Management of refractory OAB conditions

Neurotoxins and Neuromodulation

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Overactive bladder

- Urinary urgency (sudden, compelling desire to urinate which is difficult to suppress), frequency (typically > 8/day), with or without urge urinary incontinence.

- Nocturia may accompany OAB, but often exists without OAB, and has many other causes.
Evaluating OAB symptoms

- History/Physical exam

- Attempt to establish causative factors
  - neurogenic
  - infection
  - tumor
  - obstruction
Treatment strategies

- Behavioral modification
- Patient education
- Acupuncture
- Pharmacotherapy
- Neuromodulation
- Botulinum toxin
- Intravesical therapy
- Surgical intervention
- Biofeedback
- Behavioral modification
- Patient education

Efficacy

Invasiveness
Behavioral management, pharmacotherapy
Behavioral Management

- Timed voiding
- Dietary modification
- Urge Suppression Techniques
- Biofeedback
- Modest fluid restrictions
Pharmacotherapy

- Several oral and 1 topical antimuscarinic
- Dose titrations in most
- Tolerability – 2% dropout in clinical studies
- 70-80% reduction in Urge UI

- But…less that 20% taking at 1 year
<table>
<thead>
<tr>
<th>Medication</th>
<th>Route</th>
<th>Typical dose</th>
<th>Cost/Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyoscyamine (Levsin and others)</td>
<td>Oral/Sublingual</td>
<td>.125-.75 mg bid-qid</td>
<td>$ SL form fast acting</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Oral Intravesical</td>
<td>2.5-10 mg tid 5mg/30cc</td>
<td>$</td>
</tr>
<tr>
<td>Imipramine (Tofranil and others)</td>
<td>Oral</td>
<td>10-75 mg qhs</td>
<td>$ Nocturia/enuresis</td>
</tr>
<tr>
<td>Extended release oxybutynin (Ditropan XL)</td>
<td>Oral</td>
<td>5-30mg qd</td>
<td>$ Serum levels stable</td>
</tr>
<tr>
<td>Tolterodine (Detrol LA)</td>
<td>Oral</td>
<td>4 mg qd</td>
<td>$$$ Bladder selectivity</td>
</tr>
<tr>
<td>Trospium chloride (Sanctura XR)</td>
<td>Oral</td>
<td>60 mg qd</td>
<td>$$$ Quarternary amine</td>
</tr>
<tr>
<td>Solifenacin succinate (Vesicare)</td>
<td>Oral</td>
<td>5-10 mg qd</td>
<td>$$$ M2/M3 selective</td>
</tr>
<tr>
<td>Darifencacin (Enablex)</td>
<td>Oral</td>
<td>7.5-15 mg qd</td>
<td>$$$ M3 selective</td>
</tr>
<tr>
<td>Fesoterodine (Toviaz)</td>
<td>Oral</td>
<td>4-8 mg qd</td>
<td>$$$ Same metabolite as tolterodine</td>
</tr>
</tbody>
</table>
Why????

- Side effects intolerable?
- Bad advice?
- Unrealistic expectations?
- Cost?

- Lack of efficacy – OAB too severe?
Will pharmacotherapy help?
Will pharmacotherapy help?
Treatments for Refractory OAB

- Intravesical botulinum toxin (off label)
- Sacral neuromodulation
- Percutaneous tibial nerve stimulation
- Augmentation cystoplasty
- Cystectomy and continent reservoir
Botulinum toxin

- Use exclusively type A
- Both Botox® (onabotulinum) and Dysport® have been tested
- Clinical trials for neurogenic OAB have been completed FDA approval received 8/11 for onabotulinum toxin
**Botulinum toxin**

- Blocks Ach release from presynaptic nerve terminal blocking neural transmission
- Compromises intracellular protein SNAP-25
- Blocks fusion of synaptic vesicle with presynaptic membrane
- Recovery of chemodenervation in 3-6 months

Adapted from dePaiva, et al. PNAS. 1999;96:3200.
Injection sites


Smith and Chancellor, J Urol, 171:2128, 2004
Injection technique

Performed in office after administration of Lidocaine

10 minute procedure
Results: UI Episodes

Reduction in number of UI episodes compared to baseline (%)

- **300U BoNT**
- **200U BoNT**
- **Placebo**

* $p<0.05$ for differences between BoNT group and placebo
† $p<0.05$ for difference within-group changes from baseline

Schurch. J Urology, 2005
Results: Quality of Life

*\(p<0.05\) for pairwise contrasts between BoNT groups and placebo
\(\dagger p \leq 0.002\) for within-group differences from baseline

