Is the Bladder an Unreliable Witness?

Christopher Chapple
Professor of Urology
Sheffield Hallam University
Consultant Urological Surgeon
Sheffield Teaching Hospitals
NHS Foundation Trust

Visit to the
Department of Urological Sciences
The University of British Colombia
6th January 2009

Sheffield is at the centre of the UK
Disclosures

- I have acted as a consultant/or researcher to the following organisations:-
  - Astellas
  - Pfizer
  - Novartis
  - Recordati
  - Xention
  - Tanabe
Synopsis

- Innervation of the Urinary Tract
  - Neuroanatomy
  - Central Mechanisms
- Contemporary Peripheral Pharmacological Control Mechanisms
  - The importance of Afferent Mechanisms
- The Evidence Base relating to the use of Contemporary Therapy
  - Recent Meta-analyses

Innervation of the Lower Urinary Tract (LUT)

- Sympathetic
- Parasympathetic
- Somatic

- T10–L2
- S2–S4

- Inferior mesenteric ganglion
- Trigone
- Urethra
- External urethral sphincter
- Muscles of the pelvic floor
survival of the individual

survival of the species

survival of the individual

survival of the species
Fowler, de Groat and Griffith, 2008
thinly myelinated Aδ

PAG
PMC
Responses to bladder infusion among 10 normal females

Griffiths and Tadic, 2007
Responses to bladder infusion in 7 urgency-incontinent females,
Griffiths and Tadic, 2007

Cerebral control of the bladder in normal and urge-incontinent women
Griffiths, Tadic, Schaefer, and Resnick, 2007
Responses to large volumes in 3 urge-incontinent females who showed DO during scanning

"the presence of DO was associated with marked decrease in activation of the prefrontal cortex bilaterally and parts of the limbic system... This pattern of changes suggests a lack of voluntary control of the bladder with ongoing arousal."

Griffiths and Tadic, 2007

Andersson and Arner, Physiol Rev 84(3):935, 2004
Mechanism of generating LUT

Symptoms

- **Sensory:**
  - *peripheral*: increased afferent receptor excitability.
  - *central*: abnormal central processing of afferent input.

- **Motor:**
  - *peripheral*: smooth muscle contractile activity induced by neural or non-neural mechanisms.
  - *central*: involuntary parasympathetic nerve reflexes

- **Mixed**
  - Leak of urine into proximal urethra and stimulation of urethral afferents

Aetiology of Detrusor Overactivity

- The aetiology of Detrusor overactivity may be neurogenic, myogenic, or both

- **Neurogenic**
  - Reduced suprapontine inhibition
  - Damaged axonal paths in spinal cord
  - Increased afferent input

- **Myogenic theory**
  - Partial denervation
  - $\uparrow$ Excitability
  - $\uparrow$ Electrical coupling between myocytes
  - Propagation of coordinated contractions
<table>
<thead>
<tr>
<th>Ref</th>
<th>Author and Details</th>
</tr>
</thead>
</table>
| RB55 | de Groat. Urology 1997;50:36–52  
Abstract, 'Results', lines 5–9.  
Rebecca Bumand, 10/13/2004 |
| RB56 | Brading F. Urology 1997;50:57–67  
See abstract, 'Results', lines 2–5.  
Rebecca Bumand, 10/13/2004 |
Mediators in the Detrusor

Contraction
- Acetylcholine (M3, M2)
- ATP (P2X)
- 5-HT (5-HT2)
- Histamine (H1)
- Prostanoids (EP, TP)
- Leukotrienes (LTB4)
- Angiotensins (AT1)
- Bradykinin (B2)
- Endothelins (ET-A)
- Tachykinins (NK2)
- Vasopressin (V1)

