Addressing Overactive Bladder in the Female Patient

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Educational Objectives
By the end of this activity, the participant should be better able to:
1. Implement screening and measurement practices for OAB identification and evaluation in women.
2. Describe the safety, efficacy, and evidence-based role of current OAB pharmacotherapies, including differing mechanisms of action.
3. Identify and overcome barriers to OAB treatment compliance, effectively engaging patients in their self-care.
4. Apply a female patient-centric approach to OAB management with the goal of improving treatment satisfaction and overall quality of life.

Speaker Disclosure
Dr. Ellsworth has disclosed that she has no actual or potential conflict of interest in relation to this topic.
INTENDED LEARNERS
This activity is designed for primary care physicians, nurses, nurse practitioners, and physician assistants who treat female patients.

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Addressing Overactive Bladder in the Female Patient

Faculty
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Faculty Disclosure
Dr. Ellsworth has no financial relationships to disclose.

Learning Objectives
• Implement screening and measurement practices for overactive bladder (OAB) identification and evaluation in women
• Describe the safety, efficacy, and evidence-based role of current OAB pharmacotherapies, including differing mechanisms of action
• Identify and overcome barriers to OAB treatment compliance, effectively engaging patients in their self-care
• Apply a female patient-centric approach to OAB management with the goal of improving treatment satisfaction and overall quality of life

Why Screen for OAB in Women?
• It is common
• The incidence increases with age
• Significant effect on QoL – increase risk of UTIs, skin irritation/infection, falls/fractures, interrupted sleep
• Economic impact of OAB is staggering
• Women often will not bring up their symptoms until they have had symptoms for years

OAB = overactive bladder; QoL = quality of life; UTI = urinary tract infection.
Prevalence of OAB Symptoms

1 in 3 US adults ≥40 years of age reported symptoms of OAB at least "sometimes"

Age (years)  Respondents (%)
40–49  50–54  55–59  60–64  65–69  70–74  75+
Men  10  15  20  25  30  35  40
Women  20  30  40  50  60  70  80


OAB Has a Considerable Impact on QoL

SF-36 = 36-item Short-Form Health Survey

Healthy  Diabetes  Depression  OAB


Impact of OAB on QoL

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


The Economic Impact

- 2007: annual per capita cost of OAB estimated to be $1925 (75% direct medical costs, 22% lost productivity, 4% direct nonmedical costs) = $65.9 billion for estimated 34 million with OAB in the United States
- 2020: projected per capita cost of OAB $1970 (direct medical costs 77%) = $76.2 billion in 2015 and $82.6 billion in 2020

- Patient-based studies in the United States
  - 528 F (mean age 58 years): mean weekly direct cost of routine care/Pt in 2005 was $6.02 for UUI, $3.91 for SUI, and $6.35 for MUI
  - 262 women reporting any UUI-associated costs, mean cost of routine care $10.59/week

MUI = mixed urinary incontinence; SUI = stress urinary incontinence; UUI = urge urinary incontinence.

The Economic Impact

- 2007: annual per capita cost of OAB estimated to be $1925 (75% direct medical costs, 22% lost productivity, 4% direct nonmedical costs) = $65.9 billion for estimated 34 million with OAB in the United States
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Women Don’t Discuss Their OAB Symptoms – Why?

- Caretaker – busy taking care of others who may be “sicker”
- “It’s just another part of getting older”
- Fear of invasive tests and surgery
- Concerns about adverse effects of medications
- Nothing works, so why bother
- THESE CONCERNS NEED TO BE ADDRESSED

Risk Factors for OAB

- The most common risk factor for OAB is increasing age
- Other common risk factors include
  - Obesity
  - Slightly higher prevalence in African Americans than Hispanics and whites
  - Depression is associated with OAB
  - Individuals on hormone replacement therapy
  - OAB often described by patients reporting functional problems, including altered bowel function and fibromyalgia
  - Neurogenic OAB may be secondary to multiple sclerosis, Parkinson’s disease, dementia, spinal cord injury, cerebrovascular accident, and diabetes

How to Engage Patients to Discuss Their Bladder Symptoms

OAB V-8 Questionnaire
A Simplified Screening Tool

- OAB V-8 comprises first 8 items of OAB-q
- Validated as a screening tool in primary care settings
- Patients rate how bothered they are by frequency, urgency, nocturia, and UUI on a scale of 0 to 5 (not at all – a very great deal)
- Linguistically validated in 40+ other languages
- Reliability, validity, and responsiveness demonstrated in clinical trials

OAB V-8 and other clinical research and patient management tools can be accessed for free at www.oabq.com


BUT THIS CAN BE FURTHER SIMPLIFIED...

