W3: Genetics, Genomics and Metagenomics of Pelvic Floor Dysfunction

Workshop Chair: Rufus Cartwright, United Kingdom

20 October 2014 09:00 - 12:00

Start	End	Topic	Speakers
09:00	09:10	Introduction	• Rufus Cartwright
09:10	09:30	Classical epidemiology of UI and prolapse	• Heidi Brown
09:30	09:50	Linkage, twin and family studies	• Ian Milsom
09:50	10:10	Candidate gene studies of prolapse	• Jennifer Wu
10:10	10:30	Candidate gene studies of incontinence	• Pawel Miotla
10:30	11:00	Break	None
11:00	11:20	Genomics and incontinence/prolapse	• Nedra Whitehead
11:20	11:40	The urinary microbiome and overactive bladder	• Jonathon Williams
11:40	11:50	Discussion	All
11:50	12:00	Conclusions	• Rufus Cartwright

Aims of course/workshop

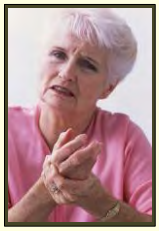
With the advent of genomic techniques, we now stand on the cusp of a revolution in our understanding of pelvic floor disorders. Identification of the genetic variants underlying the heritability of these conditions provides useful markers for clinical risk, prognosis, and treatment response, and startling 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

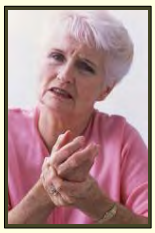
ICS 2014

Mrs. S, 68 years old



- Urinary incontinence x 5 years
- Leakage with urgency, 10x/day, 4x/night
- 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

Do we currently have good answers to her questions?

- *What are the different etiologies underlying the OAB syndrome?*
- *How is etiology linked to pathogenesis?*
- *How can we differentiate patients with separate underlying pathophysiologies?*
- *What is the relationship between pathophysiology and the success of OAB treatment?*

Ask a question for young adults

Welcome to the young adults area in the 'ask a question' section. Do you have any questions about Huntington's disease that you've always wondered about, but never had the chance to ask? Then this is your chance! Below is a panel of Huntington's disease experts to answer any questions you may have.

Feel free to send any questions you have using the form below and we will forward it to who we feel is the appropriate expert to answ your question. You are asked to provide a name, age, country and email address. We

What we DO know: Definition of Idiopathic OAB

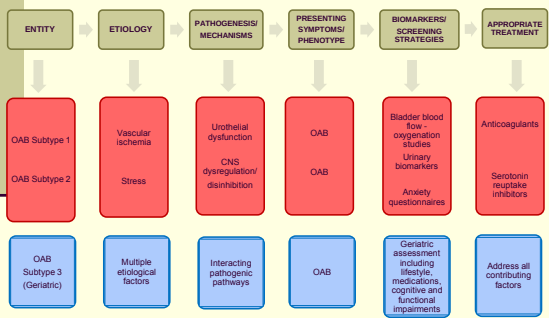
- a symptom syndrome characterized by **urinary urgency**, with or without urgency incontinence
- +/- urinary frequency
- +/- nocturia
- in the absence of pathological or metabolic disorders (UTI, bladder ca, benign prostatic enlargement, spinal cord injury) that might otherwise cause such symptoms

Abrams et al. Urology 2003;61:37-49
ICS / IUGA Joint Terminology Report, 2010

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

A Systematic Framework for OAB: A proposal



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

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

Objectives of this workshop

2nd HALF

INTERACTIVE

- 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

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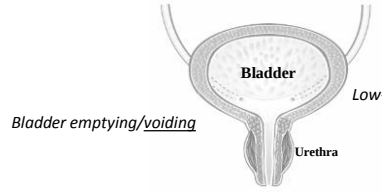
SCHOOL OF MEDICINE CASE WESTERN RESERVE UNIVERSITY

Current Pathophysiologic Hypotheses of OAB

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

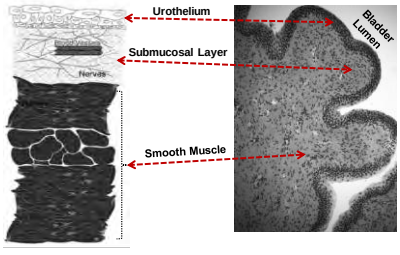
Main Bladder Functions



Bladder emptying/voiding

Low-pressure urine storage

Anatomy of the Bladder Wall



The bladder wall consists of 3 well-demarcated layers:

