Managing overactive bladder in primary care

TA Ong
Urology
One day in your clinic....

• 60-year-old man

• Leak of urine when cough and sneeze....
What type of incontinence?

- A. Cough incontinence
- B. Pressure incontinence
- C. Urge incontinence
- D. Stress incontinence
What type of incontinence?

• A. Cough incontinence
• B. Pressure incontinence
• C. Urge incontinence
• D. Stress incontinence (SUI)
• Stress UI (SUI) = involuntary leakage on effort or exertion or any sudden increase in abdominal pressure.
Can this happen to a male?
Next day in your clinic....

• 65-year-old man

• Urinary frequency and urgency.

• Occasional leak.....
What type of incontinence?

- A. Stress incontinence
- B. Overactive incontinence
- C. Urge incontinence
- D. Sensitive incontinence
What type of incontinence?

• A. Stress incontinence
• B. Overactive incontinence
• **C. Urge incontinence (UUI)**
• D. Sensitive incontinence
• Urge UI (UUI) = involuntary loss of urine accompanied by or immediately preceded by a **sudden, strong desire to void** (urgency).
Can this happen to a female?
Overactive Bladder

• OAB dry

• OAB wet
Definition of OAB

• SAME in 2018. (as in 2002; ICS)

• Urinary urgency, with or without urgency incontinence, usually accompanied by frequency and nocturia.
What if having both stress PLUS urge incontinence

• A. Combined incontinence
• B. Mixed incontinence
• C. Confused incontinence
• D. Rojak incontinence
What if having both stress PLUS urge incontinence

• A. Combined incontinence
• **B. Mixed incontinence**
• C. Confused incontinence
• D. Rojak incontinence
• Mixed urinary incontinence = symptom complex of involuntary leakage associated with both **urgency** and **effort and exertion**.
FAQ

• Which one to treat first?
Also...

• Overflow incontinence

• Functional incontinence
How to evaluate? The 3 steps....

• History (identify the problem: OAB, LUTS, SUI, UUI, overflow etc; and the CAUSE)

• Examination

• Investigation
How to evaluate? The 3 steps....

- History
- Examination
- Investigation
• DRE
• Abdomen
• Genitalia: Meatal stenosis, phimosis
• Focused neuro exam
Question

• What is the MUST-DO investigations for patients with LUTS/incontinence/OAB?
Investigations

- Important to rule out UTI or something sinister!

- **Urinalysis**
  - +/- Renal function test
  - +/- PSA
  - +/- Imaging
  - +/- uroflow
  - +/- post void residual urine
  - +/- cystoscopy
  - +/- urodynamics
One low cost, simple, often forgotten but POWERFUL tool.....
<table>
<thead>
<tr>
<th>Time</th>
<th>Type of Fluid</th>
<th>Amount</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>8:05</td>
<td>Nescafe O</td>
<td>230</td>
<td></td>
</tr>
<tr>
<td>9:28</td>
<td>Misai Kuning</td>
<td>430</td>
<td></td>
</tr>
<tr>
<td>10:00</td>
<td>Soya water</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10:41</td>
<td>Soya water</td>
<td>430</td>
<td></td>
</tr>
<tr>
<td>14:03</td>
<td>Soya water</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>15:30</td>
<td>Soya water</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>15:51</td>
<td>Soup</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>17.15</td>
<td>Soya water</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>9.12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Urodynamics

• For info only.
• $P_{det} + P_{abd} = P_{ves}$

• $P_{det} = P_{ves} - P_{abd}$
Is Urodyamics a MUST?
Treatment of OAB/Urge UI

- What is the FIRST line therapy?
- A. Conservative management
- B. Medical therapy
- C. Surgical therapy
- D. Not standard therapy
Treatment of OAB/Urge UI

<table>
<thead>
<tr>
<th>Conservative</th>
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<table>
<thead>
<tr>
<th>Urge Incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Fluid management</td>
</tr>
<tr>
<td>Timed voiding</td>
</tr>
<tr>
<td>Bladder training</td>
</tr>
<tr>
<td>PFME</td>
</tr>
</tbody>
</table>
Treatment of Urge UI