- Remember—the risk of developing OAB increases over time—screen periodically
- First simply ask:
  
  Is your bladder causing you any problems?
  
  Do you have trouble controlling your urine?

Are all patients with OAB the same?
Should they all be treated the same?

Case 1: Sally’s Trips to the Toilet

- 52-year-old female who complains of
  
  Frequency: >12 ×/day
  Urgency: "I barely get there in time"
  UI: "I won’t go on a long car trip for fear I will have an accident"
  Urine leakage with cough, laugh, sneeze
  DOES SALLY HAVE OAB?

- "I spend more time rushing to the bathroom"

Case 1: Sally (continued)

- PMH/SH: HTN, elevated cholesterol, obesity
- Meds: Diuretic, β-blocker, cholesterol lowering agent
- ROS:
  
  SUI: not bothersome – "I can control that with a Kegel and a pad"
  Bowels regular
  PE: Normal
- Lab evaluation: Urinalysis – Normal

HTN = hypertension.
Treating Sally
What to Consider to Optimize Treatment Outcomes
- What are Sally’s treatment outcomes/goals?
  - These are often task-oriented and not what we see reported in articles on OAB treatment
- Ensure that her expectations are appropriate
- Discuss improvement in lieu of cure
- Balance between symptom improvement and adverse effects
- Changing behavior takes time

Pharmacologic Therapies for OAB
- Antimuscarinic Agents
- β3-Adrenoceptor Agonists

Muscarinic Receptor-Mediated Effects in the Detrusor
- In detrusor, M3 receptor is predominant subtype mediating contraction
- Role of M2 not fully understood
- M2 receptor antagonism
  - Stabilizes bladder (detrusor) muscle
  - Increases bladder capacity
  - Diminishes frequency of involuntary bladder contractions
  - Delays initial urge to void

Currently Available Antimuscarinics
- Anticholinergic treatment options have grown over the years

Pharmacokinetics of Antimuscarinics

Not All Antimuscarinic Agents are the Same
- All are effective for treatment of OAB symptoms
- Individual differences exist in the profiles of antimuscarinics
- There is some evidence of differences among adverse effect profiles
- There are differences in tolerability profiles
- Differences exist in the route of administration and dose flexibility

Ach = acetylcholine; ATP = adenosine triphosphate; M1 = muscarinic receptor subtype 1; M2 = muscarinic receptor subtype 2; M3 = muscarinic receptor subtype 3; P2X = purinergic receptor; P2X1 = ligand-gated ion channel 1; P2X3 = ligand-gated ion channel 3; VR1 = vanilloid receptor 1; sGC = soluble guanylyl cyclase.


Muscarinic Receptor Affinity

<table>
<thead>
<tr>
<th>Anticholinergic Agent</th>
<th>M3 vs M1 Selectivity</th>
<th>M3 vs M2 Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Trospium</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Comparative Studies among Antimuscarinics

- Study populations may differ in severity of symptoms among the trials thus cannot compare results of different studies
- Comparator studies are often switch studies
- The majority of comparison studies are non-inferiority studies
- The only placebo controlled superiority study was that comparing tolterodine ER 4 mg to fesoterodine 8 mg to placebo
  - Fesoterodine 8 mg superior to tolterodine ER 4 mg in reducing UUI episodes

What Type of Improvement Can a Patient Expect?

- Reduction in UUI: up to 90% reduction in UUI
- Reduction in micturition frequency—endpoint is not 0 but normalization—about 2 to 3 less voids/day
- Dry rates (3-day diary): rates will vary with baseline severity—typically 50% to 64% (less with more severe UUI and greater with less severe UUI)

Antimuscarinic Agents: Efficacy

Pearls in Treating Patients with Antimuscarinic Agents

- Start low and titrate up as needed
- Some benefit in 2 weeks, at least 4 weeks for max response
- Be proactive about preventing/treating adverse effects
  - High discontinuation rates due to adverse effects with only 18% Pts continuing medication after 6 months
  - If failed prior antimuscarinic, start with drug that has more than 1 dose
  - Nighttime dosing may help decrease adverse effects but should not be used with trospium chloride

Which Anticholinergic Drug for OAB Symptoms in Adults?

