Overactive Bladder (OAB) and Quality of Life

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Hong Kong Continence Society
Annual Scientific Meeting
30th September, 2006
The International Continence Society (2002) defines:

- Overactive bladder as **urgency**, with or without urgency urinary incontinence, usually with frequency and nocturia
- Urgency as a sudden compelling desire to pass urine that is difficult to defer

The Urge Continuum

1. Proven direct effect
2. Effect correlated with urgency but inconsistent due to multifactorial etiology of the symptom

Chapple CR. Presented at the 3rd International Consultation on Incontinence, 2004
Other Terminology (ICS)

- Urge
  - Normal physiological desire to void that accompanies bladder filling

- Frequency
  - Complaint by patient that s/he voids too often by day, typically > 8 micturitions / 24 hours

- Nocturia
  - Waking one or more times at night to void

- Incontinence
  - Any involuntary leakage of urine

- Detrusor overactivity
  - A urodynamic diagnosis – idiopathic / neurogenic

Prevalence of OAB

- United States  
  - National Overactive Bladder Evaluation (NOBLE) Program
  - Telephone survey of 5,204 adults ≥ 18 years
  - Overall prevalence of OAB similar between men (16.0%) and women (16.9%)
Prevalence of OAB

- European Union (Milsom et al., BJUI 2001; 87: 760-766)
  - Population based survey of men and women aged $\geq 40$ years in 6 EU countries
  - 16,776 interviews conducted
  - Overall prevalence of OAB 16.6%
  - Prevalence in $\geq 75$ years : 36.6%
  - Individual symptoms:
    - Frequency 85%
    - Urgency 54%
    - Urge incontinence 36%
OAB Prevalence by Age and Gender

Milsom et al., BJUI 2001; 87: 760-766
Impact of OAB on Quality of Life

Physical Symptoms
- Gradual increase in frequency
- Increase in urgency
- Loss of sleep
- Wetting accidents

Concerns
- Women: Am I sick? Do I have cancer? I want information
- Men: Do I have a prostate problem?

Emotional
- Embarrassment
- Fear
- Frustration
- Anger
- Loss of self-esteem

Behavioural
- Job performance
- Relationship stress
- Social activities
- Drinking behaviour

Khullar V. Presented at Third Urology Summit, Thailand, Sept. 2006
Impact of OAB on Emotional Well-Being

Having this condition (OAB) ....

Milsom et al., Presented at 3rd International Consultation on Incontinence, 2004
Data on file, Pfizer Inc.
Employment Issues Related to OAB Symptoms

- I worry about interrupting meetings with frequent bathroom trips: Total 22, Women 18, Men 25*
- I’ve changed jobs or been fired because of my bladder control problem: Total 3, Women 2, Men 4
- My problem has been a factor in decisions about where I work and the hours I work: Total 8, Women 7, Men 10
- My problem has been a factor in my deciding not to continue working or to retire early: Total 7, Women 6, Men 8

*P<0.05 vs women.
Symptom Perception

Urinary problems like mine are ....

-Milsom et al., Presented at 3rd International Consultation on Incontinence, 2004
-Data on file, Pfizer Inc.
OVERACTIVE BLADDER
(n = 1916)

Spoken to a doctor 60%

Not spoken to a doctor 40%

Currently on medication 27%

Currently not on medication 73%

Never tried 73%

Tried but failed 27%

Likely to discuss with a doctor again 54%

Not likely to discuss again 46%

Likely to discuss with a doctor again 65%

Not likely to discuss again 35%

Milsom et al., BJUI 2001; 87: 760-766
EPIC Study

- 5-country telephone survey
- N = 19,165 men and women aged ≥18 years
- Conducted in Germany, Italy, UK, Sweden, and Canada (April – December 2005)
- Nationally representative sample
- Nested case-control component with 300 OAB cases per country

Irwin DE et al. Abstract presented at EAU 2006
Data on file, Pfizer Inc.
EPIC Study