Relaxation
- Noradrenaline (β)
- VIP (VPAC1/VPC2)
- PTHrP (?)
- Unknown factors

β3-Adrenoreceptor agonists in the bladder

In Vitro Function
- Adenylyl cyclase is the prototypical signalling pathway of β-AR
- Isoprenaline-stimulated propranolol-sensitive elevation of c-AMP content has been reported
Micturition frequency / 24h
Mean change from baseline to endpoint (FAS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>LSM Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=64)</td>
<td>12.3</td>
<td>-1.18</td>
</tr>
<tr>
<td>YM178 100mg bid (n=65)</td>
<td>11.3</td>
<td>-1.0</td>
</tr>
<tr>
<td>YM178 150mg bid (n=63)</td>
<td>12.3</td>
<td>-1.0</td>
</tr>
<tr>
<td>Tolterodine 4mg od (n=63)</td>
<td>11.0</td>
<td>-1.49</td>
</tr>
</tbody>
</table>

LSM changes from baseline and differences to placebo
* p<0.05 vs. placebo

Chapple EAU 2008

Why Treat with Antimuscarinics?

TTX = tetrodotoxin

Mucaricin Receptor-Mediated Effects

Mice lacking M₃ receptors have severely impaired detrusor contractility in response to muscarinic receptor stimulation

M₃ receptors and human detrusor contraction

M₃ muscarinic receptors but not M₂ mediate contraction of the porcine detrusor muscle in vitro

D. J. Sellers¹, T. Yamanishi¹, C. R. Chapple², C. Couldeel¹, K. Yasuda³ & R. Chess-Williams¹

¹ Department of Biomedical Science, University of Sheffield, Sheffield, UK; ² Department of Urology, Royal Hallamshire Hospital, Sheffield, UK; ³ Department of Urology, Daikyu University, Kanagawa Hospital, Japan

See page 246, figure 2.
Contraction of Bladder Smooth Muscle

Adapted from Chapple CR. Urology 2000;55:33-46.

Distribution and function of muscarinic receptors throughout the body

<table>
<thead>
<tr>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>M&lt;sub&gt;1&lt;/sub&gt; Cerebral cortex, hippocampus, salivary glands, sympathetic ganglia, eye</td>
<td>Memory and cognitive function, saliva and tear secretion, gastric acid secretion</td>
</tr>
<tr>
<td>M&lt;sub&gt;2&lt;/sub&gt; Smooth muscle, hippocampus, hindbrain, cardiac muscle, eye</td>
<td>Heart rate, gastric sphincter tone, tear secretion, memory</td>
</tr>
<tr>
<td>M&lt;sub&gt;3&lt;/sub&gt; Smooth muscle, salivary glands, eye, brain</td>
<td>Bladder contraction, bowel motility, saliva and tear secretion, visual accommodation</td>
</tr>
<tr>
<td>M&lt;sub&gt;4&lt;/sub&gt; Basal forebrain striatum, salivary glands</td>
<td>Unknown</td>
</tr>
<tr>
<td>M&lt;sub&gt;5&lt;/sub&gt; Substantia nigra, eye</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Adapted from Chapple CR. Urology 2000;55:33-46.

See page 48, 'Antimuscarinic drugs' section, paragraph 4 (entire).
Rebecca Burnand, 10/13/2004

MHL15  For hippocampal expression of M2 receptors see Seeger T, et al. 2004;24:10117–27. Page 10118, column 1, paragraph 1, lines 1–2.

Increased Sensitivity to Muscarinic Receptor Stimulation in Detrusor Overactivity


Contraction of the Bladder

- The main part of detrusor contraction in normal bladders is mediated via muscarinic receptors
- Part of the contraction may be atropine-resistant

TTX = tetrodotoxin

ABMA = α,β-methylene ATP
Atropine Resistance in Human Detrusor

*Increased non-cholinergic activation in*

- Neurogenic bladders
- Outflow obstruction
- Idiopathic detrusor overactivity
- Interstitial cystitis
- Ageing

**Activation of the Ageing Human Bladder**

![Graph showing contraction vs frequency for different age groups](image)

- < 50 y
- 51 - 70 y
- > 70 y

Control vs Atropine

Activation of the Ageing Human Bladder

A Cholinergic transmission vs age
B Purinergic transmission vs age


"Our results do not provide evidence for age related contractile deterioration in human detrusor muscle strips, nor do they suggest that responses to anticholinergic spasmolytic drugs change substantially with age"

J Urol, 173:2182, 2005
Normal Voiding

Urge To void

Decision to void

Bladder distension

Contraction

Activate sensory fibers

Motor activation

S2-S4
Mechanism of OAB

![Diagram of bladder distension, contraction, urgency, incontinence, reflex voiding, sensory processing, central processing, and motor activation.]