Schurch. J Urology, 2005
Patients on Anticholinergics Before & After BoNTA*

- Oxybutynin/Trospium: 4 at baseline, 12 at follow-up
- Propiverine: 3 at baseline, 6 at follow-up
- Tolterodine: 19 at baseline, 26 at follow-up
- Trospium chloride: 19 at baseline, 33 at follow-up
- Oxybutynin instillation: 5 at baseline, 6 at follow-up
- Oxybutynin oral: 58 at baseline, 80 at follow-up

*Allergan (Botox®), USA
6+ years QOL data
SCI patients

Mean # injections – 7.2
Mean interval 11 months

Impact on QOL
Multiple Sclerosis

300 U injected – 10U/site
Treatment Interval

![Box plot showing inter injection intervals for different intervals with p = 0.5.](image-url)
Drawbacks - Botox®

- Effects last about 9 months
- CIC required in approximately 10-20% of patients with neurogenic OAB
- Reimbursement – improving, about 80% providers now paying in Neurogenic OAB
Intravesical therapy

Euphoria resinifera
Intravesical therapy

- Vanilloid compounds
- Initially excite, then desensitize C fiber vanilloid receptor
- Micturition reflex and DO are suppressed
- Difficult to deliver
Neuromodulation

- Sacral
  - Interstim®

- Percutaneous Tibial
  - Urgent® PC
Mechanism of Action - Sacral

- Activation of efferent fibers to the striated urethral sphincter reflexively causes detrusor relaxation
- Activation of afferent fibers causes inhibition at a spinal or supraspinal level
  - Pudendal nerve afferents are particularly important
  - Mapping has shown that S1, S2 and S3 nerve roots contribute 4%, 60.5% and 35.5% of the overall pudendal afferent activity

*J Urol* 1999; 162: 1967-71
*Neuourol Urodyn* 1986; 5: 381-9
*Eur Urol* 1998; 33: 6
*Neurosurgery* 1997; 41:
Interstim – Test period

- Two approaches
  - In-office peripheral nerve evaluation (PNE)
  - Staged Procedure
📍 Office-based procedure
📍 With or without flouroscopy
📍 Bilateral temporary wires placed
📍 Testing period is 1 week
📍 Diary repeated during the week
📍 Return after that period for diary review and wire removal
📍 Implant scheduled if >50% improvement
Staged procedure

- Tined (permanent lead) is placed fluoroscopically.

- Lead extension is attached, and connected to external battery.

- Lead tested (diary maintained) for 3-4 weeks.
Results

Van Kerrebreck et al J Urol 2007
Sacral neuromodulation

- Urge incontinence improves in 41-100%
- Increases in voided volume
- Improvements in urinary frequency in 64% or greater

- Durability?
Durability?

Durability?

### Baseline vs. After 6 months SNM

<table>
<thead>
<tr>
<th></th>
<th>Baseline (N = 42)</th>
<th>After 6 months SNM (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of incontinent episodes/day</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Mean number of pads or diapers used/day</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

### % of patients with ≥50% improvement

- **UUI** (N = 34/41): Baseline, Long-term
- **Urgency-Frequency** (N = 25/29): Short-term, Long-term
- **UR** (N = 37/42): Short-term, Long-term
Percutaneous Tibial Nerve Stimulation

- Electrical stimulation of detrusor began in the 1950’s.
- Understanding of electrical stimulation of pelvic and sacral nerves in the 1960’s.
- McGuire first reported electrical stimulation of tibial nerve in 1983.
- Stoller reported intermittent peripheral stimulation of tibial nerve in monkeys in 1987.
- Stoller reported results of SANS device in treating urgency and frequency in 2000.
55% of patients with ≥10 voids/day, experienced at least a 25% reduction in daytime frequency (p<0.05)

22% reduction in mean 24-hour voiding frequency (p<0.05)

21% reduction or improvement in mean nighttime voiding frequency (p<0.05)

35% reduction in urge UI episodes
Urgent® PC

- Stimulation delivered via a 34 gauge needle electrode
- Needle electrode inserted above medial malleolus
- The needle electrode is connected to a battery-powered stimulator
Percutaneous Tibial Nerve Stimulation

FDA approved Jan 2011
Indication – Refractory OAB
Failed 2 antimuscarinics
12, 30 minute sessions
Randomized Trial of Percutaneous Tibial Nerve Stimulation Versus Extended-Release Tolterodine: Results From the Overactive Bladder Innovative Therapy Trial

Kenneth M. Peters,* † Scott A. MacDiarmid,‡ Leslie S. Wooldridge,§ Fah Che Leong, S. Abbas Shobeiri, Eric S. Rovner,‖ Steven W. Siegel,¶ Susan B. Tate,** Barry K. Jarnagin, Peter L. Rosenblatt†† and Brian A. Feagins‡‡

