W3: Genetics, Genomics and Metagenomics of Pelvic Floor Dysfunction
Workshop Chair: Rufus Cartwright, United Kingdom
20 October 2014 09:00 - 12:00

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<td>• Heidi Brown</td>
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<td>• Jennifer Wu</td>
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<td>Candidate gene studies of incontinence</td>
<td>• Pawel Miotla</td>
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<td>Genomics and incontinence/prolapse</td>
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<td>Conclusions</td>
<td>• Rufus Cartwright</td>
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Aims of course/workshop
With the advent of genomic techniques, we now stand on the cusp of a revolution in our understanding of pelvic floor disorders. Identification of the genetic variants underlying the heritability of these conditions provides useful markers for clinical risk, prognosis, and treatment response, and startling new insights into pathophysiology. This workshop brings together genetic epidemiologists, urologists and urogynaecologists pushing the boundaries of this field. We will review the evidence so far from the genetics of pelvic floor dysfunction, and explore how understanding of both human and microbial genomes will translate to personalized therapeutics.
Advanced clinical and research methods for unravelling the relationship between pathophysiology and the success of OAB treatment

Cara Tannenbaum, MD, MSc, Canada
Ann Hanna-Mitchell, PhD, USA
Rufus Cartwright, MD, UK

ICS 2014

Mrs. S., 68 years old

- Urinary incontinence x 5 years
- Leakage incontinence
- Type 2 diabetes, high blood pressure, chronic venous insufficiency, anxiety
- Drinks two cups of coffee and one cup of tea per day
- Medication:
  - Metformin
  - ACE inhibitor
  - Furosemide
  - Lorazepam 0.5 mg po bid for insomnia and anxiety
- On exam: obese, sacral innervation intact, no prolapse, weak pelvic floor muscles, PVR 45 ml, normal urinalysis

Mrs. S. wants you to tell her:

1) What is the underlying etiology and pathophysiology of her symptoms
2) Her prognosis with treatment

18/06/2014

Do we currently have good answers to her questions?

What are the different etiologies and pathophysiology of her problem?

How is etiology linked to pathophysiology?

What is the relationship between pathophysiology and the success of OAB treatment?

What is the relationship between pathophysiology and the success of OAB treatment?

What we DO know:
Definition of Idiopathic OAB

- a symptom syndrome characterized by urinary urgency, with or without urgency incontinence
- +/- urinary frequency
- +/- nocturia
- in the absence of pathological or metabolic disorders (UTI, bladder ca, benign prostatic enlargement, spinal cord injury) that might otherwise cause such symptoms

What we DON’T know:

1) Do sub-profiles of OAB exist?
   - Diurnal variations
   - Different precipitating factors
2) Underlying etiologies
3) Different pathogenic pathways/mechanisms?
4) Validated screening strategies and biomarkers for different sub-profiles
5) The best treatment approach according to etiology

Ask a question for young adults

Ask your questions here. We will forward it to who we feel is the appropriate expert to answer your question. You are asked to provide a name, age, country and email address. We would appreciate it if you gave your correct age, location and email address. However, you do not need to give your real name if you don’t want to. Only the name, age and it will be available to view in this section and - if you provided an email address - we will forward the answer to your email address.

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A Systematic Framework for OAB: A proposal

**ENTITY**

**ETIOLOGY**

**PATHOGENESIS/MECHANISMS**

**PRESENTING SYMPTOMS/PHENOTYPE**

**BIOMARKERS/SCREENING STRATEGIES**

**APPROPRIATE TREATMENT**

### Objectives of this workshop

**1st HALF**

- To describe our current state of knowledge regarding the pathophysiology of OAB
  - Myogenic dysfunction
  - Vascular etiologies
  - Urothelial dysfunction
  - Central nervous system dysregulation
- To highlight existing or potential biomarkers and screening strategies to help detect these pathophysiologies
- To review the evidence from randomized trials linking pathophysiology to the success of OAB treatment

**2nd HALF**

- To discuss a future framework for classifying OAB patients according to underlying etiology/pathophysiology
  - For research purposes
    - Biomarker development
    - Inclusion in clinical trials to test treatment strategies
  - In practice
    - Clinical symptoms
    - Treatment

