Oral Medications for the Management of Overactive Bladder
Disclosure

• Natasha Rodney-Cail, Pharmacist, Drug Evaluation Unit
  – DEU funded by the Drug Evaluation Alliance of Nova Scotia (DEANS).
  – DEU prepares Drug Evaluation Reports for the Atlantic Common Drug Review (ACDR)
  – Has no conflicts of interest
Presenter Disclosure

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    Professor of Urology
    Dalhousie University

• Relationships with commercial interests: none
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• Speakers Bureau/Honoraria: Pfizer, Astellas
• Consulting Fees: none
Case 1

- Karen K., age 55
- Diagnosed with OAB 6 months ago
- After lifestyle changes and behavioral therapy still reports frequency and urgency
  - Voids q2 hours during the day and 2-3 times at night
  - Rarely experiences incontinence, but wears a liner for reassurance
- Symptoms interfere with work
- Would like to try medication
  - Insurance will cover anticholinergic agents only
Case 2

John S, 80 years old
Alzheimer’s Dx MMSE = 23
MI 5 years ago
Medications:
   ASA 81 mg, ramipril 2.5 mg,
   metoprolol 25 mg, atorvastatin 20
   mg, donepezil 5 mg
BP 140/80

- ~3 urge incontinence episodes/day
- feels like bladder not empty post void
- frequently urinates at night
Urgency, with or without urge incontinence, usually with frequency and nocturia, in the absence of infection or other proven pathology.

The major symptom is the “gotta go” feeling; the sudden and strong urge to urinate that a person can’t control.

OAB is common
Rates increase with age
For example 43-77% of nursing home patients and 10-38% patients with cognitive impairment/dementia.
• Reduce distressing symptoms and improve QOL

• Reduction of incontinence is a key aim as it can affect quality of life more than urgency or frequency
  – Decrease of ~50% deemed clinically important
Before Drugs...

• Lifestyle modification
  – Decreased fluid intake if excessive
  – Elimination of bladder irritants
  – Managing constipation

• Behavioral therapy
  – Timed voiding
  – Behavioral training
Drugs Used to Treat OAB

Anticholinergics are the main drug class used to treat OAB; there are 7 available in Canada.

Mirabegron is another drug, from a different class. It became available in March 2013.
What to Consider

Efficacious
(adj.)

having the power
to produce
a desired effect
Anticholinergics

- Oxybutynin
- Tolterodine (Detrol, generic)
- Solifenacin (Vesicare, generic)
- Darifenacin (Enablex)
- Trospium (Trosec)
- Fesoterodine (Toviaz)
- Propiverine (Mictoryl)

Muscarinic Receptors

- M1 - CNS
- M2 - Heart
- M3 – Smooth muscle
- M4 - CNS
- M5 - CNS
Anticholinergic reduction in urinary incontinence

Oxybutinin IR 15 mg/day - 0.74

Solifenacin 5 mg - 0.77
Solifenacin 10 mg - 0.81

Tolterodine IR 4 mg/day - 0.5
Tolterodine ER 4 mg/day - 0.4

Fesoterodine 4 mg - 0.77
Fesoterodine 8 mg - 1.08

Anticholinergic reduction in voids

- Oxybutinin IR 15 mg/day - 0.92
- Solifenacin 5 mg - 0.99
  Solifenacin 10 mg – 1.3
- Tolterodine IR 4 mg/day - 0.71
  Tolterodine ER 4 mg/day - 0.77
- Fesoterodine 4 mg - 0.81
  Fesoterodine 8 mg - 0.93

## Comparative Efficacy Anticholinergics

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Circles = micturition/24 hours, incontinence/24 hours, QOL, urgency episodes/24 hours, nocturia/24 hours

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Clinically Relevant Differences?

Fesoterodine v.s. tolterodine XL

- Leakage episodes
  - (WMD -0.19, 95% CI -0.30 to -0.09)
- Frequency
  - (WMD -0.27, 95% CI -0.47 to -0.06)
- Urgency episodes
  - (WMD -0.44, 95% CI -0.72 to -0.16)

Solifenacin vs. tolterodine

- Leakage episodes
  - (WMD -0.30, 95% CI -0.53 to -0.08)
- Urgency episodes
  - (WMD -0.43, 95% CI -0.74 to -0.13)

Improved Urinary Incontinence

Oxybutynin

Tolterodine

Solifenacin

Darifenacin

Fesoterodine

Propiverine

Comparative Safety Anticholinergics

Circles = dry mouth, constipation, withdrawal due to AE, withdrawal due to lack of efficacy, serious AE

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Adverse Effects

Solifenacin

Tolterodine

Fesoterodine

Trospium

Discontinuation Due to Adverse Effects

Oxybutynin

Solifenacin

Trospium

Fesoterodine

Propiverine

Anticholinergic Side Effects
Cognitive Effects of Anticholinergics

• Most direct comparator RCTs have not assessed cognitive AE

• 15 RCTs have assessed cognitive effects vs. placebo
  – Unable to evaluate different cognitive effects with specific drugs
  – No study assessed cognition with chronic use

• Observational studies
  – Exposure equivalent to oxybutynin 5 mg/day for > 3 years is associated with an increased risk of dementia: HR 1.54 (95% CI 1.21 – 1.96)
Mirabegron

- Agonizes β3 receptors of the bladder detrusor muscle leading to relaxation

- Relatively selective β3 adrenergic agonist
Efficacy of Mirabegron

Superior to placebo

No difference compared to most anticholinergics
### Comparative Efficacy of Mirabegron

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Safety of Mirabegron

- Less dry mouth
- Total AE similar
- Serious AE similar
- Withdrawals due to AE similar
## Comparative Safety

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Circles = dry mouth, constipation, withdrawal due to AE, withdrawal due to lack of efficacy, serious AE

- The **GREEN** circle indicates that the ‘row’ OAB medication is significantly better than the ‘column’ OAB medication
- The **RED** circle indicates that the ‘row’ OAB medication is significantly worse than the ‘column’ OAB medication
- The **WHITE** circle indicates that there is no significant difference between the ‘row’ and ‘column’ OAB medication
- A **GREY** circle indicates that the outcome was not available for analysis

Costs

- **≤ $15**: Oxybutynin, tolterodine, tolterodine XL, solifenacin
- **$25-$50**: Trospium, darifenacin, fesoterodine
- **>$50**: Oxybutynin XL
Case 1

- Karen K., age 55
- Diagnosed with OAB 6 months ago
- After lifestyle changes and behavioral therapy still reports frequency and urgency
  - Voids q2 hours during the day and 2-3 times at night
  - Rarely experiences incontinence, but wears a liner for reassurance
- Symptoms interfere with work
- Would like to try medication
  - Insurance will cover anticholinergic agents only
Case 1 Polling Question

1. Do not treat with medication

2. Treat with an anticholinergic
   1. Efficacy consideration
   2. Safety consideration
   3. Cost consideration
**Case 2**

John S, 80 years old  
Alzheimer’s Dx MMSE = 23  
MI 5 years ago  
Medications:  
ASA 81 mg, ramipril 2.5 mg,  
metoprolol 25 mg, atorvastatin 20 mg, donepezil 5 mg  
BP 140/80

- ~3 urge incontinence episodes/day  
- feels like bladder not empty post void  
- frequently urinates at night
Case 2 Polling Question

a. Is an OAB drug indicated?

b. If so, what is the best treatment?
   a. An anticholinergic agent
   b. Mirabegron