Management of Overactive Bladder

UBC Urology Grand Rounds
5 Oct 2005
John Morrell

Sponsor: Paladin

OBJECTIVES

- Review pathophysiology of overactive bladder (OAB)
- Review options for management of OAB
INTRODUCTION

Definition of OAB (ICS): urgency ± urge incontinence, usually with frequency and nocturia, of no identifiable cause

Detrusor overactivity (ICS): urodynamics observation of involuntary contractions, replaces hyperreflexia and instability

IC and PBS: both involve pain in contrast to OAB
Prevalence of OAB (Canada)

- Corcos, Can J Urol 11: 2278, 2004

- Validated computer assisted telephone interview
- 3249 adults ≥ 35 yrs old sampled
- 603 had OAB (18.1%), women > men
- Dry OAB >>> wet OAB > mixed OAB
- Prevalence ↑ with age

Economic Impact of OAB


- Telephone survey of 5204 community dwelling adults ≥ 18 yrs (validated instrument)
- F/u survey of costs incurred in those with OAB (by mail)
- OAB dry: ≥ 4 episodes of urgency in last 4 weeks, and either frequency ≥ 8/day or use of one or more coping behaviours
- OAB wet: dry + ≥ 3 non-stress incontinence episodes in last 4 weeks
Economic Impact of OAB

- Cost associated with institutionalized patients with OAB limited to those with UI or mixed incontinence only
- Total costs: 12 billion
- Institution dwellers: 3 billion
- Community dwellers: 9 billion
- Cost per community dweller: $267/yr
- Comparable to costs of osteoporosis and breast cancer

Natural History of OAB


- No well constructed longitudinal long term, study of patients with OAB
- Keep this in mind when evaluating results of interventions…
ANATOMY AND PHYSIOLOGY

- Blavais & Wein, Contemporary Urology, 2001

- Bladder: interlacing bundles of disorganized smooth muscle, coalesces into inner long, mid circ, outer long layers at base

- Micturition reflex is initiated by sudden complete relaxation of striated sphincter

- Followed immediately by ↑ Pdet and ↓ Pure → flow

Neurophysiology of Micturition

- Storage and emptying governed by interactions b/w
  - sacral micturition centre (SMC)
  - Thoracolumbar sympathetic system
  - Pontine micturition centre (PMC)
  - Higher brain centres

- Micturition reflex coordinated by connections b/w PMC and SMC
Neurophysiology: SMC

- Autonomic component (pelvic nerve, S2-4) and somatic component (pudental nerve)
- Preganglionic fibres of efferent parasymp travel thru pelvic nerve to pelvic plexus on either side of rectum
- Postganglionic fibres innervate bladder
- Efferent activity is ↑ by stretch signalling from afferents in pelvic, hypogastric and pudental

Neurophysiology: thoracolumbar sympathetics

- Sympathetic preganglionic efferents (T10-L2) travel to sup hypogastric plexus
- Postganglionics travel in hypogastric nerve primarily to BN, proximal urethra, trigone
- Also synapse in pelvic plexus at junction of parasymp pre and post ganglionic nerves
- Functions in storage:
  - inh pre to post-ganglionic parasymp transmission (α2)
  - Promote relaxation of detrusor (β2, ± β3)
  - Internal sphincter contraction (α1)
Neurophysiology: LUT afferents

- Mechanoreceptor bladder afferents (myelinated A-delta) for sensation of distension travel in hypogastric nerve to dorsal column of lumbosacral cord
- Nociceptive afferents (unmyelinated C fibres) travel along pelvic and hypogastric nerves to lateral spinothalamic tracts
- Afferents from striated sphincter and urethra transmit proprioceptive and pain along pudental nerve
Neurophysiology: striated urethral musculature

- Motor axons from Oneuf’s nucleus (ventral horn of S2-4) → pudental nerve → striated urethral sphincter

Neurophysiology: PMC

- Coordinates micturition reflex
- Medial region controls detrusor contraction via reticulospinal tracts
- Lateral region controls sphincter contraction via corticospinal pathways
Neurophysiology: Higher centres