Conservative

Urge Incontinence

- Weight loss
- Fluid management
- Timed voiding
- Bladder training
- PFME
New: Fesoterodine
Side effects

- Dry mouth
- Dry eye
- Constipation

– n/b: **NOT** to be used in case of **GLAUCOMA**
  - MUST – BE - ASKED QUESTION!
Second line therapy

- Anticholinergics
  - Extended release
  - Transdermal patch
Meta analysis

- Meta-analysis of 50 RCTs
- >27,000 subjects with OAB
  - **UI**: Reduced by 1.73 episodes/day (placebo: 1.06)
  - **No of void**: Reduced by 2.06/day (placebo: 1.2)
- No single agent is superior to others
Are the side effects different?
Are the side effects different?

- Dry mouth, constipation... Cognitive impairment...

- Evidence??
Are the side effects different?

• Dry mouth, constipation⋯⋯ Cognitive impairment⋯⋯

• Very little high quality evidence.

• Except oxybutynin.

How many patients are still on the drug after 12 months?

• A. 100%
• B. >50%
• C. <50%
How many patients are still on the drug after 12 months?

- 14-35%

FAQ: Duration of treatment

• Controversial.

• Antimuscarinic tolterodine (extended-release, 4mg) in known responders, 65% of patients requested retreatment and 62% experienced symptom relapse.

New class of drug

- Beta$_3$- agonist: Mirabegon
B3 adrenoceptor agonist

• Mirabegon- first agent, approved by FDA in 2012.

• Indications:
  – Upfront
  – After failure of anticholinergics
  – When anticholinergics are contraindicated
  – In combination with anticholinergics
Mirabegron in Overactive Bladder: A Review of Efficacy, Safety, and Tolerability

Christopher R. Chapple,1* Linda Cardozo,2 Victor W. Nitti,3 Emad Siddiqui,4 and Martin C. Michel5

1Department of Urology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Sheffield, United Kingdom
2Department of Urology, King’s College Hospital, London, United Kingdom
3Department of Urology, NYU Langone Medical Center, New York, New York
4Astellas Pharma Europe Ltd, Chertsey, Surrey, United Kingdom
5Department of Pharmacology, Johannes Gutenberg University, Mainz, Germany
No of micturition/24 hour
No of incontinence / 24 hour

Statistically significant treatment benefit relative to placebo ($P < 0.05$) with multiplicity adjustment.

Statistically significant treatment benefit relative to placebo ($P < 0.05$) without multiplicity adjustment.

SE=standard error, FAS=f full analysis set-incontinence.
Study 046-Common treatment-emergent adverse events (≥2% in any treatment group)

<table>
<thead>
<tr>
<th>Adverse events n (%)</th>
<th>Placebo (n=494)</th>
<th>Mirabegron 50mg (n=493)</th>
<th>Tolterodine ER 4mg (n=495)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>38 (7.7 %)</td>
<td>29 (5.9%)</td>
<td>40 (8.1%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8 (1.6%)</td>
<td>14 (2.8%)</td>
<td>14 (2.8%)</td>
</tr>
<tr>
<td><strong>Dry Mouth</strong></td>
<td>13 (2.6%)</td>
<td>14 (2.8%)</td>
<td>50 (10.1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (2.8%)</td>
<td>18 (3.7%)</td>
<td>18 (3.6%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>8 (1.6%)</td>
<td>11 (2.2%)</td>
<td>7 (1.4%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7 (1.4%)</td>
<td>7 (1.4%)</td>
<td>10 (2.0%)</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>7 (1.4%)</td>
<td>8 (1.6%)</td>
<td>10 (2.0%)</td>
</tr>
</tbody>
</table>

Data are for the safety analysis set. Adverse events, defined according to the Medical Dictionary for the Regulatory Activities (MedDRA version 9.1)

Adapted from Khullar V, et al. Eur Urol 2013; 63: 283–95
Combination: Mirabegron + anticholinergic (Eur Urol 2015)

Voiding Dysfunction

Combination Treatment with Mirabegron and Solifenacin in Patients with Overactive Bladder: Efficacy and Safety Results from a Randomised, Double-blind, Dose-ranging, Phase 2 Study (Symphony)