1. Phasic smooth muscle contractions
Mechanism of OAB

1. Sensory processing
   - Bladder distension
   - Contraction
   - Incontinence

2. Enhanced afferent nerve sensitivity and firing

3. Enhanced central sensory processing
   - Activate sensory fibres
   - Sensory processing

Central processing
Mechanism of OAB

- Phasic smooth muscle contractions
- Bladder distension
- Contraction
- Incontinence

Central processing
- S2-S4
- Sensory processing
- Activate sensory fibres
- Enhanced reflex activation

Urgency

The bladder urothelium
- Not just a barrier... plays an active role in bladder function
- Has an afferent innervation with an important role in the reflex responses to bladder filling and distension
- Has a dense muscarinic receptor population, which mediates the release of a diffusible inhibitory factor that inhibits smooth muscle contraction
- It is unknown whether these receptors have a functional role, and whether this is inhibitory or excitatory

Chess-Williams R. Auton Autocoid Pharmacol 2002;22:133–45
RB59  Chess-Williams R. Autonomic & Autocoid Pharmacology 2002;22:133–45
See abstract, third bullet point.
Rebecca Burnand, 10/13/2004

RB60  Chess-Williams R. Autonomic & Autocoid Pharmacology 2002;22:133–45
See page 139, column 2, paragraph 3, lines 1–7.
Rebecca Burnand, 10/13/2004

RB61  Chess-Williams R. Autonomic & Autocoid Pharmacology 2002;22:133–45
See page 139, paragraph 4, lines 1–6.
Rebecca Burnand, 10/13/2004
Pathophysiology of Urgency

Bladder distension → Activation of sensory neurons → Chemicals neurotransmitters

Afferent nerves in the bladder

- **Distribution**: In humans and animals, afferent nerves have been identified suburothelially and in the smooth muscle.
  - suburothelially, they form a nerve plexus that lies immediately beneath the epithelial lining.
  - Some terminals are possibly located within basal parts of the urothelium.

- **Large numbers of muscarinic receptors have been identified in the bladder urothelium** — what is their function? [References]

Andersson KE. Urology 2002;59(Suppl 5a):43–50
Andersson KE. Lancet Neurol 2004;3:46–53
MHL16  Andersson KE. Urology 2002;59(Suppl 5a):43–50. See page 44, column 1, paragraph 2, lines 1–8.
Lewis_M, 10/1/2004

Lewis_M, 10/1/2004
M₃ receptors on the urothelium?

Urothelial-afferent communication
Pathophysiology of Urgency

- Bladder distension
- Activation of sensory neurons
- ATP
- Nitric Oxide
- Acetylcholine

Myofibroblasts

- Spindle-shaped vimentin positive suburothelial cells
- Close appositions with bare nerve endings and they are functionally connected via gap junctions composed on connexin 43

Interstitial Cells in the Detrusor

Smooth muscle cells

Interstitial cells

Neuron

Courtesy of K McCloskey

McCloskey and Gurney, J Urol 168:832, 2002

VACHT and c-kit
M₃ receptors on interstitial cells


Detrusor Interstitial Cells Respond to Muscarinic Receptor Stimulation

McCloskey and Gurney, J Urol 168:832, 2002
See figure 6, panels c and d.
Detrusor Interstitial Cells Respond to Muscarinic Receptor Stimulation

Effect mediated by $M_3$ receptors


Urothelial-myofibroblast-afferent communications

- Urothelium
- Chemical transmitters
- myofibroblast
- Electrical communication
- Sensory nerves
- Spinal Cord
**Urothelial-myofibroblast-afferent communications**