- PMC receives input from cortex, cerebellum, BG, thalamus, and hypothalamus
- Most input from these centres is inhibitory
- Frontal cortex and anterior cingulate gyrus most important in control of micturition
- Micturition controlled predominately by right side of brain

Neurophysiology: Receptors

- Detrussor contracted by activation of cholinergic muscarinic receptors (M1 – M5)
- M1 – 3 found in bladder
- M2 predominates (80%) but M3 felt to be primary one mediating contraction
- M2 coactivation may enhance response to M3
- M3 present in other tissues including salivary glands
- “Holy Grail” is bladder-selective antimuscarinic

Ouslander NEJM 350: 786, 2004
Neurophysiology: Receptors

Storage and Emptying

Table 23-4. REFLEXES TO THE LOWER URINARY TRACT

<table>
<thead>
<tr>
<th>Afferent Pathway</th>
<th>Efferent Pathways</th>
<th>Central Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Storage</td>
<td>1. External sphincter contraction (somatic nerves)</td>
<td>Spinal reflexes</td>
</tr>
<tr>
<td>Low level vesicular afferent activity</td>
<td>2. Internal sphincter contraction (sympathetic nerves)</td>
<td>Spinal reflexes</td>
</tr>
<tr>
<td>(pelvic nerve)</td>
<td>3. Detrusor inhibition (sympathetic nerves)</td>
<td>Spinal reflexes</td>
</tr>
<tr>
<td></td>
<td>4. Ganglionic inhibition (sympathetic nerves)</td>
<td>Spinal reflexes</td>
</tr>
<tr>
<td></td>
<td>5. Sacral parasympathetic outflow inactive</td>
<td>Spinothalamic reflexes</td>
</tr>
<tr>
<td>Micturition</td>
<td>1. Inhibition of external sphincter activity</td>
<td>Spinothalamic reflexes</td>
</tr>
<tr>
<td>High level vesicular afferent activity</td>
<td>2. Inhibition of sympathetic outflow</td>
<td>Spinothalamic reflexes</td>
</tr>
<tr>
<td>(pelvic nerve)</td>
<td>3. Activation of parasympathetic outflow</td>
<td>Spinothalamic reflexes</td>
</tr>
<tr>
<td></td>
<td>4. Activation of parasympathetic outflow to the bladder</td>
<td>Spinothalamic reflexes</td>
</tr>
<tr>
<td></td>
<td>5. Activation of parasympathetic outflow to the urethra</td>
<td>Spinothalamic reflexes</td>
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</table>
PATHOPHYSIOLOGY OF OAB

- Symptoms of OAB are usually associated with involuntary contractions of detrusor
- Detrusor overactivity has 2 interdependent causes:
  - Neurologic
  - Myogenic
- Neural abnormalities → myogenic abnormalities and vice versa
Pathophysiology: Involuntary detrusor contraction

Ouslander NEJM 2004

Pathophysiology: Neurologic abnormalities

- Neurologic abnormalities have multiple effects on micturition:
  1. Interfere with circuitry
  2. Induce changes in innervation (plasticity) → new neural pathways and control mechs
  3. Induce changes in properties of smooth muscle cells
Pathophysiology: Myogenic abnormalities

1. Extensive electrical coupling noted in smooth muscle preps from OAB patients
2. Supersensitivity to muscarinic stimulation and enhanced depolarization to K+

Pathophysiology: Role of urothelium

- Urothelial cells have sensory role
- During filling, urothelium stretches → release of ATP
- P2X₃ receptors (ligand-gated cation channel) for ATP abundant on bladder afferents
- P2X₃ Activation → afferent discharge at lower threshold
- Stretch activated ATP release is ↑ in chronic bladder disorders compared to control