### Imperative need for a systematic approach, both clinically and for research purposes

1. Easier to target therapy
   - Evaluation could be better streamlined
   - Patient response would be more predictable
   - Easier to manage patient expectations
   - Clinical practice would be more rewarding for clinicians (vs. current sense of frustration)

2. Easier to establish research priorities
   - Validated screening strategies and biomarker development
   - Easier to direct basic science research to better understand disease progression
   - Better inclusion criteria for clinical trials, based on pathophysiology
   - Elucidation of new treatment targets
**Current Pathophysiologic Hypotheses of OAB**

Ann T. Hanna-Mitchell Ph.D.
Assistant Professor
Department of Urology
Case Western Reserve University
USA

**Anatomy of the Bladder Wall**

The bladder wall consists of 3 well-demarcated layers:

- Epithelial lining (Urothelium)
- Submucosal layer (containing myofibroblasts, blood vessels and nerve endings)
- Smooth muscle (Detrusor)

**Pathophysiology of idiopathic OAB:**

**Mechanistic Insights**

**Peripheral Contributing Factors:**

Pathophysiological alterations originating in any of the tissue groups within the bladder wall

**Central Contributing Factors:**

Central alterations in neuronal signalling within the spinal cord and higher centers

**Myogenic Dysfunction**

**Detrusor Overactivity**
Increased detrusor activity: "local" modulation

**Extracellular:** at the cell membrane

**Intracellular:** within the smooth muscle cell

- Increased detrusor activity: "local" modulation

**Extracellular:**
- ATP release by the urothelium-release upregulated in OAB
- ATP release by bladder parasympathetic nerve endings-release upregulated in OAB
- ATP breakdown/"deactivation" by Ectonucleotidases-ectonucleotidase activity is decreased in detrusor samples from DO bladders

**Intracellular:**
- ATP release by bladder parasympathetic nerve endings-release upregulated in OAB (Burnstock, Purinergic Signal, 2014)
- ATP breakdown/"deactivation" by Ectonucleotidases-ectonucleotidase activity is decreased in detrusor samples from DO bladders

Increased ATP presence and decreased ATP inactivation → increased presence of ATP in the urine

**Smooth Muscle Cell Structure**

(Cell Signalling Biology - Michael J. Berridge - www.cellsignallingbiology.org - 2012)

### Urinary ATP May Be a Dynamic Biomarker of Detrusor Overactivity


**Reactive Oxygen Species**

- Reactive oxygen species (ROS) are chemically reactive molecules. Examples include oxygen ions and peroxides (e.g. H$_2$O$_2$).
- ROS are formed as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling and homeostasis.
- Reactive Oxygen Species (ROS) activate the ROCK pathway (Jin et al., AJP, 2004; Aghajanian et al., Plos One, 2009).
- Vascular inadequacy/ischaemia and metabolic dysregulation (as in DM/Metabolic Syndrome; atherosclerosis) ⇒ ↑ [ROS]

Increased levels of ROS in detrusor muscle could lead to upregulation/activation of RhoA/ROCK pathway ⇒ increased spontaneous contractile activity/hyperactivity of the detrusor

**Urine [ROS] / bladder biopsy [ROS] May Be Biomarkers of Detrusor Overactivity**

**Vascular Dysfunction**

- Vascular Etiologies
  - Arterial Occlusive Disease and concomitant bladder ischemia may produce bladder dysfunction, including detrusor overactivity (Nomiyi et al., J. Urol, 2013)
  - Elderly patients with lower urinary tract symptoms (LUTS) including DO exhibit lower bladder vascular perfusion compared with younger individuals, irrespective of gender (Pinggera et al., BJUI, 2008)

**RhoA/ Rho-associated kinase (ROCK) pathway stimulates smooth muscle contraction**


- ROCK inhibitors Y27632 and GSK-576371- shown to supress bladder overactivity in animal models

(Chacko et al., Neurourol Urodyn, 2010; Marx et al., Int. J. Urol, 2013)

**Arterial Occlusive Disease** and concomitant bladder ischemia may produce bladder dysfunction, including detrusor overactivity

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Elderly patients with lower urinary tract symptoms (LUTS) including DO exhibit lower bladder vascular perfusion compared with younger individuals, irrespective of gender

(Pinggera et al., BJUI, 2008)
Urothelial Dysfunction

The bladder urothelium:
- vital blood-urine barrier
- dynamic sensory tissue

- Breach in urothelial barrier function allows water, urea and toxic substances to pass into the underlying tissue and affect neural and/or muscle layers, resulting in symptoms of urgency and frequency!