- **Stretch**
- **P2X/P2Y**
- **ATP**
- **ACh**
- **MR**

**Myofibroblast**

- **P2Y**
- **MR**

**Efferent nerve**

**Spinal Cord**

**Electrical-chemical communication**

**Afferent nerve**

**Smooth Muscle Cell**

- **M<sub>2</sub>**
- **M<sub>3</sub> induces contraction**

**Smooth Muscle Cell**

- **M? induces spontaneous activity**

**Interstitial cell (pacemaker, propagation, not contractile)**
Muscarinic Receptors

**EFFECTS OF TOLTERODINE ON AN OVERACTIVE BLADDER DEPEND ON SUPPRESSION OF C-FIBER BLADDER AFFERENT ACTIVITY IN RATS**

OSAMU YOKOYAMA,* ANWAR YUSUF, YOSHII MIWA, NOBUYUKI OYAMA, YOSHITAKA AOKI AND HIRONOBU AKINO

*From the Department of Urology, Faculty of Medical Science, University of Pahoe, Pahoe, Japan*

"Conclusions: These results suggest that at low doses tolterodine exerts an inhibitory effect on C-fiber bladder afferent nerves, thereby, improving BC during the storage phase"

Yokoyama et al, J Urol 174:2032, 2005
Effects of Tolterodine on Bladder Capacity before and after Resiniferatoxin (RTX) Treatment

Before RTX
Yokoyama et al, J Urol 174:2032, 2005

After RTX
Tolterodine increased micturition interval and bladder capacity in both controls and in RTX treated animals, suggesting that these effects were exerted independent of RTX-sensitive afferents


Effects of Tolterodine on Afferent Neurotransmission in Normal and Resiniferatoxin Treated Conscious Rats

Petter Hedlund, Tomi Streng, Taek Lee and Karl-Erik Andersson
From the Department of Clinical and Experimental Pharmacology, Lund University Hospital (PH, TS, TL, KEA), Lund, Sweden, and Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine (KEA), Winston Salem, North Carolina

Tolterodine increased micturition interval and bladder capacity in both controls and in RTX treated animals, suggesting that these effects were exerted independent of RTX-sensitive afferents

Effects of Darifenacin on Afferent Activity in the Rat Pelvic Nerve

Aδ-fibres

C-fibres


The autonomous bladder

An emerging paradigm

- The bladder is not passive during filling/storage
  - it has inherent rhythmic activity
- Autonomous rhythmic contractions may be required for sensory monitoring of bladder volume
- CNS may exert some control through autonomic nerves
  - parasympathetic
  - sympathetic

Gillespie JI. BJU Int 2004;93:478–83

Detrusor Overactivity: Initiation of Micturition Reflex

- Spontaneous ("myogenic") contractions
- Efferent nerve (no activity)
- Afferent activity
- Distension
- Local Factors

K-E Andersson, 2007
RB63  Gillespie JI. BJU Int 2004;93:478–83
See introduction, paragraph 1, lines 1–18 and page 482, column 1, paragraph 2, all.
Rebecca Burnand, 10/13/2004
Activation of urothelial afferents can trigger urgency

1. Phasic smooth muscle contractions
2. Urine enters proximal urethra
3. Activate sensory fibres

Central processing

Sensory processing

1/13/2009
Intravesical vanilloids

Source of resiniferatoxin

Source of Capsaicin
Parasympathetic excitatory fibres

Aδ fibre afferents

 PMC

PAG

Bladder

Intravesical vanilloids

Aδ fibre afferents

 Parasympathetic excitatory fibres

Botulinum Toxin in Urology

- Dykstra et al, J Urol 139: 919, 1988
Botulinum toxin - mechanism of action

Axon terminal

Transmitter vesicle

Heavy Chain

Light Chain

St B

VAMP/Synaptobrevin

St A and E

SNAP-25

Light Chain

Heavy Chain

Botulinum toxin - mechanism of action

Botulinum Toxin

Today and Tomorrow

Overactive bladder

Interstitial cystitis

BPH

Sphincter dyssynergia

Fowler syndrome
new promising treatment options for many different urological dysfunctions. However, large controlled trials are absolutely required to establish the role of botulinum-A toxin injections…"
Neuromodulation