De Groat, Urology 2004
Pathophysiology: Role of urothelium

- Capsaicin evokes painful responses by stimulating ion channel protein vanilloid receptor-1 (TRPV1) on urothelial cells & C fibre afferents
- Endogenous TRPV1 ligand: anandamide
- Activation → NO release, excitement then desensitization of C fibre afferent
- NO release in bladder strips ↓ after removal of urothelium, denervation, or desensitization
- Bottom line: substances released from urothelium can alter excitability of afferents

ETIOLOGY OF OAB

- Ouslander NEJM 350, 2004; Dallosso BJU 92, 2003
- LUT conditions:
  - UTI, Obstruction, bladder abnormalities (stones, tumours, IC)
- Neurologic conditions:
  - Stroke, Alzheimer’s, SCI, DM neuropathy
- Functional/Behavioural:
  - Excess carbonated drinks, caffeine, alcohol, obesity
DIAGNOSIS

- Abrams and Wein, OAB Consensus Conference, 2000
  - History
  - IPSS, OAB-q, voiding diary
  - PE (GU, pelvic, rectal, lower extremity neuro)
  - U/A
  - ± uroflow, PVR, cytology, cystoscopy, UDS

MANAGEMENT OVERVIEW

- Behaviour modifications
- Classic anticholinergics (ditropan, detrol)
- New antimuscarinics (solifenacin, darifenacin, trospium)
- Botox
- Acupuncture
- Neuromodulation
Behaviour Modification

- Education
- Appropriate fluid intake, timing of intake
- Avoidance of irritants
- Managing constipation
- Physiotherapy
- Bladder training

Pelvic Physiotherapy

- Wang, Urology 63: 61, 2004
- 103 OAB women randomized to 12 wks:
  1. Pelvic floor muscle training (PFMT)
  2. Biofeedback assisted PFMT (BAPFMT)
  3. Intravaginal electrical stimulation (ES, 20 mins of ~ 50 mA, 10 Hz, twice/wk)
- Outcomes: voiding diary, pad test, QoL questionnaire, UDS
**Pelvic Physiotherapy**

**TABLE II. Comparison of changes in domains of King’s Health Questionnaire after treatment**

<table>
<thead>
<tr>
<th>QOL Domain</th>
<th>PFMT (n = 34)</th>
<th>BAPFMT (n = 34a)</th>
<th>ES (n = 35)</th>
<th>Overall</th>
<th>B vs. ES</th>
<th>P vs. ES</th>
<th>B vs. P</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health perception</td>
<td>14.66 ± 24.57</td>
<td>12.10 ± 20.28</td>
<td>16.96 ± 24.58</td>
<td>0.375</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence impact</td>
<td>0.05 ± 120.82</td>
<td>57.42 ± 51.11</td>
<td>67.05 ± 50.65</td>
<td>0.067</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role limitation</td>
<td>25.86 ± 26.57</td>
<td>30.64 ± 30.15</td>
<td>34.52 ± 31.73</td>
<td>0.669</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical limitation</td>
<td>25.29 ± 26.58</td>
<td>33.33 ± 33.88</td>
<td>28.57 ± 28.99</td>
<td>0.695</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social limitation</td>
<td>17.05 ± 21.20</td>
<td>22.76 ± 29.20</td>
<td>20.84 ± 27.45</td>
<td>0.799</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal relationships</td>
<td>2.30 ± 13.89</td>
<td>10.75 ± 26.37</td>
<td>3.57 ± 22.39</td>
<td>0.167</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotions</td>
<td>19.51 ± 29.68</td>
<td>22.22 ± 27.82</td>
<td>46.85 ± 37.33</td>
<td>0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep/energy</td>
<td>18.85 ± 26.18</td>
<td>26.88 ± 24.60</td>
<td>38.10 ± 39.51</td>
<td>0.249</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity measures</td>
<td>14.71 ± 28.27</td>
<td>20.65 ± 31.19</td>
<td>31.25 ± 27.63</td>
<td>0.003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>50.27 ± 171.62</td>
<td>185.86 ± 176.07</td>
<td>180.08 ± 176.03</td>
<td>0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: QOL = quality of life; other abbreviations as in Table I.
Data presented as the mean ± SE.
+ Value determined by subtracting post-treatment scores from pre-treatment scores.
* Denotes overall comparison among three groups using the Kruskal-Wallis test or pairwise comparison using the Mann-Whitney U test.