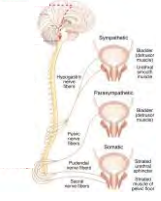
- **Epithelial lining** (Urothelium)
- **Submucosal layer** (containing ***myofibroblasts***, ***blood vessels*** and ***nerve endings***)
- **Smooth muscle** (Detrusor)

Pathophysiology of idiopathic OAB: Mechanistic Insights

Peripheral Contributing Factors:

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

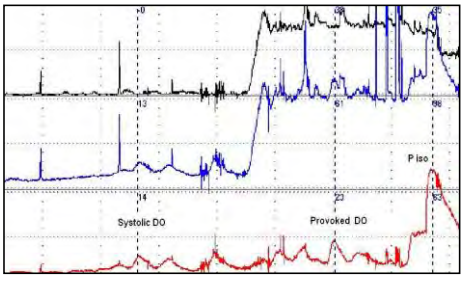
Central Contributing Factors:



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

Myogenic Dysfunction

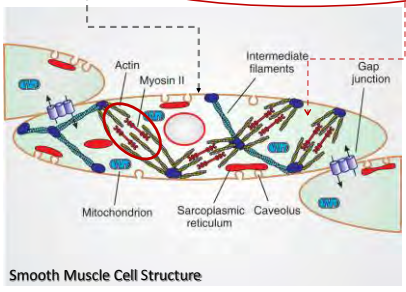
Detrusor Overactivity



Increased detrusor activity: "local" modulation

Extracellular : at the cell membrane

Intracellular: within the smooth muscle cell



Smooth Muscle Cell Structure

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

Extracellular:

Increased activation of purinergic receptors on detrusor smooth muscle

Increased ATP activity within the bladder tissue due to :

- ↑ **ATP** release by the urothelium- release upregulated in OAB
- ↑**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**

Urinary ATP May Be a Dynamic Biomarker of Detrusor Overactivity

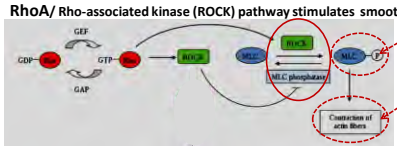
(Cheng et al., BioMed Res Int, 2014 ; Timoteo et al., Biochem Pharmacol, 2014)

Intracellular:

Altered regulation of contractile protein function is associated with increased spontaneous activity in smooth muscle including the detrusor

- Contraction of smooth muscle requires the phosphorylation of myosin

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



Rho-kinase activity --->phosphorylation of myosin light chain --> 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)

Reactive Oxygen Species

- Reactive oxygen species **(ROS)** are chemically reactive molecules . Examples include oxygen ions and peroxides (e.g. H_2O_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

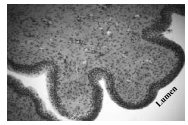
(Nomiya et al., J. Urol, 2013)

- 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)

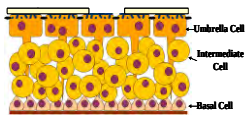
Urothelial Dysfunction

A Role for The Urothelium/Suburothelium in OAB



The bladder urothelium :

- **vital blood-urine barrier**
- **dynamic sensory tissue**



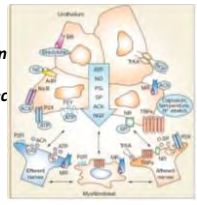
- **Breach** in urothelial **barrier** function allows **water, urea and toxic substances** to pass into the underlying tissue and affect neural and/or muscle layers, resulting in symptoms of **urgency and frequency!**

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

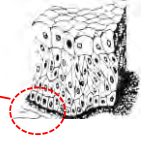
The urothelium is a dynamic sensory tissue !

Urothelial cells (UT) are Primary Transducers of Physical and Chemical Stimuli

- ***Express functional "neuronal-like" receptors/ion***
- ***Release transmitters/mediators/signaling molec***



Close proximity to bladder nerves- **potential for chemical dialogue**



Alterations in *expression of targets* and/or *release of mediators* may contribute to ***bladder instability***, ***hyperactivity*** and ***altered bladder sensation***

(Birder & Andersson ,Physiol Rev, 2013)

Interstitial cells in the bladder suburothelium/lamina propria may play an important role 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.

