Overactive Bladder: A Look at the Efficacy of Treatment and Managing Side Effects

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Disclosures

• Pfizer – advisory board, speaker, clinical trials
• Allergan – advisory board, speaker
• Astellas – advisory board

• Jones and Bartlett – Author
  – 100 Questions and Answers: Overactive bladder and Incontinence
  – 100 Questions and Answers: Overactive bladder
Learning Objectives

• Review the new AUA/SUFU guidelines on the evaluation and management of OAB
• Review the efficacy of OAB therapies, based on cause of symptoms
• Discuss methods for managing adverse effects that affect patient compliance
• Identify new treatments available

The Overactive Bladder Complex

- Urgency – sudden compelling desire to void that is difficult to defer
- Frequency – 8 or more micturitions per day
- Nocturia – awakening at Night 1 or more times to void
- Urge Incontinence – Incontinence assoc with urgency

Micturition Process

Normal Micturition Process

- Increasing bladder volume
- 1st Sensation
- Void

Intervoid Interval

Volume Voided

Micturition Process in OAB

- Increasing bladder volume
- Urgency episode
- Void (voluntary or involuntary)
- Reduced void
- Presumed normal void
- Reduced volume voided

Time

Deferment time

Multiple Etiologies Involved in OAB:
The Role of Afferent Pathways

Pathophysiology of detrusor overactivity and OAB

- Decreased capacity to handle afferent information
- Decreased suprapontine inhibition
- Increased afferent activity
- Increased sensitivity to released contraction - mediating transmitter

Adapted from Chapple CR et al. BJU Int. 2005;95:335-341.

Risk Factors for OAB

- The most common risk factor for OAB is increasing age
- Other common risk factors include:
  - Obesity
  - White people are at greater risk
  - Depression is associated with OAB
  - Individuals on hormone replacement therapy
  - Neurogenic OAB may be secondary to
    - Multiple sclerosis
    - Parkinson’s disease
    - Dementia
    - Spinal cord injury
    - CVA
    - Diabetes

Impact of Overactive Bladder on Quality of Life

- Physical
  - Limitations or cessation of physical activities

- Psychological
  - Guilt/depression
  - Loss of self-esteem
  - Fear of
    - Being a burden
    - Lack of bladder control
    - Urine odor

- Social
  - Reduction in social interaction
  - Limit and plan travel around toilet accessibility

- Occupational
  - Absence from work
  - Decreased productivity

- Domestic
  - Require specialized underwear, bedding
  - Special precautions with clothing

Tubaro A. Urology. 2004;64(suppl 1):2-6.
OAB Is Associated With Decreased QOL And Increased Morbidity

• OAB is associated with:
  – Decreased sexual function
  – Sleep disturbances
  – Decrease in normal activities
  – Fear of stigmatization
  – Poorer health status, more visits to physician and increased health risks
    • Individuals with OAB have an ave of 84% more annual visits to a physician than those without OAB (7.781 vs 5.97; p<0.05)


OAB Is Associated with Increased Morbidity

• OAB is associated with
  – Falls and fractures
  – Depression

• OAB places people at greater risk for:
  – Urinary tract infections (UTIs)
  – Perineal dermatitis

OAB Has a Considerable Impact on QoL

- Healthy
- Diabetes
- Depression
- OAB

OAB: Falls and Fractures

- Weekly OAB, UI increase risk of
  - Falls, 26%
  - Fractures, 34%
- Associated with frequency and nocturia
- Early diagnosis and treatment can potentially prevent or decrease falls and fractures

OAB-related risks

• UUI increases risk of hospitalization (30% increased risk for women, 50% for men) & elderly of being admitted to nursing homes (Brown J 2000; Thom DH et al. 1997)

• Strong association btn OAB and depression, 60% of individuals with OAB suffer from depression (Zorn BH, Montgomery H, Pieper K, Gray M, Steers WD, 1999)

Why are So Few OAB Sufferers Diagnosed and So Few Treated?