Most confidence intervals for changes measures include 0, lack of efficacy vs responsiveness of measure used.

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**Bladder Training**

- Wallace, Cochrane DSR, 2003

- Timed voiding with increasing intervals
- 10 trials, 1366 participants, predominantly female
- Inconclusive data
- Tendency to favour bladder training
- More, better research needed
### Behavioural Therapy

- Lifestyle interventions
- Bladder retraining
- Pelvic floor muscle therapy (PFMT)
  - Basic
  - Simple biofeedback - with devices
  - Advanced biofeedback - electrical stimulation

### Combination Therapy is Most Effective for Overactive Bladder

*Percent reductions in incontinence episodes after 8 weeks*

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Subjects</th>
<th>Percent Reduction</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug therapy alone (N = 18)</td>
<td></td>
<td>59.1%</td>
<td>.109</td>
</tr>
<tr>
<td>Switched to behavioral (N = 18)</td>
<td></td>
<td>77.1%</td>
<td></td>
</tr>
<tr>
<td>Behavioral therapy alone (N = 8)</td>
<td></td>
<td>57.5%</td>
<td>0.034</td>
</tr>
<tr>
<td>Drug therapy added (N = 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral therapy added (N = 27)</td>
<td></td>
<td>84.3%</td>
<td>0.001</td>
</tr>
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</table>

Combination Therapy
Conclusions

- Combination therapy is more effective than either therapy alone.
- 29% of patients randomized to oxybutynin alone chose to discontinue drug therapy and crossed over to behavioural therapy alone because of:
  - unwanted side effects
  - unwillingness to continue long-term drug therapy
- Drugs such as tolterodine with fewer side effects may encourage patients to choose combination therapy.

Anticholinergics

- Hay-Smith, Cochrane DSR, 2002
- 51 trials
- 6713 adults
- 7 medications: oxybutynin, tolterodine, trospium, darifenacin, emepronium, propiverine, propantheline

Anticholinergics vs placebo: patient perception of cure/improvement, favours anticholinergics
### Anticholinergics

#### Anticholinergics vs placebo: leakage episodes/24 hrs, favours anticholinergics

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean (SD) placebo</th>
<th>Mean (SD) anticholinergics</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (FS)</th>
<th>Weighted Mean Difference (Fixed) (95% CI)</th>
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<tr>
<td>21 number of leakage episodes</td>
<td>85.18 (1.48)</td>
<td>82.12 (1.11)</td>
<td>8.00 (0.30, 0.51)</td>
<td>1.71</td>
<td>8.00 (0.30, 0.51)</td>
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#### Anticholinergics vs placebo: micturitions/24 hrs, favours anticholinergics

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<td>32 change in leakage episodes</td>
<td>10.1 (1.7)</td>
<td>9.0 (1.4)</td>
<td>1.0 (0.3, 0.5)</td>
<td>1.71</td>
<td>1.0 (0.3, 0.5)</td>
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**Anticholinergics**

**Anticholinergics vs placebo: max cystometric capacity, favours anticholinergics**

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<th>Placebo</th>
<th>Weighted Mean Difference (Fixed)</th>
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<td>Max cystometric capacity</td>
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<td></td>
<td>Carbon 2008</td>
<td>104</td>
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<td>0.68</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>110</td>
<td>0.04</td>
<td>0.62</td>
<td>2.73</td>
<td>0.62</td>
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**Anticholinergics vs placebo: volume at first contraction, favours anticholinergics**

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Oxybutynin vs Tolterodine

- Hay-Smith, Cochrane DSR, 2005
- 49 trials
- 11,332 patients
- Primary drugs: oxybutynin, tolterodine
### Oxybutynin vs Tolterodine

