Case Consults in Overactive Bladder: An Individualized Approach to Management

3:15 p.m.–4:30 p.m. September 26, 2008 Seattle, Washington
Session 6: Case Consults in Overactive Bladder: An Individualized Approach to Management

Learning Objectives

- Differentiate available agents for the treatment of OAB based on pharmacologic and pharmacokinetic characteristics and the impact these characteristics have on efficacy, safety and tolerability.
- Implement a treatment plan for OAB that balances efficacy, safety and tolerability to improve treatment persistence and quality-of-life.

Faculty

Courtenay Moore, MD
Assistant Professor
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University

Co-director Female Pelvic Medicine & Reconstructive Surgery Fellowship
Cleveland Clinic
Cleveland, Ohio

Courtenay Moore received her medical degree from Albany Medical College in Albany, New York. After completing her internship and residency at Albany Medical College, she completed a fellowship in female pelvic medicine and reconstructive surgery at the Cleveland Clinic, Cleveland, Ohio. During her fellowship, Dr Moore was awarded the American Foundation for Urologic Disease Research Scholarship. She is currently a joint staff member staff at Cleveland Clinic Glickman Urological and Kidney Institute and the Institute of Obstetrics and Gynecology. She is also an assistant professor in the Department of Surgery at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. Dr Moore’s clinical and research interests include pelvic organ prolapse, incontinence, voiding dysfunction, female reconstructive surgery, and female sexual dysfunction. Dr Moore has published extensively in her field and is an active member in the American Urologic Society, Society for Female Urology & Urodynamics, Society for Women in Urology, and the American Urogynecologic Society.

Donna Y. Deng, MD
Assistant Professor
University of California, San Francisco
San Francisco, California

Donna Y. Deng gained her medical degree at the University of California, Davis, then completed her internship and residency in urology at University of California, San Francisco (UCSF). She then completed a fellowship in the area of urinary incontinence, pelvic reconstructive surgery, neurourology, and urodynamics at University of California, Los Angeles (UCLA). Dr Deng is currently assistant professor in residence in the Department of Urology at University of California, San Francisco (UCSF).

Dr Deng’s clinical interests include urinary incontinence, voiding dysfunction, neurourology, and pelvic reconstruction for prolapse and fistula repair. Her research interests involve examining the molecular basis of, and hormonal effects on, incontinence. She is an investigator on the UCSF Specialized Center of Research (SCOR) in Lower Urinary Tract Function grant. The program’s “bench to bedside” collaborative research paradigm facilitates translation of epidemiologic and laboratory research into clinical improvements for the prevention and treatment of incontinence and voiding dysfunction. Dr Deng is also currently actively involved in studying and developing the use of stem cell in the treatment of urinary incontinence and bladder function.

Faculty Financial Disclosure Statements
The presenting faculty reported the following:

Dr Moore has no relationships to disclose.
Dr Deng has no relationships to disclose.
**Education Partner Financial Disclosure Statements**

The content collaborators at Strategic Consultants International have reported the following:

Alison L. Howe, managing director, Sarah H. Diffen, associate project director, Carol Richardson, senior account assistant have nothing to disclose.

**Drug List**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>darifenacin</td>
<td>Enablex</td>
</tr>
<tr>
<td>oxybutynin</td>
<td>Ditropan, Oxytrol</td>
</tr>
<tr>
<td>solifenacin</td>
<td>VESIcare</td>
</tr>
<tr>
<td>trospium chloride</td>
<td>Sanctura</td>
</tr>
<tr>
<td>tolterodine</td>
<td>Detrol</td>
</tr>
</tbody>
</table>

**Off-Label**

| botulinum toxin A | Botox |

**Suggested Reading List**


Case Consults in Overactive Bladder: An Individualized Approach to Management

What is Overactive Bladder (OAB)?

OAB is defined as Urgency... with or without Incontinence... usually with Frequency... and Nocturia.

No infection present or other obvious pathology

Wein AJ et al. Urology. 2002; 60(suppl 5A):7-12

Innervation of the Lower Urinary Tract


OAB and Common Urinary Disorders

Adapted from Wein AJ. Am J Manag Care 2000; 6(11 suppl):S559-S564

Urge versus Stress Incontinence

Smith PP, et al. CMAJ 2006;175(10):1233-1240

Adapted from Holroyd-Leduc JM, et al. JAMA 2004;291(8):986-995

What is Overactive Bladder?