Paul Abrams a,*, Con Kelleher b, David Staskin c, Tomasz Rechberger d, Richard Kay e, Reynaldo Martina f, Donald Newgreen f, Asha Paireddy f, Rob van Maanen f, Arwin Ridder f
Combination: Mirabegron + anticholinergic (Eur Urol 2015)

SYMPHONY: Combination better
Efficacy and Safety of Mirabegron Add-on Therapy to Solifenac in Incontinent Overactive Bladder Patients with an Inadequate Response to Initial 4-Week Solifenac in Monotherapy: A Randomised Double-blind Multicentre Phase 3B Study (BESIDE)
Mirabegron after anticholinergic failure: Eur Urol 2016

BESIDE: Adding mirabegron helps!
2018
Platinum Priority – Voiding Dysfunction

Editorial by XXX on pp. x–y of this issue

Long-term Safety and Efficacy of Mirabegron and Solifenacin in Combination Compared with Monotherapy in Patients with Overactive Bladder: A Randomised, Multicentre Phase 3 Study (SYNERGY II)
Fig. 1 – Study design. *Once daily.
Summary: Combo > Mono; well tolerated

| Table 3 – Change from baseline to EOT in mean number of incontinence episodes/24 h and mean number of micturitions/24 h |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Incontinence episodes/24 h                                   | Mirabegron (n = 301)                                          | Combination (n = 1184)                                         | Solifenacin (n = 297)                                         |
| Baseline, mean (SE)                                          | 3.2 (0.2)                                                     | 3.0 (0.1)                                                     | 3.1 (0.2)                                                     |
| EOT, mean (SE)                                               | 1.5 (0.2)                                                     | 1.0 (0.1)                                                     | 1.2 (0.1)                                                     |
| Adjusted change from baseline to EOT, mean (SE)              | -1.6 (0.1)                                                    | -2.0 (0.1)                                                    | 1.0 (0.1)                                                     |
| Difference combination vs monotherapy, mean (SE)             | -0.5 (0.1)                                                    | NA                                                            | -0.1 (0.1)                                                    |
| 95% CI                                                       | -0.7 to -0.2                                                 | NA                                                            | -0.4 to 0.1                                                  |
| p value                                                      | <0.001                                                        | NA                                                            | 0.002                                                        |
| Micturitions/24 h                                            | Mirabegron (n = 301)                                          | Combination (n = 1184)                                         | Solifenacin (n = 297)                                         |
| Baseline, mean (SE)                                          | 10.5 (0.1)                                                    | 10.5 (0.1)                                                    | 10.7 (0.2)                                                    |
| EOT, mean (SE)                                               | 8.4 (0.2)                                                     | 8.0 (0.1)                                                     | 8.5 (0.2)                                                     |
| Adjusted change from baseline to EOT, mean (SE)              | -2.1 (0.1)                                                    | -2.6 (0.1)                                                    | 2.2 (0.1)                                                     |
| Difference combination vs monotherapy, mean (SE)             | -0.5 (0.2)                                                    | NA                                                            | -0.4 (0.2)                                                    |
| 95% CI                                                       | -0.8 to -0.2                                                 | NA                                                            | -0.7 to -0.1                                                  |
| p value                                                      | <0.001                                                        | NA                                                            | 0.004                                                        |
Meta-analysis

Summary:
Mirabegron- less SE
Efficacy of combination Tx
In refractory OAB…

• Sacral neuromodulation or peripheral tibial nerve stimulation (PTNS)

• Intradetrusor injection of onabotulinumtoxinA

• Bladder augmentation
Botox

- Systemic Review
- 1,380 patients
- Reduction in no of micturition/24 hr – 29%
- Reduction in no of incontinence – 59%

Newer formulation & work in progress

- Dysport (abobotulinumtoxinA)

- Method of delivery: electromotive drug administration and liposome instillation
New drugs on the horizon…

• Next B3-agonists (XX-begron⋯)
  • Neurokinin receptor antagonists
  • Alpha-adrenoceptor antagonists
  • Nerve growth factor inhibitors
  • Gene therapy
  • Stem cell–based therapies
Summary

• The problem is there

• To diagnose

• To start with conservative measures, then medications.

• Medications: Anticholinergics, B3 agonist.

• Specialized centres for 3rd line therapy