<table>
<thead>
<tr>
<th>Study</th>
<th>Other drug</th>
<th>Oxybutynin</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (C)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Tolerance versus oxybutynin</td>
<td>Detrol</td>
<td>0.11/19</td>
<td>0.11/19</td>
<td>45.8</td>
<td>1.02 [0.79, 1.29]</td>
</tr>
<tr>
<td>Mahon 1999</td>
<td>Detrol</td>
<td>0.11/19</td>
<td>0.11/19</td>
<td>57.4</td>
<td>1.12 [0.87, 1.46]</td>
</tr>
<tr>
<td>Subtotal (DF) (C)</td>
<td>Detrol</td>
<td>0.11/19</td>
<td>0.11/19</td>
<td>100.0</td>
<td>1.08 [0.96, 1.25]</td>
</tr>
<tr>
<td>2 Trospium chloride versus oxybutynin</td>
<td>Detrol</td>
<td>0.11/19</td>
<td>0.11/19</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
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<td>Subtotal (DF) (C)</td>
<td>Detrol</td>
<td>0.11/19</td>
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<td>Not estimable</td>
</tr>
<tr>
<td>3 Propylanthidine versus oxybutynin</td>
<td>Detrol</td>
<td>0.11/19</td>
<td>0.11/19</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
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<td>Detrol</td>
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- **Oxybutynin vs Tolterodine**: cure or improvement, favours Detrol

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<th>Weight (C)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Tolerance versus oxybutynin</td>
<td>Detrol</td>
<td>0.11/19</td>
<td>0.11/19</td>
<td>45.8</td>
<td>1.02 [0.79, 1.29]</td>
</tr>
<tr>
<td>Mahon 1999</td>
<td>Detrol</td>
<td>0.11/19</td>
<td>0.11/19</td>
<td>57.4</td>
<td>1.12 [0.87, 1.46]</td>
</tr>
<tr>
<td>Subtotal (DF) (C)</td>
<td>Detrol</td>
<td>0.11/19</td>
<td>0.11/19</td>
<td>100.0</td>
<td>1.08 [0.96, 1.25]</td>
</tr>
<tr>
<td>2 Trospium chloride versus oxybutynin</td>
<td>Detrol</td>
<td>0.11/19</td>
<td>0.11/19</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Subtotal (DF) (C)</td>
<td>Detrol</td>
<td>0.11/19</td>
<td>0.11/19</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>3 Propylanthidine versus oxybutynin</td>
<td>Detrol</td>
<td>0.11/19</td>
<td>0.11/19</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Subtotal (DF) (C)</td>
<td>Detrol</td>
<td>0.11/19</td>
<td>0.11/19</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

- **Oxybutynin vs Tolterodine**: dry mouth, favours Tolterodine
Oxybutynin vs Tolterodine: withdrawals due to adverse effects, favours tolterodine

Oxybutynin and Tolterodine: ER vs IR formulations and dry mouth, favours ER
Oxybutynin vs Tolterodine

<table>
<thead>
<tr>
<th>Study</th>
<th>Other dose</th>
<th>2mg</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29 0.5mg versus 2mg</td>
<td>n/N</td>
<td>8/0</td>
<td>0.0</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>8/122</td>
<td>78/129</td>
<td>Test for heterogeneity chi-square=0.0.012</td>
<td>100.0</td>
<td>0.80 [0.53, 0.99]</td>
</tr>
<tr>
<td>Test for overall effect=0.0 p&lt;0.0</td>
<td>100.0</td>
<td>0.80 [0.53, 0.99]</td>
<td>100.0</td>
<td>0.80 [0.53, 0.99]</td>
<td></td>
</tr>
<tr>
<td>22 1mg versus 2mg</td>
<td>n/N</td>
<td>50/123</td>
<td>76/129</td>
<td>Test for heterogeneity chi-square=0.00 [0.41]</td>
<td>100.0</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>50/123</td>
<td>76/129</td>
<td>Test for heterogeneity chi-square=0.00 [0.41]</td>
<td>100.0</td>
<td>1.17 [1.03, 1.32]</td>
</tr>
<tr>
<td>Test for overall effect=2.02 p&lt;0.005</td>
<td>100.0</td>
<td>1.17 [1.03, 1.32]</td>
<td>100.0</td>
<td>1.17 [1.03, 1.32]</td>
<td></td>
</tr>
</tbody>
</table>