- Oxybutynin IR vs tolterodine IR: tolterodine might be preferred for reduced risk of dry mouth
- Extended-release oxybutynin and tolterodine preferable as less risk of dry mouth
- Solifenacin has better efficacy and less risk of dry mouth compared to tolterodine IR
- Fesoterodine has superior efficacy compared to tolterodine ER but a higher risk of dry mouth


Antimuscarinic Effects Beyond the Bladder

CNS = central nervous system.

Adverse Effects of FDA Approved Antimuscarinic Agents for OAB

<table>
<thead>
<tr>
<th>Drug/Strength</th>
<th>Dry Mouth</th>
<th>Constipation</th>
<th>Dry Eyes</th>
<th>Dyspepsia</th>
<th>Dizziness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin ER (5-30 mg QD)</td>
<td>34.9%</td>
<td>8.7%</td>
<td>3.1%</td>
<td>4.5%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Oxybutynin IR (5-20 mg QD)</td>
<td>12.4%</td>
<td>15.1%</td>
<td>3.8%</td>
<td>6.0%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Oxybutynin TDS</td>
<td>4.1%</td>
<td>3.3%</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Tolterodine ER (4 mg QD)</td>
<td>23.4%</td>
<td>5.9%</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
<td>&gt; 5%</td>
</tr>
<tr>
<td>Solifenacin (5-10 mg QD)</td>
<td>10.0%</td>
<td>5.4%</td>
<td>0.3%</td>
<td>1.4%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Trospium CI (20 mg BD)</td>
<td>20.1%</td>
<td>9.5%</td>
<td>1.2%</td>
<td>1.2%</td>
<td>n/a</td>
</tr>
<tr>
<td>Darifenacin (7.5-15 mg QD)</td>
<td>20.2%</td>
<td>14.8%</td>
<td>2.1%</td>
<td>2.7%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Fesoterodine (4 mg QD)</td>
<td>17.8%</td>
<td>4.2%</td>
<td>1.4%</td>
<td>1.6%</td>
<td>–</td>
</tr>
<tr>
<td>Fesoterodine (8 mg QD)</td>
<td>34.6%</td>
<td>6.0%</td>
<td>3.7%</td>
<td>2.3%</td>
<td>–</td>
</tr>
</tbody>
</table>

TDS = Transdermal system.

Comparison of Adverse Events in the Elderly


AUA/SUFU Guidelines

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


Minimizing Adverse Effects from Anticholinergics – Constipation

- Baseline bowel function
  - Ask about bowel frequency and stools
  - Many patients restrict fluid in hopes of decreasing frequency, incontinence
- If infrequent stools/constipation
  - Increase fluid intake
  - Increase dietary fiber
  - Osmotic laxative
  - If no improvement, consider gastrointestinal evaluation

Minimizing Adverse Effects from Anticholinergics – Xerostomia (Dry Mouth)

- www.essology.com/PDF/DryMouthMedications.pdf has a 23-page list of medications that can cause xerostomia
- Tips for treating dry mouth
  - Sip cool water throughout the day
  - Drink milk – lubricates oral mucosa
  - Restrict caffeine and alcohol intake
  - Use of sugar-free gum stimulates saliva flow
  - Salivary tablets, oral balance, biotene toothpaste, recaldent products
Managing OAB in the Elderly

- Concerns regarding anticholinergic use in elderly
  - Many commonly prescribed drugs have anticholinergic properties
  - Clinical manifestations of anticholinergic toxicity are likely to be nonspecific (e.g., cognitive impairment) and reflect the effects of cumulative anticholinergic burden
  - No clinically available laboratory test to assess anticholinergic levels


Drugs with Strong Anticholinergic Properties

- Antihistamines
- Antiparkinson agents
- Skeletal muscle relaxants
- Antidepressants
- Antipsychotics
- Antimuscarinics (urinary incontinence)
- Antispasmodics


Case 2: Sylvia

- 78-year-old female with multiple medical problems and OAB
  - Meds: HCTZ, amlodipine, sertraline, calcium, vitamin D, laxative PRN
  - Lives alone – depends on daughter
  - "I worry about being a burden to my daughter, she has enough to do"
  - Daughter worries about her falling during her rush to bathroom particularly at night
  - Her OAB is bothersome and pads/diapers are expensive
  - Tried oxybutynin 5 mg BID – not effective enough and intolerable dry mouth and constipation