Ano/genital Stimulation

TENS

SANS

Evidence – TENS and SANS

Frequency and Nocturia improve with TENS

No conclusive data on either
Sacral Root Stimulation
Interstim (Medtronic)

Advantages
Tined lead vs PNE

- Less prone to migrate
- (+) response: lead same position
- (-) response: explants easily
- Long screen period:
  - Changes in electrical settings
  - Neuro-physiological studies
### Sacral nerve stimulation RCTs

#### Improvement in symptoms

<table>
<thead>
<tr>
<th></th>
<th>Stimulation</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weil 2000</td>
<td>85%</td>
<td>5%</td>
</tr>
<tr>
<td>n = 39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt 1999</td>
<td>76%</td>
<td>5%</td>
</tr>
<tr>
<td>n = 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hassouna 2000</td>
<td>56%</td>
<td>4%</td>
</tr>
<tr>
<td>n = 43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Sacral nerve stimulation RCTs

#### Improvement in QOL (SF36)

<table>
<thead>
<tr>
<th></th>
<th>Relative improvement</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weil 2000</td>
<td>60 v 59</td>
<td>NS</td>
</tr>
<tr>
<td>n = 39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt 1999</td>
<td>46 v 36</td>
<td>0.0008</td>
</tr>
<tr>
<td>n = 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hassouna 2000</td>
<td>77 v 48</td>
<td>0.0001</td>
</tr>
<tr>
<td>n = 43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sacral nerve neuromodulation: correlation between clinical and urodynamic success (6 months follow-up, n=48)

- Success: >50% improvement in leaking episodes and/or pad use
- Success (no overactivity) 41.7%
- Success (overactivity still present) 10.4%
- Failed (no overactivity) 4.2%
- Failed (overactivity still present) 43.7%


Antimuscarinics for OAB Treatment

Rationale for Treatment

Blockade of muscarinic receptors at both detrusor and non-detrusor sites may prevent OAB symptoms and detrusor overactivity without depressing the contraction during voiding.
The Normal Micturition Cycle

Storage phase

First sensation to void

Normal desire to void

Emptying phase

Bladder pressure

>98% of the cycle is spent filling

Bladder filling

Normal desire to void

Bladder filling

Lower Urinary Tract Symptoms

Weak stream

Dysuria

Incontinence

Frequency

Urgency

Incomplete emptying

Hesitancy

Nocturia

Symptoms

?
“The Bladder is an Unreliable Witness”¹

- The bladder
  - Symptoms are not disease-specific
- The patient
  - Difficulties in reporting symptoms
    - Embarrassment
    - Underestimate seriousness: “normal part of aging”
    - Lack of knowledge or low expectation of treatment
- The clinician
  - Clinical skills: failure to elicit specific history
  - Bias, variations in practice and knowledge

¹ Turner Warwick 1979
**Historical Background**

- ‘Bladder irritability’
  - Hunter 1786

- ‘Dyssynergic detrusor dysfunction’
  - Hodgkinson 1963

- ‘Detrusor instability (bladder overactivity)’
  - Turner -Warwick and Bates 1970

- ‘Detrusor Hyperreflexia’
  - ICS 1988

- ‘Idiopathic detrusor (bladder) overactivity
  /Neurogenic detrusor (bladder) overactivity

**Overactive Bladder**

*Overactive bladder* is an empirical diagnosis used as the basis for initial management after assessing

- lower urinary tract symptoms,
- physical findings,
- urinalysis, and other indicated evaluation
Prevalence of OAB
Age and Sex

![Prevalence of OAB graph]

Based on results of NOBLE study – Stewart WF, et al. World J Urol 2003;20:327–33

Prevalence of OAB
Wet (with urgency incontinence) by age

![Prevalence of OAB graph]

Based on results of NOBLE study – Stewart WF, et al. World J Urol 2003;20:327–33
Prevalence of OAB
Dry (without urgency incontinence) by age

Based on results of NOBLE study – Stewart WF, et al. World J Urol 2003;20:327–33

OAB Syndrome: A symptomatic sequence

What Is Urgency?