(Birder & de Groat, Nat Clin Pract Urol, 2007)

CNS Dysregulation

- Disruption of bladder reflexes at the level of the spinal cord and/or pontine micturition center in the brain stem

- Abnormal central processing of bladder afferent signaling and/or cognitive manipulation may produce perceptions of urinary urgency in idiopathic OAB patients

(McCloskey, Neurourol Urodyn, 2010; Kanai et al., Neurourol Urodyn, 2014)

Central nervous system dysregulation in OAB

- A role for sub-urothelial/lamina propria interstitial cells with modified coupling characteristics has also been suggested to play a role in the development of idiopathic OAB.

(Birder & de Groat, Nat Clin Pract Urol, 2007)
How can this knowledge of bladder physiology/pathophysiology be applied to customize treatment strategies, leading to improved outcomes?
Clinical biomarkers and screening strategies

Rufus Cartwright
MRC Research Training Fellow
Dept. of Epidemiology & Biostatistics and Dept. of Urogynaecology
Imperial College London

Disclosures

Financial
Grant funding: Astellas, UK Continence Society, Imperial BRC, IUGA, ICS, Imperial Healthcare Charity, Genesis Research Trust.
Salary support: NIHR, UCB Pharma
Speaker fees / travel: Astellas, UCB Pharma, NIHR

Non-financial
Editor: BJOG
Committees: IUGA Fellows, EAU Thromboprophylaxis Guideline

Overview

• What is overactive bladder?
• What is a biomarker?
• Myogenic dysfunction
  – Detrusor overactivity, the “classic” biomarker of OAB
  – Video urodynamic signs
  – Bladder Wall Thickness
• CNS dysregulation
  – fMRI for urgency
• Vascular aetiologies
  – Serum CRP
  – NIRS
• Urothelial dysfunction
  – Urinary NGF
  – Urinary BDNF
  – Urinary MCP-1
• Hypothesis free research
  – ‘Omics and biomarker discovery

What are biomarkers?

• Any objectively measurable indicator of a disease process (pathology)
• Three broad purposes
  – Used to diagnose a disease or condition
  – Used as a tool to assess the severity or progression of a disease
  – Used as an indicator of disease prognosis, including prediction of response to specific therapies

Myogenic Dysfunction
Detrusor Overactivity

“A diagnosis by symptoms and urodynamic investigations, made when involuntary detrusor muscle contractions occur during filling cystometry” ICS / IUGA Joint Terminology Report, 2010

Do OAB symptoms predict DO?

- Unselected population of 4,500 women with LUTS
- Only 54% of women with OAB had DO
- 32% of women without OAB still had DO
  
  Digeseu et al, 2003

- Multivariate logistic regression of factors predicting DO in cohort of 551 women
- Cardinal symptoms of OAB namely urgency, frequency and UUI were not found to be statistically significantly associated with DO
  
  Aschkenazi et al, 2007

DO does not predict success of anticholinergics

- 352 elderly patients with OAB
- 76% proven to have DO
- No significant difference in response to oxybutynin between patients without and those with DO
  
  Malone-Lee et al, 2003

- 308 OAB patients randomised to tolterodine or placebo
- 50% proven to have DO
- Significant benefits in tolterodine arm regardless of urodynamic diagnosis
  
  Malone-Lee et al, 2007

- 260 OAB patients aged >18 randomised to placebo / fesoterodine 4mg/8mg/12mg
- 54% with proven DO
- Significant dose response in each fesoterodine arm regardless of urodynamic diagnosis
  
  Nitti et al, 2009

Detrusor overactivity does not predict outcome from sacral nerve stimulation

- 104 patients undergoing test stimulation for intractable urgency and UUI
- 64% success rate
- Equal success in DO and non-DO group
  
  South et al, 2007

- 111 patients having permanent stimulator implanted
- 6 month follow up
- No difference between groups with and without DO
- Remission of DO not a predictor of clinical success
  
  Groenendijk et al, 2008

Why is detrusor overactivity not a good clinical prognosticator?