Mirabegron

- FDA approved June 2012
- Selective β3-adrenoceptor agonist
- Activates β3 adrenoceptor on the detrusor muscle of bladder to facilitate filling of bladder and storage
- Does not affect detrusor contractility


Managing OAB in Sylvia

- Older Pts experience more adverse effects than younger Pts
- Age-related changes in central cholinergic transmitter systems
- AGS antimuscarinics “potentially inappropriate medications and classes to avoid in older adults”
  - Many commonly prescribed drugs have anticholinergic properties
  - Clinical manifestations of anticholinergic toxicity are likely to be nonspecific and reflect the effects of cumulative anticholinergic burden
  - Lack of available tests to assess anticholinergic levels


Case 2: Sylvia (continued)

- Fluid intake
  - 1 cup of caffeinated coffee in AM
  - 1 cup of tea in the afternoon
  - 1 glass of milk with dinner
- Bowel history
  - Moves her bowels 2 x/week
  - Takes a stool softener and laxative PRN

"I take enough medications – Can something else be done?"
"I don't drink much fluids during the day – Why do I still have to go so frequently?"
Mirabegron
Prescribing Information

• Starting dose 25 mg with or without food
• Effective within 8 weeks, may increase to 50 mg
• Do not cut, crush, or chew
• Max dose 25 mg 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 recommended; don’t use in severe uncontrolled HTN

Efficacy of Mirabegron
Results of 7 Clinical Trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>N</th>
<th>Voids per 24 hours</th>
<th>Mean Incontinence Episodes per 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO</td>
<td>M 25 mg</td>
<td>M 50 mg</td>
</tr>
<tr>
<td>DRAGON</td>
<td>927</td>
<td>-1.46</td>
<td>-1.88</td>
</tr>
<tr>
<td>SCORPIO</td>
<td>1074</td>
<td>-1.37</td>
<td>-1.94</td>
</tr>
<tr>
<td>ARIES</td>
<td>1323</td>
<td>-1.05</td>
<td>-1.66</td>
</tr>
<tr>
<td>CAPRICORN</td>
<td>1230</td>
<td>-1.19</td>
<td>-1.93</td>
</tr>
<tr>
<td>Taurinus</td>
<td>2483</td>
<td>-1.02</td>
<td>-1.29</td>
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<tr>
<td>JAPAN</td>
<td>1139</td>
<td>-0.86</td>
<td>-1.67</td>
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<tr>
<td>ASIA</td>
<td>1136</td>
<td>-1.46</td>
<td>-2.04</td>
</tr>
</tbody>
</table>

M = mirabegron; PBO = placebo; Tolt = tolterodine

Adverse Effects of Mirabegron

• SCORPIO
  - HTN 5.9% in M 50 mg and 7.7% PBO
• CAPRICORN
  - HTN 5.3% PBO, 6.9% M 25 mg, 7.0% M 50 mg
• ARIES
  - Overall TEAEs comparable between PBO and M 50 mg
• DRAGON
  - Maximum increase of 1.9 mmHg in BP of Pts treated with mirabegron at any dose level (not statistically significant compared with PBO)
  - No significant changes in HR with PBO, M 25 mg, M 50 mg

Adverse Effects of FDA Approved β3-Adrenoreceptor Agonist for OAB

<table>
<thead>
<tr>
<th></th>
<th>Headache</th>
<th>Constipation</th>
<th>Dry Eyes</th>
<th>Hypertension</th>
<th>Dizziness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirabegron (25-50 mg QD)</td>
<td>0.6%</td>
<td>0.9%</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Headache, Constipation, Dry Eyes, Hypertension, Dizziness

Why Might Mirabegron be a Good Choice for Sylvia?

• Wagg reviewed the data from three 12-week, randomized Phase III trial, and tolerability data from a 1-year safety trial to evaluate efficacy and tolerability of mirabegron in patients aged ≥65 and ≥75 years
  - Mirabegron 25 mg and 50 mg QD reduced mean # incontinence episodes and the mean micturition frequency from baseline to final visit in both age groups and improvements greater than PBO

Incidence of Adverse Effects in Patients ≥65 and ≥75 Years with Mirabegron

<table>
<thead>
<tr>
<th>Age Category</th>
<th>≥65 years</th>
<th>≥75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO (n = 142)</td>
<td>M 25 mg (n = 154)</td>
</tr>
<tr>
<td>Headache</td>
<td>8.4%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.5%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.5%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

**Diagnosing and Treating OAB Improves QoL**

- Diagnosed vs not diagnosed elderly OAB had higher MCS scores and SF-6D health utilities and less activity impairment
- Treated vs never treated had higher MCS and SF-6D health utilities, less activity impairment, fewer OAB Sx, lower odds of having bladder problems or incontinence
- Significantly greater diagnosis- and treatment-related benefits on MCS and activity impairment among elderly respondents (>65 years)

MCS = mental component summary.


