change from baseline in the mean number of UUI episodes over the 6-month period (months 1, 2, 3, 4, 5 and 6)

Secondary Outcomes:
- Efficacy outcomes:
  - 15% with complete resolution of UUI
  - Quality of life (QOL)
  - Duration of response
- Adverse events

Botox Injection Technique

- 100 units
- 10 units/cc
- 10-30 injection sites
- Trigone sparing
- Office procedure
- Topical anesthetic

Primary Outcome:
Reduction in Mean UUI Episodes/Day Over 6 Months

Change in UUI Episodes/Day

- Anticholinergics: 3.36 UUI Episodes/Day
- Botox: 3.29 UUI Episodes/Day

P=0.81

Secondary Efficacy Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Anticholinergics</th>
<th>Botox</th>
<th>P value</th>
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<tbody>
<tr>
<td>Urgency Incontinence</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Complete Resolution</td>
<td>13%</td>
<td>27%</td>
<td>0.003</td>
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<tr>
<td>Quality of Life:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OABq-SF Severity</td>
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<td>-44.1</td>
<td>0.87</td>
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<tr>
<td>OABq-SF QOL Scale</td>
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<td>37.1</td>
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<tr>
<td>PFDI-SF</td>
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<td>-48.2</td>
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<tr>
<td>PFIQ-SF</td>
<td>-32.8</td>
<td>-33.9</td>
<td>0.88</td>
</tr>
</tbody>
</table>

ABC Adverse Events

- Rate and Median Duration of CIC Use (required only in the Botox group per study protocol)
  - 5% at 2 months
  - 3% at 4 months
  - 1% at 6 months
- Urinary tract infections (p<0.001)
  - 37% Botox group
  - 14% Anticholinergic group
- Dry mouth (p=0.02)
  - 58% Anticholinergic group
  - 31% Botox group

Conclusions

- Anticholinergic therapy and Botox 100 units:
  - Both significantly improve:
    - Urgency urinary incontinence
    - Quality of Life
  - No significant difference between treatment groups
- Botox compared to anticholinergics:
  - Two-fold likelihood of complete resolution of UUI
  - Higher transient urinary retention and UTI
  - Less dry mouth

Posterior Tibial Nerve Stimulation (PTNS)

- Discovered as part of transcutaneous patch tibial nerve stimulation
- Stoller investigated direct needle stimulation since it is a terminal projection of S3
- Technique involves 34 G needle placement in office 3-5 cm above medial malleolus and ground pad on same foot near arch
- 12 weekly sessions for 30 min each
- Responses usually in 5-6 sessions and if improved after 12 sessions, maintenance therapy with sessions approximately monthly
**Posterior Tibial Nerve Stimulation**

- SUmiT Trial:
  - Study of Urgent PC vs. Sham Effectiveness in Treatment of Overactive Bladder
  - N=220, randomized to active vs. sham stimulator
  - 13 weeks 53% vs. 21% improved
  - Rare adverse events
  - Maintenance is recommended monthly but currently only covered Q3 months by Medicare.

**Conclusions**

- First line therapy for OAB is inexpensive and accessible and should include weight loss for the treatment of incontinence
- Physical activity should be packaged as “fun” not exercise
- New second line therapies include B3 agonist Myrbetriq
- Intravesical Botox is now approved as 3rd line therapy
- For patients with contraindications to Interstim®, PTNS is a feasible and effective office procedure

**References**

5. Fantl JA et al. AHCPR Publication No 96-0682;1996.