- A sensation associated with abnormal bladder behaviour during the filling phase
- Difficult to define and explain to others who have not experienced it
- Quite distinct from normal urge

Classification of Lower Urinary Tract Symptoms (LUTS)

<table>
<thead>
<tr>
<th>Storage</th>
<th>Voiding</th>
<th>Post-micturition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Slow stream</td>
<td>Post-micturition dribble</td>
</tr>
<tr>
<td>Urgency</td>
<td>Splitting or spraying</td>
<td>Feeling of incomplete emptying</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Intermittency</td>
<td></td>
</tr>
<tr>
<td>Incontinence</td>
<td>Hesitancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Straining</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Terminal dribble</td>
<td></td>
</tr>
</tbody>
</table>
4th International Consultation on Incontinence

July 5-8, 2008
Palais des Congrès - Porte Maillot, Paris - France

Co-Sponsored by
International Consultation on Urological Diseases (ICUD)
International Society of Urology (SIU)
In collaboration with
the major international associations of urology,
gynecology and urodynamics
Committee 8: Drug Treatment

Chairmen: K-E Andersson (USA), C R Chapple (UK),

Members: L Cardozo (UK), F Cruz (Portugal), C Hampel (Germany), H Hashim (UK), M Michel (Holland), C Tannenbaum (Canada), A Wein (USA)

Herbison BMJ 2003;326:841

- 32 RCTs
- 6800 pts
  - Less leaks
  - Less voids
  - Increased MCC
- RR 1.29 – 1.54
- P<0.0001
**Herbison BMJ 2003;326:841**

- Outcomes not relevant to patients
- QOL not included
- Drugs lumped together

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes not relevant to patients</th>
<th>QOL not included</th>
<th>Drugs lumped together</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Study 2</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Study 3</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

---

**European Urology**

**The Effects of Antimuscarinic Treatments in Overactive Bladder: A Systematic Review and Meta-Analysis**

Christopher Chapple, Vik Khullar, Zahava Gabrielson, Julie Ann Dooley

*Sheffield Teaching Hospitals NHS Trust, Royal Hallamshire Hospital, Urology Research, 2 Floor Office, Glossop Road, Sheffield, S10 2JF, UK*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*

*Department of Urology, University of California, San Francisco, CA, USA*
The Effects of Antimuscarinic Treatments in Overactive Bladder: An Update of a Systematic Review and Meta-Analysis

Christopher R. Chapple\textsuperscript{a,b}, Vik Khullar\textsuperscript{b}, Zahava Gabriel\textsuperscript{c}, Dominic Muston\textsuperscript{d}, Caty Ebé Bitoun\textsuperscript{d}, David Weinstein\textsuperscript{d}

\textsuperscript{a}Sheffield Teaching Hospital NHS Trust, Royal Hallamshire Hospital, Urology Research, Sheffield, UK
\textsuperscript{b}Imperial College, St. Mary’s Hospital, London, UK
\textsuperscript{c}Neron Evidence Development Ltd., UK
\textsuperscript{d}Paris, France
Review – Neuro-urolgy

A Systematic Review and Meta-Analysis of Randomized Controlled Trials with Antimuscarinic Drugs for Overactive Bladder

Giacomo Novara, Antonio Galfano, Silvia Secco, Carolina D’Elia, Stefano Cavallini, Vincenzo Picarra, Walter Arshani

1. I.R.C.C.S. Istituto Ortopedico Veneto (I.O.V.), Padova, Italy
2. Department of Oncological and Surgical Sciences, Urology Clinic, University of Padua, Italy

984 Medline
910 Embase
669 Web of Science

1637 citations
1466 excluded based on screening of the abstracts using general criteria

191 potentially relevant articles identified for further review
138 Articles excluded after full-text review due to:
Antimuscarinics for diseases other than OAB
Phase I studies
Incomplete data reporting
RCT on obsolete drugs
Duplicate publications
Post-hoc analyses of RCTs

53 articles included in meta-analysis
(50 RCTs and 3 pooled analyses)
**Fig. 2** - Forest plot of relative risk of all-cause withdrawals versus placebo for each included treatment and dose.