**Impact of OAB Treatment on QoL of Patients >60 Years with Associated Pathologies**

- 1434 Pts >60 years with newly diagnosed OAB and 1 associated pathology (UTI or genital skin infection, sleep disorder, depression, HTN) recruited
- First visit: evaluated and started on therapy – completed HRQoL SF-12
- Second visit (4-6 months later): HRQoL re-evaluated
- Significant improvement in HRQoL found on second visit
- Lower score in female gender


**Future Management: Combination Therapy**

- Antimuscarinics mainstay of OAB Rx, but persistence often limited by insufficient efficacy and adverse effects
- Mirabegron has a different mechanism of action, and has been shown to significantly reduce micturition frequency and incontinence episode frequency compared to placebo with low incidence of adverse effects
- Combination with reduced doses may improve tolerability without compromising efficacy

**Symphony Trial**

- Phase 2, factorial, randomized, double-blind, parallel-group, placebo- and monotherapy-controlled trial
- 1306 patients randomized to 12 weeks of Rx in 1 of 12 groups
  - 6 combination groups (solifenacin 2.5, 5, or 10 mg plus mirabegron 25 or 50 mg)
  - 5 monotherapy groups (solifenacin 2.5, 5, or 10 mg or mirabegron 25 or 50 mg)
- Placebo


**Symphony Trial Results**

- Compared with S 5 mg, all combinations with S 5 mg or S 10 mg significantly improved mean volume voided
- 3 combination groups significantly reduced micturition frequency compared with S 5 mg (S 5 mg + M 50 mg, S 10 mg + M 25 mg, S 10 mg + M 50 mg)
- All combinations but S 2.5 mg + M 25 mg significantly reduced urgency episodes compared to S 5 mg
- No dose-related trends in TEAEs, BP, HR, PVR, or lab or ECG parameters noted between combination and monotherapy; constipation slightly increased in combination therapy

S = solifenacin; M = mirabegron.


**BESIDE Trial**

- Goal: Evaluate efficacy, safety, and tolerability of combination (S 5 mg and M 50 mg) vs. S 5 mg or S 10 mg in OAB patients remaining continent after 4 weeks S 5 mg
- Individuals incontinent on daily S 5 mg during 4-week single-blind run-in randomized 1:1:1 to double-blind daily combination or S 5 mg or S 10 mg for 12 weeks
- Patients receiving the combination were started on M 25 mg increasing to M 50 mg after week 4

**BESIDE Trial Results**

- 2174 patients randomized
  - Combination = 727
  - S 5 mg = 728
  - S 10 mg = 719
- Combination Rx superior to S 5 mg
  - Significant improvement in
    - Daily incontinence ($P = .001$)
    - Daily micturitions ($P < .001$)
    - Incontinence noted in a 3-day diary ($P = .014$)
- Combination Rx superior to S 10 mg for daily micturitions
- Combination Rx noninferior to S 10 mg in UUI episodes/24 hours, change from baseline in PPBC score, mean # pads/24 hours, mean volume voided

**Take Home**

- OAB is common in women
- Women remain underdiagnosed and undertreated
- Pharmacotherapy with an antimuscarinic agent or β3-adrenoceptor agonist are effective and safe second-line therapies and allow for more personalized treatment strategies
- Setting proper expectations and managing adverse effects is important to improve persistence
- Evaluation and treatment does impact QoL
Medication Index

Primary Care Women's Health Forum: Addressing Overactive Bladder in the Female Patient

The following medications were discussed in this presentation. The table below lists the generic and trade name(s) of these medications.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>Norvasc</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>Enablex</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>Toviaz</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>Myrbetiq</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Ditropan XL, Gelnique, Oxytrol</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Vesicare</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Detrol</td>
</tr>
<tr>
<td>Trospium</td>
<td>None</td>
</tr>
</tbody>
</table>