Primary Objectives
- Estimate the prevalence of OAB, MUI, SUI, and other LUTS in the general population
- Evaluate the impact of OAB, MUI, SUI, and other LUTS on patient bother and QOL

Secondary Objectives
- Investigate risk factors and comorbidities associated with OAB, MUI, and SUI
- Assess prevalence of patient coping and health care-seeking behaviours with respect to OAB, MUI, and SUI
- Conduct exploratory evaluation of bothersomeness and overall impact on mood/depression, sexuality, family, and work productivity

Irwin DE et al. Abstract presented at EAU 2006
Reilly K et al. Abstract presented at EAU 2006
Data on file, Pfizer Inc.
EPIC: Definition of OAB ‘Bothered’ Population

- Subjects achieved one of the criteria below to be classified as bothered
  - Patient perception of bladder condition (PPBC)
    - Positive response indicating bladder condition caused some minor, moderate or severe problems
  - OAB-specific QOL instrument (OABq Symptom Bother Scale)
    - Score $\geq 15$ for men and $\geq 20$ for women

*Milsom I et al. Abstract to be presented at: 36th ICS*
EPIC: Symptom Bother and Medication Consultation for OAB

51.4% of patients who reported bother sought medical care from a health care provider versus only 21.2% of patients who did not report bother

Data on file, Pfizer Inc.
EPIC: Women and Men With OAB Make Lifestyle Changes

Data on file, Pfizer Inc.

*C = 0.05 OAB with UI vs controls and OAB without UI within gender

*COPING TECHNIQUES*

Women

- Limit fluids
- Absorbent products
- Exercises
- Non-Rx products
- Any

Men

- Limit fluids
- Absorbent products
- Exercises
- Non-Rx products
- Any
EPIC: Women and Men With OAB Report Increased Depressive Symptoms

CES-D Score and Self-Reported Depression

*P ≤ 0.05 OAB vs controls Data on file, Pfizer Inc.
EPIC: Individuals With OAB Are Less Likely to Be Employed

Percent of Respondents Currently Employed

*P = 0.05 OAB with UI vs controls and OAB without UI within gender

Data on file, Pfizer Inc.
EPIC Study: Conclusions

- Large multi-national study including more than 19,000 subjects
- OAB is similarly prevalent in men (10.8%) and women (12.8%)
  - EPIC was the first study to use the updated 2002 ICS definition
- Slightly more than 50% of OAB patients reported symptom bother
  - Bother was reported more frequently among women with UI
- Individuals with OAB
  - Have significantly more depressive symptoms
  - Are less likely to be employed
Economic Burden of OAB

Total OAB cost estimated at $12.0 billion in the US in 2000

Routine care 36%
Pharmacological 10%
Lost Productivity 7%
Physician visits 6%
Surgical 5%
Other 8%
Additional nursing home admissions 16%
Urinary tract & skin infections 12%
Physician visits 6%
Surgical 5%
Broken bones & falls 4%
Home care 2%
Diagnosis 1%
Longer hospital LOS 1%
Routine care 36%

Prevalence, treatment, OAB related consequences and productivity: Based on the NOBLE program of 5,204 English speaking US adults via a telephone survey, case control method used. Costs obtained from a variety of sources. Institutional costs used data from a previous study. (Wagner 1995)

Hu et al. Urology 2003; 61(6) : 1123 – 1128
Initial Evaluation of OAB

- History: medical, neurologic, genitourinary
- Prior treatment and results
- Bladder diary and questionnaire
- Urinalysis: culture if urinalysis positive; cytology in patients with suspected CIS
- Physical exam: general, abdominal, pelvic, rectal, neurologic
Further Tests

- Post-void residual urine
- Uroflowmetry
- Urodynamic study
- Cystoscopy
Treatment Options for OAB

- Behavioral therapy
- Pharmacological treatment
- Surgical management
Behavioral Therapy