Tolterodine dosing: favours 4 mg/day

Transdermal Oxybutinin

- Oral oxybutinin undergoes extensive first pass metabolism to active metabolite, N-desethyloxybutinin
- \([N\text{-desethyloxybutinin} = 4-10\text{[oxybutinin]}\]
- N-desethyloxybutinin responsible for s/e
- Transdermal dosing yields lower \([N\text{-desethyloxybutinin]}\]
Transdermal oxybutynin

- RCT of 530 adults with urge or mixed UI
- 12 weeks followed by 12 week open-label does titration (1.3, 2.6, 3.9 mg)
- 3.9 mg daily significantly reduced weekly incontinence episodes, daily urinary frequency, increased average volume voided, and improved QoL
- Adverse Events
  - pruritis 10-16% versus placebo 6%
  - Dry mouth: 7% versus 8%

**Transdermal oxybutynin versus tolterodine ER**

- 12 week RCT of transdermal oxybutynin, tolterodine ER, and placebo
- 361 adults who previously responded to anticholinergics
- Significant decrease in UUI episodes, increase in voided volume, improvement in symptoms and QoL
  - tolterodine and oxybutynin versus placebo (P<0.05)
  - No significant difference between treatment groups
- Pruritis: oxy (14%) versus placebo (4%) (P<0.05)
- Dry mouth: oxy (4.1%), tol (7.3%), placebo (1.7%)


**Solifenacin (Vesicare)**

- Selective M3-receptor antagonist
- Bladder selective compared to salivary gland
  - In vitro and in vivo animal models - more than tolterodine or oxybutynin
- Dose dependent effect on salivary gland secretion - but similar to placebo

Ikeda et al. NS Arch Pharm 2002; 366:97-103
Smulders et al. ICS Heidelberg 2002, Abstr. 4
Solifenacin (Vesicare)

- **Multicentre 12 week RCT**
- 1281 patients with OAB and UUI – 1033 evaluated
- Solifenacin 2 mg, 5 mg, once daily versus tolterodine 2 mg bid or placebo
- Sig. reduction in urge episodes/24h
  - Placebo (-32.7%); Solifenacin 5 mg (-51.9), 10 mg (54.7%); not sig. reduction with tolterodine (-37.9%)  
- Sig. reduction in incontinent episodes with Solifenacin but not with Tolterodine (-1.4 versus -1.1)
- Sig. improvement in frequency and voided volume with all 3 drugs

Chapple et al. BJU Int 2004; 93:303-

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Solifenacin: Side effects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>5 mg (once daily)</th>
<th>10 mg (once daily)</th>
<th>Tolterodine 2 mg (twice daily)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>289</td>
<td>279</td>
<td>268</td>
<td>283</td>
<td>1077</td>
</tr>
<tr>
<td>Discontinuing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Averse event</td>
<td>10 (3.7)</td>
<td>9 (3.2)</td>
<td>7 (2.7)</td>
<td>5 (1.9)</td>
<td>31 (3.8)</td>
</tr>
<tr>
<td>Consent withdrawal</td>
<td>11 (3.7)</td>
<td>11 (3.9)</td>
<td>7 (2.6)</td>
<td>8 (3.0)</td>
<td>36 (3.3)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2 (0.7)</td>
<td>1 (0.1)</td>
<td>2 (1.0)</td>
<td>6 (2.1)</td>
<td>11 (1.2)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>5 (1.8)</td>
<td>4 (1.4)</td>
<td>0</td>
<td>3 (1.1)</td>
<td>12 (1.1)</td>
</tr>
<tr>
<td>Insufficient response</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
<td>1 (0.4)</td>
<td>3 (1.0)</td>
<td>8 (0.7)</td>
</tr>
<tr>
<td>Patient died</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.0)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>2 (0.2)</td>
<td>8 (0.8)</td>
</tr>
<tr>
<td>Total</td>
<td>289</td>
<td>279</td>
<td>268</td>
<td>283</td>
<td>1077</td>
</tr>
</tbody>
</table>