• Patients don’t discuss with physician
  – Embarrassment
  – Fear of invasive procedures or need for surgery
  – Perception of lack of available treatment
• Physician doesn’t ask
  – Too busy
  – One more thing to screen for
  – Don’t understand the impact
  – Not life-threatening
  – Patient will bring it up if bothered

Differential Diagnosis

• Polydipsia
  – frequency occurs with nl or large volume voids and intake is matched

• Interstitial cystitis/bladder pain syndrome
  – bladder pain and/or pelvic pain (incl dyspareunia) key component

• Nocturnal polyuria
  – > 20-33% of total 24 hr urine output during sleep
    • Sleep disturbances, vascular and/or cardiac disease and other medical conditions often assoc with nocturnal polyuria

Evaluating OAB –AUA/SUFU Guideline

• Diagnostic process to document symptoms and signs that characterize OAB

• Exclude other disorders that could be the cause of the patient’s symptoms

• Minimum requirement – careful history, physical examination and urinalysis
OAB Symptoms

Evaluating OAB – A Simplified Approach

Initial Evaluation
- Focused history
- Exam focused physical
  - Abdominal
  - Pelvic
  - Neurologic
- Urinalysis
- Degree of bother

Supplemental Aids
- Bladder diary
- Post void residual
- GOAL – to rule out other conditions which may cause/mimic OAB

Further Evaluation

- Urodynamics, cystoscopy, US not indicated in initial eval of uncomplicated pt.

- Postvoid residual –
  
  Not necessary – if being treated with first-line behavioral interventions or uncomplicated patients

  Necessary - obstructive sx, hx of incontinence or prostatic surgery, neurologic dz and in men with sx prior to starting antimuscarinic therapy

(Gormley EA et al. Diagnosis and Treatment of Overactive Bladder (Non-neurogenic) in Adults: AUA/SUFU Guideline. www.auanet.org)
A Super Simple Approach to Screening

• First simply ask

  Is your bladder causing you any problems?

  Do you have trouble controlling your urine?

Indications for Referral to Urologist

• Hematuria – microscopic or gross
• Significant pelvic organ prolapse
• Recurrent UTIs
• Increased post void residual
• Failure to improve with medical therapy
• Prior pelvic surgery
Treatment of OAB

Management Strategies and Patient Education

- Education regarding normal bladder function
- OAB is a symptom complex with variable and chronic course
- Setting patient expectations
  - Getting better versus getting cured
  - Often task oriented for patient instead of number (ie watch a movie without interruption)

First- Line Treatments: 
Behavioral Therapies

- Education
- Diet
- Modifying bladder function by changing voiding habits
  - Timed voiding
  - Delayed voiding
- Behavioral training
  - Pelvic floor muscle therapy
  - Biofeedback


Dietary Regulation

- Fluids
  - Alcoholic beverages
  - Carbonated beverages
  - Soda—caffeine
  - Milk—milk products
  - Coffee—even decaffeinated
  - Tea
  - Citrus juice
  - Fluid restriction
  - WATER IS THE BEST

- Foods
  - Citrus fruits
  - Tomatoes
  - Tomato-based products
  - Highly spiced foods
  - Sugar
  - Honey
  - Chocolate
  - Corn syrup
  - Artificial sweeteners
Impact of Behavioral Modifications

- 8% weight loss in obese women reduced incontinence episodes per week by 47% (28% in control group), decreased UUI episodes by 42% (26% in controls)
- 25% reduction in fluid intake reduced frequency and urgency
- Reducing caffeine intake decreases voiding frequency

Behavioral Therapies

- Generally equivalent to or superior to medications in reducing incontinence episodes, improving voiding parameters and QoL

Additive Effect of Combining Behavioral And Drug Therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Reduction in UI, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral</td>
<td>-57.5%</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Combined Therapy</td>
<td>-88.5%</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>-72.7%</td>
<td>.001</td>
</tr>
<tr>
<td>Combined Therapy</td>
<td>-84.3%</td>
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</table>

Second-Line Treatments

- Anti-Muscarinics
- Beta-Agonists
Muscarinic Receptor-Mediated Effects In the Detrusor

• In the detrusor, the postjunctional \( M_3 \) receptor is the predominant subtype mediating contraction
• Role of \( M_2 \) not fully understood
• \( M_3 \) receptor antagonism
  – Stabilizes bladder (detrusor) muscle
  – Increases bladder capacity
  – Diminishes frequency of involuntary bladder contractions
  – Delays initial urge to void


Pharmacologic Therapy: The Evolution of Anti-Muscarinics

• 1965 – Oxybutynin
• 1998 – Tolterodine IR, Oxybutynin ER
• 2000 – Tolterodine ER
• 2003 – Transdermal Oxybutynin
• 2004 – Trospium chloride, Solifenacin, Darifenacin
• 2007 - Trospium chloride once daily (Sanctura XR)
• 2008 (Nov) – Fesoterodine (Toviaz)
• 2009 (Jan) – Oxybutynin gel (Gelnique)
Not All Antimuscarinic Agents Are the Same

• All antimuscarinics are effective for treatment of OAB symptoms
• Individual differences exist in the profiles of antimuscarinics
• There is some evidence of differences among AE profiles
• There are differences in tolerability profiles