Behavioral modification for overactive bladder

- Delayed voiding
- PFE Biofeedback
- Timed voiding
- Education Reinforcement
- Charts Diaries
- Fluid diet management

Wein, AJ. Urology 2003; 62(Suppl 5B): 20 – 27
Behavioral Therapy

- Improvement in incontinence episodes reported > 50%
- Combination of behavioral therapy and drug therapy is more effective than the use of either alone

Wein, AJ. Urology 2003; 62(Suppl 5B): 20 – 27
Bladder Training: Results

2002 – 2005

Male 72
Female 66

Bladder Training: Age range
Bladder Training: Results

Voided frequency before and after bladder training

<table>
<thead>
<tr>
<th>Times of Micturition</th>
<th>Number of Patients</th>
</tr>
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<tbody>
<tr>
<td>&lt;7 times/day</td>
<td>15</td>
</tr>
<tr>
<td>8-10 times/day</td>
<td>24</td>
</tr>
<tr>
<td>11-15 times/day</td>
<td>21</td>
</tr>
<tr>
<td>16-20 times/day</td>
<td>13</td>
</tr>
<tr>
<td>21-25 times/day</td>
<td>17</td>
</tr>
<tr>
<td>&gt;25 times/day</td>
<td>10</td>
</tr>
</tbody>
</table>
Bladder Training: Results

Maximum urine voided before and after bladder training

Before

After

- <50ml: 0, 0
- 51-100ml: 16, 0
- 101-150ml: 25, 8
- 151-200ml: 34, 14
- 201-300ml: 40, 42
- 301-400ml: 34, 13
- 401-500ml: 18, 6
- >500ml: 22, 4
Bladder Training: Results

Level of satisfaction before and after bladder training

<table>
<thead>
<tr>
<th>Level of satisfaction</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very satisfied</td>
<td>112</td>
</tr>
<tr>
<td></td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Very unsatisfied</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
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<td>0</td>
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</tbody>
</table>

Level of satisfaction
Pharmacologic Therapy

- Antimuscarinic agents (men and women)
- Alpha-1 adrenergic receptor antagonists (male LUTS)
- 5-Alpha reductase inhibitors (male LUTS)
Antimuscarinic Agents

- Mainstay of treatment for OAB
- World-wide use around US $6.11 billion per year
Antimuscarinics: What They Do

- Increase bladder capacity
- Decrease amplitude of detrusor contractions
- Improve symptoms of urge incontinence more effectively than placebo (in studies using drugs only, not behavior therapy)
Antimuscarinics: What They Don’t Do

- Eliminate unstable bladder contractions
- Increase “warning time”
- Improve patient’s ability to suppress unstable bladder contractions
Antimuscarinics: General Principles

- Contraindicated in narrow-angle glaucoma
- Most bothersome side effect: dry mouth
  - May need to stop therapy
  - Titrate dose to symptoms relief vs S/E
  - If one drug not effective or poorly tolerated, try another one
- Use as adjuncts to behavior therapy
Oxybutynin (Ditropan)

- Marked affinity for muscarinic M2, M3 receptors in urinary bladder
- Even greater affinity for muscarinic receptors in:
  - Cerebral cortex M1,4,5 (confusion)
  - Cardiac tissue M2 (palpitation)
  - Parotid gland M1,3 (dry mouth)
  - Eye M4 (blurred vision)
Oxybutynin

- Therapeutic efficacy
  - Decreased frequency 20%
  - Decreased incontinence episodes 40-50%
  - Increased mean voided volume 20-30%

- May cause urinary retention in elderly patients

† May cause urinary retention in elderly patients
Oxybutynin

- Side effects
  - Dry mouth 70-80%
  - Constipation 15%
  - Drowsiness 12%
  - Blurred vision 5%

- Overall adverse events 50-90%
- Treatment withdrawal 25-40%
Bladder and M-Receptor Subtype Selective Agents