**Urgent® PC vs Drug Therapy**
Patients with Objective Improvements at 12 Weeks

- Voids per Day: 73% (Urgent PC), 74% (Extended Release Tolterodine)
- Urge Incontinence: 80% (Urgent PC), 73% (Extended Release Tolterodine)
- Nighttime Voids: 70% (Urgent PC), 61% (Extended Release Tolterodine)
PTNS vs. Tolterodine

Constipation, dry mouth not reported in PTNS arm
Long term data
Long-term objective data

- **Mean Voids**
  - Subjects w/ 6 mo voiding diary (n=30)
  - Subjects w/ 12 mo voiding diary (n=25)

- **Mean Urge Incontinence Episodes**
  - Subjects w/ 6 mo voiding diary (n=30)
  - Subjects w/ 12 mo voiding diary (n=25)

- **Mean Nocturia Episodes**
  - Subjects w/ 6 mo voiding diary (n=30)
  - Subjects w/ 12 mo voiding diary (n=25)

- **Mean Volume Per Void (cc)**
  - Subjects w/ 6 mo voiding diary (n=30)
  - Subjects w/ 12 mo voiding diary (n=25)

- **Mean Moderate to Severe Urgency**
  - Subjects w/ 6 mo voiding diary (n=30)
  - Subjects w/ 12 mo voiding diary (n=25)

- **OAB-q Symptom Severity Scores**
  - Subjects w/ 6 mo voiding diary (n=30)
  - Subjects w/ 12 mo voiding diary (n=25)

Statistically significant reduction at 12 months compared to both 3 month and 6 month scores (p=0.0001 and 0.0002, respectively).
Randomized Trial of Percutaneous Tibial Nerve Stimulation Versus Sham Efficacy in the Treatment of Overactive Bladder Syndrome: Results From the SUmiT Trial

Kenneth M. Peters,*† Donna J. Carrico, Ramon A. Perez-Marrero,‡ Ansar U. Khan, Leslie S. Wooldridge,§ Gregory L. Davis|| and Scott A. MacDiarmid¶

Urgent® PC vs. Sham Treatment

Percent subject indicating moderately or markedly improved on GRA

PTNS 54.5%
Sham 20.9%

p<0.001
Unknowns about PTNS

- Will it work in Neurogenics?
- How frequent is ongoing stimulation needed?
- Can percutaneous energy be applied (no needle)?
- Can patients do it at home?
Enterocystoplasty

◆ Goals

- Increase bladder capacity
- Create low pressure reservoir
- Preserve continence
- Protect kidneys from effects of prolonged elevated intravesical pressures
- Dissipate unstable detrusor contractions
Enterocystoplasty

- **Efficacy**
  - Success rates vary
  - Subjective and objective improvements have been reported in 70-97% of patients
Enterocystoplasty

◆ Problems
  – UTI’s
  – Need for catheterization
  – Mucous production
  – Cancer risk (remote, but real)
  – Surveillance required
### Results

<table>
<thead>
<tr>
<th>Lead author</th>
<th>Segment</th>
<th>n</th>
<th>Capacity</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kockelberg</td>
<td>Ileum</td>
<td>45</td>
<td>+18%</td>
<td>71% @ 20 mos</td>
</tr>
<tr>
<td>BJU, 68: 38, 1991</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hasan</td>
<td>Ileum</td>
<td>48</td>
<td>+92%</td>
<td>83% @ 3 mos</td>
</tr>
<tr>
<td>BJU, 76: 551, 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flood, HD</td>
<td>Ileum±</td>
<td>122</td>
<td>+305%</td>
<td>95% @ 37 mos</td>
</tr>
<tr>
<td>Neurourol. 14:297</td>
<td>Cecum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomski SB</td>
<td>Ileum</td>
<td>14</td>
<td>+149%</td>
<td>18 months</td>
</tr>
<tr>
<td>Neurourol. 14:231</td>
<td>Sigmoid</td>
<td>12</td>
<td>+216%</td>
<td>37 months</td>
</tr>
<tr>
<td>Ginsberg</td>
<td>Ileum</td>
<td>26</td>
<td>+300%</td>
<td>96% @ 55 mos</td>
</tr>
</tbody>
</table>
Ileovesicostomy

Add chimney to bladder
Surgically straightforward
Ureters intact

Bladder may not drain well
Recurrent UTI’s
Mucous production
Ileal conduit

- Definitive procedure
- +/- Cystectomy
- Best drainage of urine

- Irreversible
- Lifelong monitoring of kidneys needed
- Stoma may present problem for some
Conclusions

- Surgical intervention only as last resort

- Growing comfort with Botox - now FDA approved in Neurogenic OAB

- Neuromodulation possibilities growing

- Match patient expectations with procedure