Similarities and Differences Between the Different Anticholinergic Agents

• Method of Delivery
• Dose flexibility
• Efficacy
• Tolerability
• Safety
**Comparison of Agents**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>DELIVERY</th>
<th>MECH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>7.5mg, 15mg</td>
<td>pill</td>
<td>Can’t cut, crush, chew</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>4mg, 8mg</td>
<td>pill</td>
<td>Can’t cut, crush, chew</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>3.8mg -30mg</td>
<td>pill, liquid, patch, gel</td>
<td>Patch 2x/wk, gel QD, oral once(XL) to TID (IR)</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>5mg, 10mg</td>
<td>pill</td>
<td>Can’t cut, crush, chew</td>
</tr>
<tr>
<td>Tolterodine LA</td>
<td>2mg, 4mg</td>
<td>pill</td>
<td>Can open</td>
</tr>
<tr>
<td>Trospium chloride XR</td>
<td>60 mg</td>
<td>pill</td>
<td>Can’t cut, crush, chew – can’t pm dose</td>
</tr>
</tbody>
</table>

**Comparison Amongst Agents**

- Study populations may differ in severity of symptoms amongst the trials thus cannot compare results of different studies

- Comparator studies are often switch studies

- The majority of comparison studies are noninferiority studies

- The only placebo controlled superiority study was that comparing Detrol LA 4mg to Toviaz 8mg to placebo
  - Toviaz 8mg superior to Detrol LA 4mg in reducing UUI episodes
Gormley et al. AUA/SUFU guideline. www.auanet.org
AUA/SUFU OAB Guidelines

• Transdermal oxybutynin (patch or gel) is effective in reducing incontinence episodes, with dry mouth rates that appear to be lower than with oral oxybutynin IR or ER

(Gormely EA et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU Guideline. www.auanet.org)

Pearls in Treating Patients with OAB

• Identify most bothersome symptom

• Make sure patient’s expectations are realistic

• Start low and titrate up as needed

• Most patients will see some benefit within 2 wks, but it will often take at least 4 wks for maximum response – pts need to modify behavior also

• Be proactive about preventing/treating side effects
Pearls in Treating Patients with OAB

- If a pt has failed prior antimuscarinic therapy, start with an agent that has more than one dose
- Night-time dosing may help decrease adverse effects but should not be used with tropsium chloride
- Pts who are refractory to behavioral and medical therapy should be evaluated by an appropriate specialist (AUA/SUFU guidelines. www.auanet.org)

What Type of Improvement Can A Patient Expect?

- Reduction in UUI – up to 90% reduction in UUI
- Reduction in micturition frequency – endpoint is not zero but normalization – about 2 - 3 less voids/day
- Dry rates (3-day diary) – rates will vary with baseline severity – typically 50 – 64% (less with more severe UUI and greater with less severe UUI)
Patient-reported reasons for discontinuing overactive bladder medication

• Expectations about treatment efficacy and side-effects are the most important considerations in discontinuing OAB medications for most patients
• 11% noted general aversion to taking medication
• Interventions to promote realistic expectations about rx efficacy and side-effects may enhance adherence

Precautions to Use of Anticholinergics

Contraindicated in Pts with
• Urinary retention
• Gastric retention
• Uncontrolled narrow angle glaucoma
• Known hypersensitivity to the drug or its ingredients

Use with caution in pts with
• Clinically significant bladder outlet obstruction
• Decreased GI motility
• Controlled narrow angle glaucoma
• Myasthenia gravis
Beyond the Bladder

Adverse Events of Antimuscarinic Agents

Key Muscarinic Receptors

Iris/ciliary body $M_4$
Lacrimal gland $M_3$
Salivary glands $M_3$
Heart $M_2$ (heart rate)
Gallbladder $M_3$
Stomach $M_4$
Colon $M_3$
Bladder $M_3$ (detrusor muscle)

AUA/SUFU Guidelines

“Clinicians should manage constipation and dry mouth before abandoning effective antimuscarinic therapy”

Minimizing AEs in Patients on Anticholinergics for OAB

• Baseline bowel function
  – Ask about bowel frequency and stools
  – Many pts fluid restrict in hopes of decreasing frequency, incontinence
  – If infrequent stools/constipation
    • Increase fluid intake
    • Increase dietary fiber
    • Osmotic laxative
    • No improve consider GI evaluation
  • (Toney, Agrawal. Practical Gastroenterology, May 2008)
Don’t Just Ask Are You Constipated? Character and Frequency