**Fig. 3** - Forest plot of relative risk of any- or all-cause adverse event versus placebo for each included treatment and dose.
Antimuscarinics

Non-subtype selective
- Atropine, hyoscyamine
- Propantheline
- Tolterodine
- Fesoterodine
- Trospium
- Solifenacin

Subtype selective (M₃)
- Darifenacin
### ICI assessments

<table>
<thead>
<tr>
<th>Antimuscarinics</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Trospium</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Propantheline</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Atropine, hyoscyamine</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

### Drugs with mixed actions

**Antimuscarinic + other actions**

- **Oxybutynin**
- **Propiverine**
- **(Dicyclomine)**
- **(Flavoxate)**
ICI assessments

<table>
<thead>
<tr>
<th>Drugs with mixed actions</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Propiverine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>(Dicyclomine)</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>(Flavoxate)</td>
<td>2</td>
<td>D</td>
</tr>
</tbody>
</table>

Antidepressants

Imipramine

- Antidepressant; complex pharmacological profile, including non-subtype selective antimuscarinic effect

- Possible effects on AVP release and renal proximal tubular Na$^+$ and water reabsorption
"Imipramine prolonged the PR (p<0.001), QRS (p<0.001) and QTc (p<0.001) intervals, increased the heart rate (p<0.001) and lowered T-wave amplitude (p<0.05)"

ICI assessment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipramine</td>
<td>3</td>
<td>C*</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>2</td>
<td>B*</td>
</tr>
</tbody>
</table>

* Should be used with caution. Not approved for the indication
Vasopressin analogues

Vasopressin

Desmopressin (DDAVP)

Desmopressin

- Antidiuretic, no direct bladder effect
- No direct cardiovascular actions
### ICI assessment - nocturia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmopressin</td>
<td>1</td>
<td>A*</td>
</tr>
</tbody>
</table>

* Beware hyponatremia and water retention

### ICI assessment - OAB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmopressin</td>
<td>2</td>
<td>C*</td>
</tr>
</tbody>
</table>

* Beware hyponatremia and water retention
### ICI assessments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha_1 )-AR antagonists</td>
<td>1</td>
<td>D</td>
</tr>
<tr>
<td>(alfuzosin, doxazosin, terazosin, tamsulosin)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ICI assessments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Grade</th>
<th>Level</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta_2 )-AR agonists</td>
<td></td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>(terbutaline, salbutamol, clenbuterol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \beta_3 )-AR agonists</td>
<td></td>
<td>2</td>
<td>B</td>
</tr>
</tbody>
</table>
## ICI assessments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil)</td>
<td>1</td>
<td>B</td>
</tr>
</tbody>
</table>

## ICI assessments

**Cox inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>2</td>
<td>C</td>
</tr>
</tbody>
</table>
Drugs for OAB/DO

Toxins

Vanilloids (intravesical)
- Capsaicin
- Resiniferatoxin

Botulinum toxin (bladder wall)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin*</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Resiniferatoxin*</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Botulinum toxin A**</td>
<td>2</td>
<td>A</td>
</tr>
<tr>
<td>Botulinum toxin B**</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

*Intravesical; **Bladder wall

ICI assessments

Neurogenic DO

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin*</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Resiniferatoxin*</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Botulinum toxin A**</td>
<td>2</td>
<td>A</td>
</tr>
<tr>
<td>Botulinum toxin B**</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

*Intravesical; **Bladder wall
ICI assessments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resiniferatoxin*</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Botulinum toxin A**</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Botulinum toxin B**</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

*Intravesical; **Bladder wall

Summary

- Antimuscarinics are still the mainstay of overactive bladder treatment
- Surgery remains a last resort for the small number of patients who can’t be managed by pharmacotherapy
Conclusions

- Multiple efferent and afferent pathways are involved in LUT function.
- Potential pharmacologic targets for OAB exist in the CNS (cerebral cortex, midbrain, spinal cord) and periphery (LUT).
- Both sensory and motor pathways are future potential targets for pharmacological intervention.