- Greater affinity for bladder muscarinic receptors, especially M3-subtype
- Better tolerability in the treatment of OAB

- Tolterodine
  - Immediate release (IR)
  - Extended release (ER)

- Solifenacin
Tolterodine ER vs IR vs placebo:
Efficacy

Change in number of incontinence episodes/24h after 12 weeks treatment:
tolterodine 4 mg qd and tolterodine 2 mg bid vs placebo

- Placebo
- Tolterodine 2 mg bid
- Tolterodine 4 mg qd

*P<0.001 vs placebo
†P<0.005 vs IR

Van Kerrebroeck et al. Urology 2001;57:414-421
Reduction in Frequency (Micturition / 24 Hours)

Van Kerrebroeck et al. Urology 2001;57:414-421

*P < .001 vs placebo.
Increase in Mean Volume Voided per Micturition

* \( P = .0001 \) versus placebo.

Van Kerrebroeck et al. Urology 2001;57:414-421
## Tolterodine ER: Tolerability

### Most Commonly Reported Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine ER</td>
<td>Placebo</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>23</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4</td>
</tr>
</tbody>
</table>

References:

Van Kerrebroeck et al. Urology 2001;57:414-421
Effectiveness of Antimuscarinic Agents

- Cochrane Review (Herbison et al BMJ 2003;326: 841–844)

- Meta-analysis of 32 randomized trials comparing antimuscarinic agents to placebo in treatment of OAB (N=6800)

- Outcomes measured: symptomatic and urodynamic improvements, and side effects

- Conclusion: Although statistically significant, the differences between antimuscarinic agents and placebo were clinically small, apart from the increased rate of dry mouth for the active treatment group
Cochrane Review: Pitfalls

- Inadequate / inappropriate control group (placebo)
- Heterogeneous patient groups (e.g. polyuric patients not excluded, mixing of neurogenic and idiopathic DO patients)
- Majority of included studies only measured objective endpoints – only two examined health-related quality of life (HRQL) outcomes

Khuller V. et al. Urology 2006; 68(Suppl 2A):38-48
Need for Subjective Measures

- OAB is a condition defined by its symptoms
- Objective measures (e.g. UDS, bladder diaries) provide insight into underlying pathophysiology, but are not predictive of the subjective outcomes (i.e. impact on QOL)
- Assessment of treatment efficacy in OAB clinical trials using validated patient reported outcomes (PROs) is important and recommended by the ICS

Brubaker L et al. Urology 2006; 68 (Suppl 2A): 3-8
## Summary of Commonly Used HRQL Instruments

<table>
<thead>
<tr>
<th>HRQL Instrument</th>
<th>Disease-Specific Domains</th>
<th>Global HRQL Domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaudenz Appraisal Questionnaire</td>
<td>Urge Score</td>
<td>Travel, Physical activities, Feelings, Relationships, Overall HRQL</td>
</tr>
<tr>
<td></td>
<td>Stress Score</td>
<td></td>
</tr>
<tr>
<td>Incontinence Impact Questionnaire (IIQ)</td>
<td>None</td>
<td>General health, Severity measures, Role / physical / social limitations, Personal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>relationships, Emotional problems, Sleep and energy, Overall HRQL</td>
</tr>
<tr>
<td>King’s Health Questionnaire (KHQ)</td>
<td>Incontinence impact Symptom severity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Outcomes Study Short Form-36 (SF-36)</td>
<td>None</td>
<td>Physical / mental component summaries</td>
</tr>
<tr>
<td>Urogenital Distress Inventory (UDI)</td>
<td>Irritative symptoms Urge symptoms</td>
<td>Overall HRQL</td>
</tr>
</tbody>
</table>

Khuller V. et al. Urology 2006; 68(Suppl 2A):38-48
Effects of Antimuscarinic Agents on HRQL in OAB