- Very poor test-retest reliability in normal practice
  
  Rahmanou et al, 2008

- Very difficult to improve reliability of interpretation of cystometrogram
  
  Zimmern et al, 2006

- Very poor adherence to recommended standards
  

- Very poor inter-rater reliability between different centres
  
  Renganathan et al, 2008
Videourodynamics

- First urodynamic studies in 1880's
  Mosso and Pellacani, 1882
- First synchronised with cineradiography in 1950's
  Enhorning et al, 1964
- Screening fluoroscopy with the real time recording of a cystometrogram
- Simultaneous evaluation of physiology and functional anatomy
- Videocystourethrography often described as the 'gold standard'
  Turner-Warwick, 1979

Videocystourethrography

NICE CG40
- "It has not been shown that carrying out urodynamic investigations before initial treatment improves outcome."

Limited Indications
- Complex cases in tertiary referral clinic
- Previous failed incontinence surgery
- Recurrent urinary tract infection

Imaging alternatives to video urodynamics?

- Bladder wall thickness
- fMRI for urgency
- Near infrared spectroscopy of brain oxygenation
Detrusor hypertrophy

- Detrusor overactivity occurs spontaneously
- To prevent leakage the pelvic floor and urethral sphincter are co-contracted
- Detrusor muscle as a smooth muscle continues to contract
- Isometric contraction leads to detrusor hypertrophy

Measurement of Bladder Wall Thickness

- Transvaginal probe
- Urethra visualised as hypoechoic stripe
- Measurements made perpendicular to epithelium

Relationship between diagnosis, detrusor pressure and BWT

Kuhn et al 2010

Linear association between detrusor pressure at maximum flow and BWT

Serati et al 2010

BWT as marker of DO

- Systematic review of 5 studies
- With 5 mm cut off - sensitivity between 40-84% and specificity between 78-89%
  Latthe et al, 2010
- But no association in the large multicentre BUS study Latthe et al, 2014
- And no response to solifenacin in the SHRINK study (n=547) Robinson et al, 2013

Vascular Dysfunction
Serum Markers of Metabolic Syndrome Elevated in OAB

- CRP shows homogeneous results
- Consistently elevated in OAB wet and dry
  

- Other markers including B-type natriuretic peptide and adipokinin now being investigated
  

CNS Dysregulation

Characteristic Brain Response to Bladder Filling In OAB Patients

- Reproducible patterns of activation during MRI urodynamics
  
  Griffiths et al, 2005

- Moderate correlations with self rated symptoms severity
  
  Tadic et al 2010

- Now reproduced by other groups
  
  Pontari et al 2010, Komesu et al, 2011

- And replicated using Near Infrared
  
  Farag et al, 2013

Near Infrared Brain Spectroscopy – Sakakibara et al, N&U 2014

Urothelial Dysfunction

- The urothelium plays an important sensory role
- Urothelial inflammation may explain increased BWT
- Patients with refractory OAB commonly have chronic histological cystitis
- Many inflammatory urine markers have been tested for association with OAB
Inflammatory Urinary Biomarkers

• Urinary NGF
• Urinary BDNF
• Urinary PGE2
• Urinary MCP1

Inflammatory Biomarkers are Non-specifically elevated in LUTS

• BDNF reported to be greatly increased in OAB compared to normal controls; and responsive to treatment. Antunes-Lopez et al J Urol 2013, Wang et al, 2014
• Unable to replicate result in representative population Bhide et al, 2014
• MCP-1 reported to be 2-3 fold elevated in UUI compared to normal controls; Tyagi et al, 2011, Ghoneim et al, 2012
• Unable to replicate result in representative population Tolkon et al, 2014