Donna Y. Deng, MD
Assistant Professor
University of California, San Francisco
San Francisco, CA
How Prevalent is OAB?

Adapted from Stewart WF, et al. World J Urol 2003;20:327-336

Prevalence of OAB with Urge Incontinence

Adapted from Stewart WF, et al. World J Urol 2003;20:327-336

Prevalence of OAB versus Other Common Disorders

Adapted from Stewart WF, et al. World J Urol 2003;20:327-336

Impact of OAB on Quality-of-life (QoL)

Cost of OAB in the US (2000)

Costs estimated from the National Overactive Bladder Evaluation (NOBLE) Program

Cost of OAB (Billions $)

- Diagnosis: $77 million
- Indirect costs: $827 million
- Routine care: $1.6 billion
- Treatment: $2.8 billion
- Treatment Consequences: $3.9 billion


Diagnostic Tips: Why OAB Matters

Courtenay Moore, MD
Assistant Professor
Cleveland Clinic Lerner College of Medicine
Cleveland Clinic, Cleveland, OH

Case Scenario 1: New Patient, Long-standing Problem!

- 45-year-old woman attends her PCP for a routine check up. Despite being summer she is wearing dark pants.
- She says she feels “low” and “very tired” – she asks if this is a menopause symptom.

ARS Question

- How confident are you in diagnosing and effectively treating patients with overactive bladder?
  1. Very confident
  2. Confident
  3. Not very confident
  4. Not at all confident

ARS Question

- Why might you suspect OAB?
  1. She wakes 2–3 times during the night
  2. She uses the bathroom ~12 times per day
  3. She is wearing dark pants in summer
  4. She is ‘tired’ and ‘low’
  5. All of the above

Questioning reveals that she wakes 2–3 times a night to use the bathroom; she uses the bathroom ~12 times per day.

Urinalysis was negative for infection.
Postvoid residual volume not measured.

Limited role in neurologically normal female.
Risk Factors for Incontinence That May Also Influence OAB

- Immobility
- Diabetes
- Fecal impaction
- Stroke
- Diminished cognitive status or delirium
- Lumbar disk disease
- Use of diuretics and hypnotics
- Obesity (female)
- Hysterectomy, vaginal or bladder surgery
- Multiple vaginal deliveries
- Urinary tract infections
- Risk factors

Risk of...

- UTIs
- Skin infections
- Falls and fractures
- Depression
- Long-term hospitalization, poorer health outcomes

Greater risk of...

Complications of OAB: Falls and Fractures

Type and frequency of incontinent episodes assessed in 6049 women by questionnaire. Follow-up for falls and fractures every 4 months

Increased risk in OAB patients (%)

Falls: 28%
Fractures: 34%

- Weekly OAB, UI, frequency and nocturia increase the risk of falls and fractures
- Early diagnosis and treatment has the potential to prevent / decrease falls and fractures

OAB: Medical Complications

- Greater risk of...
- UTIs
- Skin infections
- Falls and fractures
- Depression
- Long-term hospitalization, poorer health outcomes

Thoughts of Female Patients Before They Actively Sought Treatment: Results of a US National Survey

- Agreed / strongly agreed (%)*
  - I thought it was something I had to live with 64
  - I did not want to take medications 55
  - I dealt with it by wearing pads 54
  - I was uncomfortable / embarrassed 51
  - I did not feel it was enough of a problem to bother with 51
  - I thought I was too young to have this problem 46
  - I did not want anyone to know 44
  - The healthcare provider I saw did not ask me about OAB or urinary health 44
  - I was not aware anything could be done about it 32
  - I was afraid the doctor might recommend surgery 27

*Respondents included patients currently being treated, lapsed in treatment, and never treated (n=685)

OAB Patients: Reasons for Seeking Treatment

- Concerned that:
  - Condition could get worse
  - Leaks / urine loss is a symptom of a more serious condition
  - Condition is not normal
  - Others may smell odor caused by leakage / involuntary urine loss
  - Possibility of an embarrassing accident

Diagnosis of OAB: History

- The first complaint may not be the chief complaint
- When asking these questions:
  - respect the patient’s situation
  - consider a treatment plan
  - aim for patient-centered medicine

- Do you use absorbent pads to keep from wetting your clothes?
- In an unfamiliar place, do you make sure you know where the restroom is?
- Do you go to the bathroom so often that it interferes with your activities?
- Do you limit fluid intake when away from home so that you don’t need to worry about finding a restroom?
- Do you avoid places without a restroom?