- A systematic review and meta-analysis (Khullar V et al. Urology 2006; 68 (Suppl 2A): 38 – 48)
- 56 randomized trials of antimuscarinic agents from 1966 to Aug 2004 analysed
- 45% reported HRQL and/or PROs
- Results from meta-analyses of placebo-controlled trials showed statistically significant improvements in several areas of HRQL for antimuscarinic therapy
Surgical Therapy for OAB

- When non-surgical treatment fails
- Options:
  - Augmentation cystoplasty
  - Urinary diversion
  - Neuromodulation
  - Denervation
  - Detrusor injection of botulinum toxin
Botulinum Toxin (BTX)

- Produced by spore-forming, Gram +ve, anaerobic Clostridium Botulinum
- 7 distinct serological subtypes (A-G), only A&B commercially available
- BTX-A: Botox (Allergan), Dysport (Ipsen)
- Binds to pre-synaptic terminal at the NMJ and prevents ACh release and inhibits muscle contraction
- Antinociceptive effect on bladder tissue?
BTX-A : Dosage and Side Effects

- Lethal dose: 39 – 40 units/kg (ie 2800 units in 70kg man)

- Therapeutic dose:
  - Botox: 100 – 300 units
  - Dysport: 750 – 1000 units

- Systemic side effects not common
  - Transient muscle weakness

- Local complications
  - Urinary retention in non-neurogenic cases
BTX – Urological Applications

(Off-Label use)

- Detrusor sphincter dyssynergia
- Bladder
  - Detrusor overactivity (neurogenic / non-neurogenic)
  - Interstitial cystitis? (Anti-nociceptive effect)
- BPH
BTX in Treatment of OAB

- 1st described by Stohrer et al. in 1999 for treatment of neurogenic detrusor overactivity
- 62% ↑ mean max. bladder capacity, 46% ↓ max. Pdet (Schuch et al., 2000)
- Subsequent large series (n=200, Reitz et al. 2003) showed:
  - Significant increase in mean maximum bladder capacity and decrease in mean maximum Pdet at 3 & 9 months FU
  - Average interval between injection: 11 months
BTX in Treatment of OAB

- Extended to refractory idiopathic detrusor overactivity – Radziszewski et al. 2001
- Results similar to neurogenic group
- Modified technique for IDO (Smith & Chancellor, 2005):
  - 100 units Botox, 10 injection sites into trigone and bladder base
  - Subjective improvement in 80% patients
  - Onset 7–10 day post injection, durable responses up to 6 months
  - No urinary retention or elevated PVR
Intravesical Injection of Botulinum Toxin A into Detrusor Muscle

- Flexible cystoscope with needle injector
- 30 sites, 1mL per injection
- Trigone spared
Intravesical Injection of Botulinum Toxin A into Detrusor Muscle
Botox: Pre-op Urodynamic Study
Botox: Post-op Urodynamic Study
Follow-Up at 2 Months

- Anticholinergics discontinued
- Urgency much improved
- Frequency and functional capacity improved
- Still mild urge incontinence, but can hold for >60min
- Needs some straining towards the end of voiding
- QOL definitely improved, just returned from vacation in Japan (1st vacation in many years!)
Overactive bladder (OAB) is a symptomatic diagnosis based on the presence of urgency, with or without urge incontinence, and usually accompanied by frequency and nocturia.

It is a widely prevalent condition and affects men and women equally.

OAB has a significant negative impact on the patient’s quality of life.
Antimuscarinic therapy is the mainstay of treatment for OAB.

Newer agents with increased tissue and M-receptor subtype selectivity have improved patient tolerance and compliance.

They have proven effect on both objective measures and health-related quality of life parameters in OAB treatment.
In assessment of clinical efficacy of OAB treatment, HRQL measures need to be considered.

When non-surgical therapy fails, minimally invasive therapy in the form of intra-detrusor injection of Botulinum Toxin provides a promising way of improving symptoms and quality of life.