Hypothesis Free Research
The Promise of ‘Omics

Family studies

Family Studies - OAB

• Familial aggregation for urgency incontinence, and nocturnal enuresis
• An affected first degree relative confers 1.5-3.7 fold increased risk 

Beta 3 adrenoceptor rs4994 and overactive bladder in women

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<th>Study</th>
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<td>Honda 2006</td>
<td>2.49 (1.47, 4.20)</td>
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<td>Ferreira 2011</td>
<td>2.41 (1.38, 4.21)</td>
<td>43.31</td>
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<td>Overall (heterogeneity = 0.0%, p &gt; 0.938)</td>
<td>2.46 (1.67, 3.69)</td>
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• Venice Rating BAA – Moderate epidemiological credibility
What are ‘Omics?  

- Genomics – the study of genetic variants across the whole genome  
- Transcriptomics – the study of gene expression for all genes  
- Metabolomics – the study of all metabolites in serum, urine or other body fluids  
- Microbiomics – the study of all colonising microorganisms, (usually bacteria) using their DNA “signatures”

Genome-wide association studies  

- GWAS look for the associations of millions of common genetic variants right across the genome  
- Require very large sample sizes to compensate for multiple hypothesis testing  
- Provide novel insights into physiology, pathology, and treatment

GWAS – Urge Incontinence  

- 1115 differentially expressed genes in detrusor overactivity (p<.001)  
- M3 muscarinic receptor most overexpressed gene  

Bladder Transcriptomics  

- Cartwright et al, 2014
Urine Metabolomics

- Metabolomics is a high-throughput technology
- Quantitatively measures metabolites within a biological sample
- Nocturia is associated with a differing urinary metabolic biomarker profile compared to urgency
- Differences in pathophysiology between the two symptoms

Bray et al, 2014

OAB Biomarkers Summary

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Conclusions

- A wide variety of biomarkers have been discovered for OAB
- The clinical utility of these markers is without exception unclear
- No evidence that any existing putative biomarker predicts treatment response
- May reflect extremely limited efficacy, and non-specific action of OAB drugs
A systematic review of pathophysiology and the success of OAB treatment: Methods and Findings

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ICS 2014

State of the art

What do we know about the relationship between pathophysiology and the success of OAB treatment?

Methods:
- Systematic review of the literature
- All randomized treatment trials of OAB

Outcomes:
- Frequency of profiling for underlying pathophysiology
- Summary of the effectiveness of OAB treatment among individuals with different pathophysiologic profiles

Identification of OAB RCTs

1958 records identified through database searching

KEYWORDS: overactive/hyperactive/urge bladder + randomized trial
624 Medline
852 Embase
115 CINAHL
367 Cochrane CENTRAL and Database of Systematic Reviews
From January 1, 1980 to August 12, 2013

992 records screened

966 articles removed
duplicates, editorial, comments, thesis

992 records screened

239 full-text OAB treatment trials included

Article Screening and Assessment

Excluded studies
- Not OAB (with or without incontinence)
- Not a clinical trial
- Not adults
- Not human
- Sub-analysis from original RCT (i.e. pooled data, post-hoc, subgroup analysis, etc.)
- Pharmacokinetic or safety study, not effectiveness of treatment
- Men with concomitant outflow obstruction
- Neurogenic OAB

Pathophysiologic profiling

In the methods of the trial, search for evidence of:

1) Urothelial dysfunction
   - participants characterized by findings from bladder biopsies of urothelial/suburothelial tissue or the results of urine collection for urothelial cell analysis, biomarkers, or protein expression.

2) Myogenic dysfunction
   - identified by documentation of involuntary detrusor contractions on urodynamic testing.

3) Central nervous system/stress-related/perceptual disturbances
   - by brain imaging studies or measurement of serum or urine CRF or cortisol.
   - also considered scores on validated anxiety or depression questionnaires, or systematic screening of participants for a diagnosis of depression or anxiety.