Effective questioning is vital


Diagnosis of OAB: Additional Probing Questions

**URGENCY**
- Do you have to rush to the bathroom?
- Is it a sudden, intense feeling so you have to urinate immediately?

**FREQUENCY**
- Do you feel that you urinate too often during the day?
- Do you urinate >8 times a day?

**INCONTINENCE**
- When you feel the urge to go to the bathroom, do you have leaks or wetting accidents?

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**INCONTINENCE**
- When you feel the urge to go to the bathroom, do you have leaks or wetting accidents?

Differential Diagnostics

<table>
<thead>
<tr>
<th>Presenting Symptom</th>
<th>OAB</th>
<th>Bladder Cancer</th>
<th>Urinary Tract Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urge incontinence</td>
<td>1/3</td>
<td>Occasionally</td>
<td></td>
</tr>
<tr>
<td>Nocturia</td>
<td>Rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>x</td>
<td>Occasionally</td>
<td></td>
</tr>
<tr>
<td>Dysuria</td>
<td>x</td>
<td>Occasionally</td>
<td></td>
</tr>
<tr>
<td>Pyuria</td>
<td>x</td>
<td>Rare</td>
<td></td>
</tr>
</tbody>
</table>

Assessment of OAB

**Symptoms**
- Onset
- Duration
- Severity
- But hersomeness

**Medical History**
- Neurological
- Gastrointestinal
- Dietary
- Previous surgery
- Obstetric
- Medications

**Physical Exam**
- Neurological
- Pelvic
- Rectal
- Menstrual status
- Weight / BMI
- Abdomen
- Gastrointestinal

**Laboratory**
- Urinalysis
- Urine culture
- PSA* in age-appropriate men

**Additional / Optional**
- Voiding diary
- Post residual volume
- Cystoscopy
- Uroflowmetry

Medication May Worsen Symptoms of OAB

Sedatives
- Alcohol, caffeine, diuretics
- Anticholinergics
- Other than antimuscarinics (e.g., antidepressants)
- α-agonists
- β-blockers
- Calcium channel blockers
- ACE inhibitors
- Cholinesterase inhibitors

More than half of women surveyed who discussed OAB with their PCP waited >1 year before raising the issue
- Many attempted self-management of symptoms
- 85% of women had to raise the issue with their physician
- Only 34% of patients diagnosed with OAB receive treatment
Case Scenario 1 Continues

- She knows the exact location of the restrooms in your practice
- Often has urgency and sometimes buys pads
- Rarely incontinent but worries she “might be”
- A diagnosis of OAB and a decision to treat is made

Tailoring Therapy to Meet Individual Needs

Donna Y. Deng, MD
Assistant Professor
University of California, San Francisco
San Francisco, CA

ARS Question

- What is your first-line treatment?
  1. Antimuscarinic agent
  2. Behavioral modifications – “bladder training”
  3. Kegel exercises
  4. All of the above

Specific Aims of Treatment

For urge incontinence
- Eliminate (ideally) incontinence episodes
- Reduce / eliminate pad use

For daytime frequency
- Reduce frequency of bathroom visits
- Reduce impact on daily activities

For urgency
- Improve ability to control need to void
- Reduce reliance on being “near a bathroom”

Goals of therapy


Non-pharmacological Interventions for OAB

Frequent urination leads to detrusor overactivity. The following interventions may be helpful

**Behavioral modification**
- Bladder control training
  - Voiding habits
  - Bladder diaries
- Pelvic-muscle exercises
  - Identify, isolate, contract, relax
  - Biofeedback
  - Electrical stimulation