Major side-effects
- Dry mouth  | 13 (4.6) | 39 (1.4) | 57 (21.5) | 42 (1.5) |
- Constipation | 5 (1.8) | 20 (7.3) | 21 (8.0) | 7 (2.6) |
- Blurred vision | 7 (2.5) | 10 (3.6) | 16 (6.0) | 4 (1.5) |

Chapple et al. BJU Int 2004; 93:303-
Darifenacin (Enablex)

- Highly selective M3-receptor antagonist
- Displays some selectivity for bladder in the dog model
- Originally developed for treatment of irritable bowel syndrome
  - inhibits bowel motility (dog model)
  - inhibits resting and food-stimulated colonic motility
- 1996 abstract:
  - 2.5 mg: no efficacy and no effect on salivation
  - 10 mg: efficacy but significant effects on salivation


Darifenacin (Enablex)

- Multicentre 12 week RCT
  - 561 patients with OAB and UUI
  - 3.75 mg, 7.5 mg, 15 mg once daily versus placebo
  - Rapid onset of effect within 2 weeks
  - Sig. reduction in incontinence episodes
    » 7.5 mg (-67.7%); 15 mg (-72.8%); placebo (-55.9%)
  - Sig. improvement in frequency, frequency of urgency, not in nocturia
  - Mild-to-moderate dry mouth (20-30% versus 8.5%)
    and constipation (15% versus 6.7%)
  - No CNS or cardiac side effects

**Trospium (Sanctura)**

- Atropine derivative with low lipophilicity
- Does not cross BBB; Less CNS effects than oxybutynin
- Cardozo et al. BJU Int 2000; 85:659
  - 208 patients; placebo RCT; significant increase in capacity, volume at unstable contraction (P=0.005); patient’s perception of efficacy (P=0.005)
  - Side effects similar to placebo
- U.S. randomized trials completed – Results expected to confirm European trials
- 10,000 patients in 20 clinical trials already reported

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**Trospium**


- Review of 20 clinical trials with >10,000 patients
- 4 RCTs, 3 comparative studies, and most post-marketing surveillance studies
- All age groups, neurogenic, enuresis
Trospium

<table>
<thead>
<tr>
<th>Table 2 Frequency of side effects summing up to 10,759 patients from post-marketing surveillance studies (From [20–22, 39, 41])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
</tr>
<tr>
<td>Dryness of mouth</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Visual disorders</td>
</tr>
<tr>
<td>Abnormalities of heart rate</td>
</tr>
<tr>
<td>Nausea/other gastrointestinal side effects</td>
</tr>
<tr>
<td>Residual urine</td>
</tr>
<tr>
<td>Other complaints</td>
</tr>
<tr>
<td>Total percentage of patients with adverse events</td>
</tr>
</tbody>
</table>

Botulinum poisoning first described as result of sausage poisoning in Germany 1700

C. botulinim identified in 1897

Active neurotoxins are bi-peptides disulphide linked

Toxins binds to unidentified nerve terminal receptor

Toxin is internalized where it interferes with NT release

Botox
Smith, JU 171; 2128, 2004
Botox

Release of ACh and activation of receptor

Smith CP. J Urol 2004;171:2128-213

Botox

Release prevented by BTX-A
**Botulinum toxin A**

- 4 small studies with idiopathic OAB, many more studies of neurogenic bladders
- Injected in multiple sites in bladder endoscopically
- Dilution/dosing not determined
- 59 patients
- 20/30 improved continence for up to 8 months\(^1\)
- 12 improved at one month\(^2\)
- 4/7 improved\(^3\)
- 8/10 improved\(^4\)


---

**Estrogen Therapy**

- Evidence-based review
- 87 References
  - included non–placebo-controlled studies
- Efficacy
  - SUI: probably not
  - UUI: probably not
  - Urgency: maybe