4) Vascular ischemia — reviewers suggested there was not enough evidence - nixed

Outcome assessment

In the methods of the trial, search for evidence that urgency outcomes were assessed re: effectiveness of treatment

- Objective measures such as reductions in daily episodes of urinary urgency or urgency incontinence recorded on bladder diaries
- Subjective improvements of urgency on validated urgency scales
- An increase in the cystometric volume at strong desire/maximum volume to void.

The number of involuntary contractions per tracing, urinary frequency, the mean volume voided, the volume at first desire to void, incontinence-specific quality of life and the current perception threshold were not considered valid measures of urgency.
Results
n=239 RCTs

Frequency of pathophysiologic profiling=
20% (n=48/239)

AND frequency of including urgency outcomes =
42% of 20% (n=20/48)

Distribution of pathophysiologic profiles

20 RCTs included

- 0 RCTs
- Abnormalities in urothelial cell layer of the bladder
- Abnormal central nervous system processing
- 1 trial:Interstitial cell expression

- 4 trials
- Comparison of same treatment in OAB patients with and without involuntary detrusor contractions (urodynamic testing)

- 15 trials
- Suspected myogenic dysfunction, randomized to different therapeutic strategies

Interstitial cell pathology and success of OAB treatment

- 1 trial determined the response of suburothelial myofibroblasts to botox treatment in idiopathic OAB patients
  (Roosen et al, Eur Urol, 2009)

- Method:
  - 11 OAB patients injected with 200 units botulinum toxin A vs 10 controls without OAB
  - Bladder biopsies before and after treatment were studied with immunohistochemical labeling for expression of the gap-junction protein connexin 43 and the membrane receptor c-kit

Interstitial cell pathology and success of OAB treatment

- Results:
  - Participants with OAB had more gap junctions and higher expression of connexin 43 compared to controls at baseline testing
  - After treatment: No change in connexin 43 immunoreactivity expression in OAB patients despite clinical improvement
  - No difference was observed in c-kit expression at baseline between idiopathic OAB patients and controls, nor were changes noted at follow-up in either group

Involuntary detrusor contractions and success of OAB treatment

- 4 trials: DO vs no DO
  - 3 trials: antimuscarinic therapy (oxybutynin, tolterodine ER or fesoterodine ER)
    (Daly et al, J Physiol 2007; Nils et al, BJU Int 2010; Mahrenlee & Buhler, BJU Int 2008)
  - 1 trial: vaginal estradiol
    (Carinci et al, J Obstet Gynaecol 2001)

- Main results:
  - No differences in urgency outcomes on bladder diary measurement between patients with or without urodynamically documented involuntary detrusor contractions, regardless of treatment

Effectiveness of OAB treatment compared to placebo for involuntary detrusor contractions

- 8 trials compared active treatment to placebo

- Main results:
  - Transdermal estradiol + naproxen 250 mg p.o. bid
  - Botulinum toxin A 200-unit injection
  - Oxybutynin 5 mg p.o. bid
  - Cizolirtine 800 mg p.o. daily
  - Placebo effect
Effectiveness of OAB treatment compared to placebo