**Surgical procedures**
- Sacral nerve stimulation
- Botulinum Toxin A
- Augmentation cystoplasty

**Non-pharmacological Interventions for OAB: Behavioral Modifications**

Burgio KL. *Am J Men’s Health* 2009;3(3):75-86

Bladder control training
- Learn “timed voiding” (by gradually increasing length of time between trips, patients can train bladder to hold more and go less)
- Bladder diaries

Pelvic-muscle exercises
- Also called Kegel exercises
- Improvement of urethral resistance and urinary control
- Primary treatment intervention for stress incontinence (SI)

- Patients with severe symptoms are refractory to behavioral treatment

Burgio KL. *J Am Acad Nurse Pract* 2004; 16(10 Suppl): 4-7
Burgio KL. *Urology* 2003; 60(Suppl 1): 72-6
Pelvic Floor Muscle (Kegel) Exercises

- Reducing stress urinary incontinence (20% cure, 50–70% improvement rate)
- Aims to prevent sudden falls in urethral pressure by a change in pelvic floor muscle morphology, position, neuromuscular function
- Leads to a decline in detrusor and increase in urethral pressures and suppression of the micturition reflex
- Involves:
  - isolation of pelvic floor muscle contraction and elimination of co-activation strategies
  - muscle training of the levator ani
  - automatization of pelvic floor muscle activity in daily life

Di Benedetto, Minerva Ginecol 2004;56(4):353-369

Non-pharmacological Therapy: Reduction of Frequency of Incontinence Episode

Women aged 52–92 years with urge urinary incontinence or mixed incontinence with urge as predominant pattern

4 sessions (8 weeks) of biofeedback assisted behavioral treatment

<table>
<thead>
<tr>
<th>Biofeedback</th>
<th>Oxybutynin 2.5–5 mg tid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction (%)</td>
<td>-100</td>
<td>-80</td>
</tr>
<tr>
<td>(n=62)</td>
<td>(n=65)</td>
<td>(n=63)</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td>p&lt;0.05</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>


Additive Effect of Combining Behavioral and Drug Therapies

Mean reduction in UI (%) | Behavioral therapy | Drug therapy |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=8)</td>
<td>(n=27)</td>
<td></td>
</tr>
</tbody>
</table>
| 4 sessions (8 weeks) behavioral training followed by behavioral training plus drug therapy (Combined therapy) p<0.05
| Drug therapy first then behavioral therapy added (Combined therapy) p=0.001 |


Location and Role of M1, M2, M3 Muscarinic Receptors

- Cerebral cortex
- Hippocampus
- Salivary glands
- Ciliary muscle
- Eyes
- Smooth muscle (bronchus)
- Cardiac muscle
- Eyes
- Smooth muscle (bladder, bowel)
- Salivary glands
- Brain
- Hind brain

Impacts:
- Memory, cognitive function
- Saliva, tear secretion
- Bladder contraction*
- Bowel motility
- Saliva, tear secretion
- Visual accommodation

*Primary mediators detrusor contractility in the bladder


Comparison of Anticholinergic OAB Medications

<table>
<thead>
<tr>
<th>Affinity* for muscarinic receptor subtypes</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normally crosses BBB</td>
<td>Yes</td>
<td>Tertiary amine</td>
<td></td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>1.0</td>
<td>6.7</td>
<td>0.67</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>3.0</td>
<td>3.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>7.3</td>
<td>46.0</td>
<td>0.79</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>25</td>
<td>125</td>
<td>10</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>0.79</td>
<td>0.65</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Binding affinity estimates (K, in nM)


Treatments for OAB: Antimuscarinic Agents

- Oxybutynin
- Tolterodine
- Trospium
- Solifenacin
- Darifenacin
Anticholinergic Medications for OAB: Receptor Affinity

<table>
<thead>
<tr>
<th>Medication</th>
<th>M3:M1 selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>Non-selective (M3:M1=1.5:1)</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Non-selective (M3:M1=0.6:1)</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>M3 (M3:M1=9:1)</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Non-selective (M3:M1=2.5:1)</td>
</tr>
<tr>
<td>Trospium</td>
<td>Non-selective (M3:M1=1.5:1)</td>
</tr>
</tbody>
</table>