Estrogen Therapy for OAB: A Meta-analysis

- Review of published literature from 1969 to 1999
- Included 10 randomized studies
  - estrogen (n = 239)
  - placebo (n = 215)
- Estrogen administered systemically or locally for various times (3 weeks to 6 months)


Estrogen Therapy for OAB: A Meta-analysis

- Estrogen significantly better than placebo at improving
  - urge incontinence
  - diurnal frequency
  - nocturia
  - bladder capacity
  - volume at first sensation
- Topical estrogen significantly better than placebo for all efficacy variables including urgency
- Systemic estrogen significantly better than placebo for incontinence episodes, but not for other efficacy variables

Estrogen: Conclusions

- Mixed evidence that exogenous estrogen is effective in treating urge incontinence or OAB
- Increasing evidence favoring the use of local (e.g., VagiFem or Estring) versus systemic estrogen
- Use of hormone replacement therapy in combination with other therapies for OAB, including antimuscarinics, remains unreported

Accupuncture

Emmons, Obs & Gyne 106: 138, 2005

- 44 women received acupuncture designed to address OAB, 4 treatments
- Needles placed bilaterally on inner legs, outer knee folds, low back, midline low abdo (total 7 needles)
- Needles placed then twisted clockwise until warmth or tightening sensed (deqi)
- Controls had needles placed at locations designed for relaxation
**Accupuncture**

- Primary endpoint: # of incontinent episodes reduced by 59% vs 40% (not sign)
- Significant improvement in frequency, urgency, functional bladder capacity, incontinence impact questionnaire score
- No significant adverse effects
- Comparable to results seen with anticholinergics

**Neuromodulation**

- Underlying principle: reflex inhibition of pelvic efferents through stimulation of afferent input in pudental and sacral roots.
- Inhibitory effect of afferent stimulation in humans has been determined
51 patient with refractory urgency-frequency

Excluded: cap < 100, abnormal upper tracts, neurogenic bladder, SUI, pelvic pain synd.

Trial test stimulation of sacral nerves (perc stim of S3,4)

Those with successful trial went on to implantation of Interstim device

- SC implanted device includes neurostimulator, lead placed adjacent to targetted sacral nerves and extension connecting the two
- 25 assigned to stimulation
- 26 assigned to std medical therapy
- Cross over at 6 months
- Primary endpoints: number of voids/day, volume/void, degree of urgency before void
Sacral Neuromodulation

- Significant drop in number of voids daily from 16.9 to 9.3 (p < 0.0001), no change in control group
- Significant increase in voided volume from 118 to 226 (p < 0.0001)
- Explant in one due to therapy related bowel dysfunction
- When turned off at 6 months, return to baseline
- Sustained clinical benefit 18 – 24 months
- Significant improvement in QoL (SF-36)

Neuromodulation: InterStim

- Option for those who fail conservative medical therapy
- Must demonstrate relief during test stimulation
- Neurostimulator is implanted subcutaneously in upper buttock or abdomen
- Lead is placed adjacent to appropriate sacral nerve and attached to neurostimulator
- Approved in Canada, available in Halifax, Montreal, Toronto, Edmonton
InterStim, Medtronics

Neuromodulation: NeoControl

- Extracoporeal magnetic innervation
- Pulsed magnetic field (5 Hz intermittently for 10 minutes, rest, 50 Hz intermittently for 10 min)
- Patients sit fully clothed on chair for 20 min x 2/week for 6 week course
- How stimulation suppresses detrusor contraction is not known
Well documented increase in cystometric capacity, inhibition of detrusor overactivity, reduction of OAB symptoms acutely

Short term symptomatic improvement in ~75%

Mixed long term data

> 1 million patients in US yet little literature
SUMMARY

- Anticholinergics effective
- Best evidence for tolterodine 4 mg ER OD vs other anticholinergics
- Even better when combined with behavioural modification
- Sacral neuromodulation option in refractory cases
- Paucity of literature supporting “Stretch and Burn”