Minimizing AEs in Patients on Anticholinergics for OAB- Xerostomia

- [www.essology.com](http://www.essology.com) has a 23 page list of medications that can cause xerostomia
- Tips for treating dry mouth
  - Sips cool water throughout the day
  - Drink milk – lubricates oral mucosa
  - Restrict caffeine and alcohol intake both cause dry mouth
  - Use of sugar-free gum stimulates saliva flow
  - Saliva sure tables, oral balance, biotene toothpaste, recaldent
Xerostomia Therapies

Anti-muscarinic Therapy and the Frail OAB patient- AUA/SUFU Guideline

• “caution in prescribing antimuscarinics in frail OAB pt (mobility deficits, weight loss and weakness without medical cause and who may have cognitive deficits”
  – Use of OAB meds may have a lower therapeutic index and a higher adverse drug event profile
  – Begin with lowest possible dose and increase slowly

Gormley et al. www.auanet.org
What Happens When An Anticholinergic Agent Fails

- Is the failure due to lack of efficacy or intolerable side effects?
- Is the patient using the highest tolerable dose?
- Is behavioral therapy being utilized?
- Have you identified the patient’s expectations?
- Are the patients expectations realistic?

Options When An Anticholinergic Agent Fails

- Try another anticholinergic agent, one with ability to dose escalate
- Add/optimize behavioral therapy
- Try Mirabegron – beta agonist for OAB
- Third Line therapies
  - Neuromodulation – approved for OAB
  - Botulinum toxin injection -recently approved for NDO
  - Bladder augmentation – last resort
Mirabegron

- Selective beta-3 adrenoceptor agonist
- Activates beta-3 adrenoceptor on the detrusor muscle of bladder to facilitate filling of bladder and storage
- Does not affect detrusor contractility
- Recently approved by the FDA
Mirabegron – Prescribing Information

- Starting dose – 25mg with or without food
- Effective within 8 wks, may increase to 50mg
- Do not cut, crush or chew
- Max dose 25mg with severe renal impairment or moderate hepatic impairment
- ESRD and severe hepatic impairment – not recommended
- Mirabegron is a CYP2D6 inhibitor
- May increase BP – BP checks rec – don’t use in severe uncontrolled HTN
  - (prescribing information Mirabegron (Myrbetriq), Astellas)

Clinical Trials of Mirabegron

- Multicenter Randomized, double-blind, parallel group PBO trials, 1 in US/Canada (1329 pts) and other in Europe/Australia (1987 pts)

- Co-primary endpoints
  - 1. change from baseline to wk 12 in mean # of UUIs/24 hrs
  - 2. change from baseline to wk 12 in mean # micturitions/24 hrs

- Secondary endpoints
  - Change from baseline to wk 12 mean vol voided
  - Change from baseline to wk 4 mean # UUIs/24 hrs
  - Change from baseline to wk 4 mean # micturitions/24 hrs

- Impact on QoL assessed
  - (EAU 26th Annual Congress: Posters 885 and 886. March 21, 2011)
Clinical Trials of Mirabegron (Astellas): Primary and Secondary Endpoints
Adjusted Mean$^*$ (standard error) Change from Baseline

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>PBO</th>
<th>Mirabegron 50mg</th>
<th>Mirabegron 100mg</th>
<th>PBO</th>
<th>Mirabegron 50mg</th>
<th>Mirabegron 100mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-Primary endpts at end of trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># incontinence episodes</td>
<td>-1.13</td>
<td>-1.47$^*$</td>
<td>-1.63$^*$</td>
<td>-1.17</td>
<td>-1.57$^*$</td>
<td>-1.46$^*$</td>
</tr>
<tr>
<td></td>
<td>(0.112)</td>
<td>(0.114)</td>
<td>(0.117)</td>
<td>(0.113)</td>
<td>(0.113)</td>
<td>(0.115)</td>
</tr>
<tr>
<td># micturitions/ 24 hrs</td>
<td>-1.05</td>
<td>-1.66$^*$</td>
<td>-1.75$^*$</td>
<td>-1.34</td>
<td>-1.93$^*$</td>
<td>-1.77$^*$</td>
</tr>
<tr>
<td></td>
<td>(0.132)</td>
<td>(0.133)</td>
<td>(0.135)</td>
<td>(0.110)</td>
<td>(0.111)</td>
<td>(0.110)</td>
</tr>
<tr>
<td>Key secondary endpts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume voided/ micturition (ml) at final visit</td>
<td>7.0 (2.41)</td>
<td>18.2$^*$ (2.44)</td>
<td>18.0$^*$ (2.47)</td>
<td>12.3 (1.99)</td>
<td>24.2$^*$ (2.01)</td>
<td>25.6$^*$ (2.00)</td>
</tr>
<tr>
<td># incontinence episodes/24 hrs at wk 4</td>
<td>-0.72 (0.116)</td>
<td>-1.20$^*$ (0.119)</td>
<td>-1.18$^*$ (0.122)</td>
<td>-0.65 (0.118)</td>
<td>-1.04$^*$ (0.118)</td>
<td>-1.03$^*$ (0.120)</td>
</tr>
<tr>
<td># micturitions/24 hrs at wk 4</td>
<td>-0.77 (0.127)</td>
<td>-1.19$^*$ (0.129)</td>
<td>-1.37$^*$ (0.131)</td>
<td>-0.77 (0.096)</td>
<td>-1.16$^*$ (0.097)</td>
<td>-1.29$^*$ (0.096)</td>
</tr>
</tbody>
</table>