Ikeda K, et al. Naunyn Schmiedebergs Arch Pharmacol 2002;266: 97-103

Treatment for OAB: Oxybutynin

Structure: Tertiary amine

Metabolism: Cytochrome P450, P3A4; active metabolite desethyloxybutynin

Selectivity: Non-selective

Dosing: 5 mg, 10 mg, 15 mg qd (approved ≤ 30 mg qd)


Treatment for OAB: Oxybutynin ER

Efficacy: Mean change from baseline

Safety / tolerability (10 mg)
- Dry mouth: 29%
- Constipation: 7%
- Headache: 6%
- Blurred vision: 1%
- CNS adverse events:
  - somnolence: 2%
  - dizziness: 4%


Treatment for OAB: Oxybutynin Transdermal System

Metabolism: Active metabolite desethyloxybutynin

Dosing: Transdermal, twice-weekly (delivery rate 3.9 mg/d)

Safety / tolerability
- Dry mouth: 4.1%
- Constipation: 3.3%
- Application site reactions
  - Mild: 7.4%
  - Moderate: 14%
  - Severe: 5%


Treatment for OAB: Tolterodine

Structure: Tertiary amine

Metabolism: Cytochrome P450 2D6; active metabolite 5-OH-methyl derivative

Selectivity: Non-selective, M1, M2 and M3 (8x lower affinity than oxybutynin*)

Dosing: 2 mg, 4 mg qd

*Tested in guinea pig parotid gland


Treatment for OAB: Tolterodine

Efficacy: Double-blind RCT* (12 weeks)

Safety / tolerability (2 mg bid)
- Dry mouth: 35%
- Constipation: 7%
- Headache: 7%
- CNS adverse events:
  - somnolence: 3%
  - dizziness: 5%
- CV adverse events:
  - prolongation of QT interval with 2 mg bid and 4 mg bid doses

Mean change from baseline
- *RCT = randomized controlled trial
- *Statistically significant difference from placebo; p value not specified

## Treatment for OAB: Trospium Chloride

<table>
<thead>
<tr>
<th>Structure</th>
<th>Quaternary amine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>Excretion</td>
<td>70% cleared renally; 20% excreted unchanged</td>
</tr>
<tr>
<td>Selectivity</td>
<td>Non-selective</td>
</tr>
<tr>
<td>Dosing</td>
<td>ER 60mg qd (≥1 hour before meals or on empty stomach)</td>
</tr>
</tbody>
</table>

**Physicians’ Desk Reference. 61st ed. Thomson PDR: 2007**

### Efficacy
- Double-blind parallel group RCT (12 weeks)

### Safety / Tolerability
- Dry mouth: 20.1%
- Constipation: 9.6%
- Headache: 4.2%
- CV adverse events: no prolongation of QT interval with trospium

Mean change from baseline

**RCT = randomized controlled trial; *p <0.05; **p < 0.001 vs placebo**

## Treatment for OAB: Solifenacin

<table>
<thead>
<tr>
<th>Structure</th>
<th>Tertiary amine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>Cytochrome P450; active metabolite 4R-hydroxy solifenacin</td>
</tr>
<tr>
<td>Half-life</td>
<td>40.2–57.6 hrs</td>
</tr>
<tr>
<td>Selectivity</td>
<td>M1–M3 selective vs M2</td>
</tr>
<tr>
<td>Dosing</td>
<td>5 mg, 10 mg qd</td>
</tr>
</tbody>
</table>


### Efficacy
- Double-blind parallel group multicenter RCT (12 weeks)

### Safety / Tolerability
- Dry mouth: 10.9%
- Constipation: 5.4%
- Blurred vision: 3.8%
- CNS adverse events: dizziness: 1.8%
- CV adverse events: prolongation of QT interval with 10 mg and 30 mg doses

Mean change from baseline

**RCT = randomized controlled trial; *p<0.05 vs placebo; **p<0.01; ***p<0.001 vs placebo**

## Treatment for OAB: Darifenacin

<table>
<thead>
<tr>
<th>Structure</th>
<th>Tertiary amine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>Cytochrome P450 3A4 and 2D6</td>
</tr>
<tr>
<td>Selectivity</td>
<td>High affinity for M3</td>
</tr>
<tr>
<td>Dosing</td>
<td>7.5 mg, 15 mg qd</td>
</tr>
</tbody>
</table>