<table>
<thead>
<tr>
<th>Source</th>
<th>Pathophyslogic profile(s)</th>
<th>n</th>
<th>Intervention(s)</th>
<th>Urgency assessment</th>
<th>Efficacy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams et al. (1998)</td>
<td>Detrusor overactivity (DO)</td>
<td>293</td>
<td>Tolterodine 2mg bid or oxybutynin 5mg tid or placebo</td>
<td>Bladder diary</td>
<td>Oxybutynin significantly better than placebo. No difference between tolerodine and placebo. Improvement with the combined transdermal estradiol plus suppression combination only. No improvement with estradiol alone.</td>
</tr>
<tr>
<td>Brem et al. (1995)</td>
<td>DO</td>
<td>16</td>
<td>Transdermal estradiol 0.03 mg alone or in combination with naproxen 250 mg bid or placebo</td>
<td>Bladder diary</td>
<td>Improvement with the combined transdermal estradiol plus suppression combination only. No improvement with estradiol alone.</td>
</tr>
<tr>
<td>Zat'ura et al. (2009)</td>
<td>DO</td>
<td>135</td>
<td>Cizolirtine citrate 800 mg vs. oxybutynin 15 mg vs. placebo</td>
<td>Bladder diary</td>
<td>Cizolirtine and oxybutynin groups improved compared to placebo. No difference between cizolirtine and oxybutynin.</td>
</tr>
<tr>
<td>Dugas et al. (2012)</td>
<td>DO</td>
<td>257</td>
<td>Oral clonidine 75 µg/d vs. 150 µg/d vs. placebo Intravesical resiniferatoxin 50mM 100mL vs. placebo</td>
<td>Bladder diary</td>
<td>No difference between groups in intent-to-treat analysis. Placebo superior to resiniferatoxin.</td>
</tr>
<tr>
<td>Rios et al. (2007)</td>
<td>DO</td>
<td>58</td>
<td>Trospium chloride 15 mg tid vs. placebo</td>
<td>Bladder diary</td>
<td>No difference between groups in intent-to-treat analysis. Placebo superior to resiniferatoxin.</td>
</tr>
</tbody>
</table>

No difference between 2 different treatments in urgency outcomes

- 3 comparative trials

Main results: No between-group differences
- tolterodine 2 mg p.o. bid VS oxybutynin 5 mg p.o. bid
- propiverine 15 mg p.o. bid VS tolterodine 2 mg p.o. bid
- cizolirtine 800 mg p.o. daily VS oxybutynin 15 mg p.o. bid

Similar effects of OAB conservative management interventions

- 1 conservative management trial
  - Burgio KL, JAND 2002

Main results:
- All participants improved
- No between group difference
Similar improvement with pelvic floor muscle exercises vs oxybutynin

- 1 trial (Kafri R, Int Urogynecol J Pelvic Floor Dysfunct 2007)

- Intervention: pelvic floor muscle exercises vs oxybutynin ER 5 mg p.o. daily

- Main results:
  - Improvement in both groups
  - No between-group differences

No impact of botulinum toxin A site injection on treatment responses

- 3 different trials compared different sites of botulinum toxin A injection on treatment responses

- Population studied: OAB patients refractory to antimuscarinic treatment

- Main results: No between-group differences

Interpretation

- Only 20% of RCTs of idiopathic OAB (n=48) (20%) profiled participants on underlying pathophysiology
- Less than half of these (n=20) reported treatment efficacy for urgency symptoms by pathophysiological sub-type.
- No studies investigating the effect of treatment on urothelial dysfunction with biomarkers or tissue samples
- No studies profiled on CNS dysfunction
- No effect of Botox on interstitial cell protein expression
- No discriminating effect of treatment on patients with involuntary detrusor contractions – misclassification?

Next steps for consideration

- Better classification of underlying etiology of OAB
  - Biomarkers?
  - Screening strategies?
  - Clinical correlates?

- Are involuntary detrusor contractions specific for etiology?
  - Problem of common symptom pathway

- Are treatments specific to underlying root causes?
  - Problem of non-specific mechanisms of action

- The cost of sub-classifying OAB by pathophysiology
A Systematic Framework for OAB

1. **Identity**
   - OAB Profile 1
     - Vascular ischemia
   - OAB Profile 2
     - Stress

2. **Etiology**
   - Unilateral dysfunction
   - OAB, detrusor overactivity

3. **Pathogenesis/Mechanisms**
   - Blood flow, bladder, urinary function
   - Anxiety, motivation

4. **Presenting Symptoms/Phenotype**
   - Geriatric OAB
     - Interacting pathogenic pathways

5. **Biomarkers/Screening Strategies**
   - Geriatric assessment including lifestyle, medications, cognitive, functional impairments

6. **Appropriate Treatment**
   - Address all contributing factors

**OAB Profile 1**
- Vascular ischemia
- Stress

**OAB Profile 2**
- Unilateral dysfunction
- OAB, detrusor overactivity

**Geriatric OAB**
- Interacting pathogenic pathways
- Geriatric assessment including lifestyle, medications, cognitive, functional impairments

**Address all contributing factors**