$^*$ Least-square means adjusted for baseline, sex and geographical region.

*Session 8: Mirabegron – Adverse Events – Phase III trials

- No significant CV events in the mirabegron groups
- Overall incidence HTN similar across groups
- No effect on QT interval
- Dry mouth, sim to PBO 3%, tolt 10%
- Overall, treatment-emergent AEs similar btn PBO, mirabegron (50 and 100mg) and tolt

(EEU 26th Annual Congress: Posters 885 and 886. March 21, 2011)
Surgical Procedures: Sacral Nerve Stimulation (Neuromodulation)

- 2-step process
  - Initial test stimulation
  - If good response, permanent stimulator implanted
- Small doses of electric current sent to sacral nerve
- FDA approval
  - 1997: Urge incontinence
  - 1999: Urinary retention and urgency/frequency symptoms


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Percutaneous Tibial Nerve Stimulation (PTNS)

- RX protocol – once/wk for 12 wks, 30 min/session
- Pts who respond may require occ rxs to sustain
- 2010 – FDA clearance incl OAB
- OrBIT Trial – 73% pts who responded to rx cont for 1 yr and were able to sustain improvement with rx Q 21 days (MacDiarmid SA et al. J Urol 2010; 183: 234-240)

- Urgent PC Neuromodulation System
Botulinum Toxin For OAB

- FDA approved for both OAB and neurogenic detrusor overactivity in patients who are not satisfied with prior antimuscarinic therapy
- Administered via cystoscopic injection into the detrusor
- Requires re-treatment, although often lasts 6 months

Botulinum Toxin
Anticholinergic Therapy vs Onabotulinumtoxin A for Urgency Urinary Incontinence (Visco et al. NEJM 2012)

- 10 center randomized, dble-blind, PBO-controlled trial in women with mod-severe UUI
- 5 or more UUI on 3 day diary
- Anticholinergic naïve or had received up to 2 anticholinergics other than solifenacin, darifenacin or trospium chloride
- 1:1 randomization Botox 100U or solifenacin starting at 5 mg with option to escalate or switch to trospium XR
Results

• Mean reduction in UUI episodes/day – 3.4 episodes/day in anticholinergic group vs 3.3 in Botox group
• Reduction in daily UUI episodes maintained in both groups for 6 mos of active rx phase
• Higher baseline frequency of UUI episodes/day assoc with greater reduction in UUI episodes (p<0.01)
• Botox group more likely to report complete resolution of UUI (27% vs 13%, p=0.003)

Results (cont)

• QoL and patient reported outcome parameters improved in both groups
• Adverse events
  – Need for CIC per protocol (PVR > 300cc or > 150ml assoc with moderate of greater bother)
  – 5% in Botox group at 2 mos, 3% at 4 mos and 1% at 6 mos
  – More women in Botox group had UTI (33% vs 13%, p<0.001)
FutureTherapies

• Solabegron – beta agonist
  – Phase I and II studies completed
  – Phase III trials not yet initiated

Conclusion

• OAB remains a highly prevalent, underdiagnosed and undertreated condition
• Despite the impact of QoL and associated morbidities patients are afraid to bring it up and doctors often don’t ask
• A history and physical examination and urinalysis are the primary components of the evaluation
Conclusion

• An assessment of bother helps identify those who may benefit from treatment
• Despite improvements in OAB symptoms, persistence with anticholinergics remains limited
• Management of side effects – dry mouth and constipation may improve persistence
• Care should be used in treating frail elderly patients with anticholinergics

Conclusion

• Mirabegron is a new oral OAB therapy with a different MOA
• Third line therapies include: percutaneous tibial nerve stimulation and sacral nerve stimulation and botulinum toxin
• Future therapies include solabegron