**Physicians’ Desk Reference. 61st ed. Thomson PDR: 2007**

### Efficacy
- Double-blind multicenter RCT (12 weeks)

### Safety / Tolerability
- Dry mouth: 20.2%
- Constipation: 14.8%
- CNS adverse events: dizziness: 0.9%
- CV adverse events: no prolongation of QT interval with darifenacin

Mean change from baseline

**RCT = randomized controlled trial; *p<0.05 vs placebo**
Treatment for OAB: Effect of Darifenacin on Urgency

- Multicenter, double-blind, randomized, placebo-controlled study (n=439)
  - 12 weeks of treatment
    - 15 mg/day; percentage change from median baseline
- Urgency severity decreased by 17%**
- Urgency episodes decreased by 29%**
- Micturition frequency decreased by 15%***

**p<0.01, ***p<0.001 vs placebo (Wilcoxon test)


Dosing of Treatments for OAB

- Once-daily dosing is preferable for compliance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>7.5 mg (or 15 mg qd if required)</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>5 mg (or 10 mg qd if required)</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>4 mg qd</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>5 mg bid, tid, qid</td>
</tr>
<tr>
<td>Trospium chloride</td>
<td>ER 5, 10, 15 mg qd (up to 30 mg qd)</td>
</tr>
</tbody>
</table>

Yagoda SB, Br J Pharmaco 2006;147 (Suppl 2):S80-87


ARS Question

Which treatment would you prescribe for our 45-year-old woman?
1. Oxybutynin
2. Tolterodine
3. Darifenacin
4. Solifenacin
5. Trospium

Achieving Continence with Acceptable Tolerability

Courtney Moore, MD
Assistant Professor
Cleveland Clinic Lerner College of Medicine
Cleveland Clinic, Cleveland, OH

Case Scenario 2: An Older Patient with Ongoing Symptoms

- 65-year-old female patient tells you during a routine BP assessment that she had an incontinence episode trying to get to the bathroom

- Several years ago she was prescribed oxybutynin but seldom took them due to dry mouth

Co-morbidities in Elderly Patients with OAB

- Diagnosed comorbid condition (%)


Nitti VW, Rev Urol 2002; 4 Suppl (4): S2-6
Tolerability of OAB Treatments

- Side-effects of anti-cholinergics
  - Dry mouth
  - Constipation
  - Urinary retention
  - Gastro-esophageal reflux
  - Blurred vision
  - Cardiovascular effects
  - Cognitive effects

Staskin DR, Drugs Aging 2005; 22(12):913-38

Contraindications of Antimuscarinic Therapy

- Uncontrolled narrow-angle glaucoma
- Gastric retention
- Urinary retention
- Patients who are at risk of these

Case Scenario 2 (Cont’d)

- After reading the prescribing information, the patient returns concerned that “OAB medications cause memory loss and heart problems”
- Her sister has Alzheimer’s disease and she doesn’t “want to go the same way”
- She is also concerned about her BP medications

What are the Similarities and Differences Between OAB Treatments?

- Delivery systems
- Pharmacokinetics and metabolism
- Muscarinic receptor selectivity
- Dosing schedules
- Efficacy and tolerability
- Product information – safety warnings

Comparison of M₃ Selectivity of OAB Agents: Relative Binding Affinity

<table>
<thead>
<tr>
<th></th>
<th>M₃ vs M₁</th>
<th>M₃ vs M₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>2.6</td>
<td>12</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>0.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Galantamine</td>
<td>1.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Propiverine</td>
<td>0.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>1.5</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Heading CE, Curr Opin Invest Drugs 2006;3:321-325

M₃ Receptor Selectivity: Advantages

- Maintained efficacy
- Less severe dry mouth
- No effects on HR
- Fewer cognitive AEs

M₃ is the primary functional receptor in detrusor
M₁ and M₂ are evident in salivary glands; M₃ selectivity may result in lower severity than combined antagonism
Tachycardia is related to M₂ antagonism
M₁ is involved in cognition

Cognitive Performance: Oxybutynin vs Diphenhydramine

Double-blind placebo-controlled crossover study to assess cognitive function in 12 patients aged 65–76 years old, taking oxybutynin IR 5 mg or oxybutynin IR 10 mg or diphenhydramine 50 mg.

Random regression analysis showed:
- Significant impairment in memory and speed with oxybutynin (7/15 measures)
- Significant cognitive impairment with diphenhydramine (5/15 measures)

*Selective reminding
*Digit symbol substitution
*Reaction time
*Pattern memory

Diphenhydramine used as positive control.

OAB Medications: CNS Impairment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Self-reports: Diary data</th>
<th>Surrogate physiological data: EEG, sleep</th>
<th>Performance: Cognitive data</th>
<th>Case reports &amp; post-marketing surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>N/A</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Trospium</td>
<td>X</td>
<td>X</td>
<td>Uncertain</td>
<td></td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Uncertain</td>
<td>X</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

N/A = not available

Cardiac Safety: QT Interval Prolongation

- QT interval prolongation can cause potential adverse outcomes:
  - Cardiac syncope and sudden death
  - Torsades de pointes
  - Associated with congenital prolonged QT syndromes
  - Also associated with drug effect in certain instances

- FDA approval requires post-marketing surveillance to exclude the possibility of fatal arrhythmia

Antimuscarinics: Mean QTcF Increase From Baseline

<table>
<thead>
<tr>
<th>Medication</th>
<th>Therapeutic dose 2-4 x therapeutic dose</th>
<th>Mostifloxacin (positive control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>No increase</td>
<td>No increase</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>2 (-3.6) msec</td>
<td>8 (4, 13) msec</td>
</tr>
<tr>
<td>Trospium</td>
<td>No increase</td>
<td>No increase</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1.16 (-2.99, 5.3) msec</td>
<td>5.63 (1.48, 9.77) msec</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Post marketing reports</td>
<td></td>
</tr>
</tbody>
</table>

FDA guidance states that a >5 msec to <20 msec QT prolongation is inconclusive in regards to risk of arrhythmia.

Treatment with Antimuscarinic Agents for OAB: Summary

- Higher affinity for M3 receptor subtype results in...
- Fewer cognitive AEs
- Fewer visual AEs
- Less dry mouth
- Fewer cardiovascular AEs

Which treatment would you prescribe for the 65-year-old woman in our second case study?

1. Oxybutynin
2. Tolterodine
3. Darifenacin
4. Solifenacin
5. Trospium
Case Scenario Challenge

What if the patient was male?

Differentiating OAB From Benign Prostatic Hyperplasia (BPH)

- Storage and/or voiding symptoms are commonly suffered by male patients
- Treatment of lower urinary tract symptoms most commonly begins by targeting outlet symptoms of BPH
- Accurate identification of the underlying cause is vital


Initial Evaluation for OAB

Physical exam:
- Abdominal exam: Evaluate for tenderness or masses
- Digital rectal exam: Evaluate rectal tone, prostate size, shape and consistency and detect prostatic implications in symptoms
- Neurological exam

Laboratory tests:
- Urinalysis or microscopic exam: Check for blood, protein, glucose or signs of infection
- Prostate-specific antigen (PSA) offered to age-appropriate males; refer if abnormal
- Blood sugar testing suggested
- Urine cytology (optional)

AUA Guideline on the management of benign prostatic hyperplasia 2003

Indications for Referral

- History of recurrent urinary tract infections or other infection
- Microscopic or gross hematuria
- Prior genitourinary surgery
- Elevated prostate-specific antigen
- Abnormal prostate exam (nodules)
- Suspicion of neurologic cause of symptoms
- Findings or suspicion of urinary retention
- Meatal stenosis
- History of genitourinary trauma
- Uncertain diagnosis
- Pelvic pain


OAB Medications in Male Patients

- Muscarinic receptor antagonists
  - only therapy currently approved for OAB
  - lower urinary tract symptoms (LUTS) due to OAB

Concern that antimuscarinics theoretically impair detrusor contractility
- may cause urinary retention in men

Behavioral therapy

Key Questions Covered

- What is overactive bladder (OAB)?
- How prevalent is OAB?
- What is the impact of OAB?
- How does OAB impact on patients’ quality-of-life?
- How is OAB diagnosed?
- What treatments are available for OAB?
- How do these treatments compare?