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

CNS Dysregulation

Central nervous system dysregulation in OAB

- ❑ 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

(Fowler et al., Nat Rev Neurosci, 2008)

How can this knowledge of bladder physiology/pathophysiology be applied to customize treatment strategies, leading to improved outcomes ?

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Clinical biomarkers and screening strategies

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Editor: BJOG
Committees: IUGA Fellows, EAU Thromboprophylaxis Guideline

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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 MCP1
- Hypothesis free research
  - 'Omics and biomarker discovery

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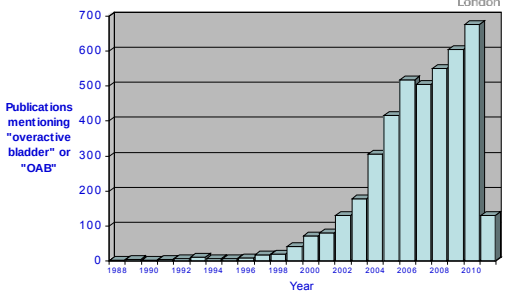

- Treating OAB as a uniform clinical entity has led to a huge rise in publications
- But may have suppressed research endeavoring to understand the underlying causes of OAB symptoms

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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

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Myogenic Dysfunction

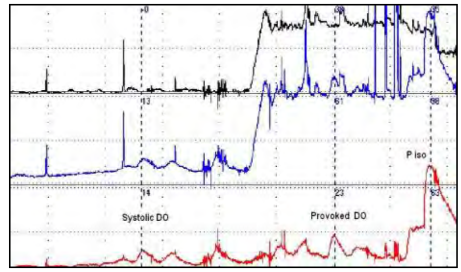
Detrusor Overactivity

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


REVIEW ARTICLE

An International Urogynecological Association (IUGA)/International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Floor Dysfunction

Detrusor Overactivity



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

Digesu 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 with DO
- Significant benefits in tolterodine arm regardless of urodynamic diagnosis **Malone-Lee et al, 2009**
- 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

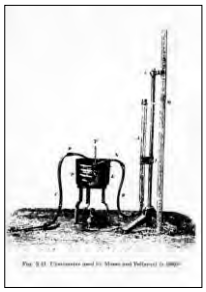
Groenendijk et al, 2008

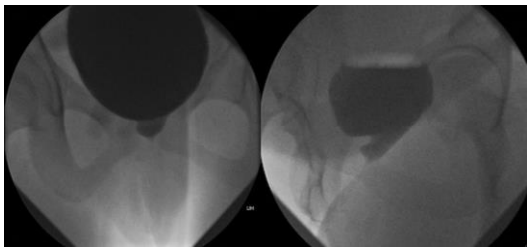
Why is detrusor overactivity not a good clinical prognosticator?

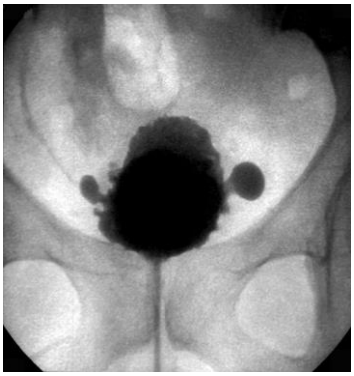
- Very poor test-retest reliability in normal practice
  Rahmanou et al, 2008
- Very difficult to improve reliability of interpretation of cystometrogram Zimmern et al, 2006
- Very poor adherence to recommended standards
  Schaefer et al, 2001; Sullivan et al, 2005; Renganathan et al, 2007
- Very poor inter-rater reliability between different centres
  Renganathan et al, 2008

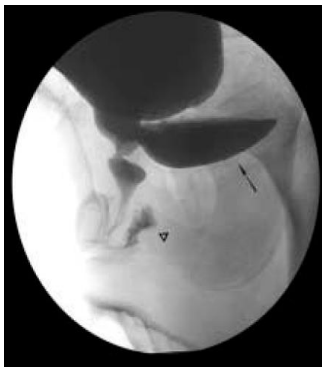
Videourodynamics

- 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

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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

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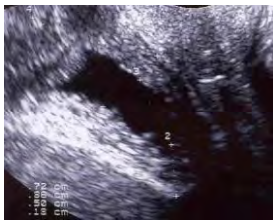
Measurement of Bladder Wall Thickness

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



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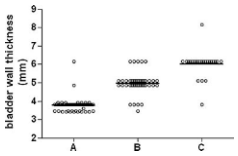
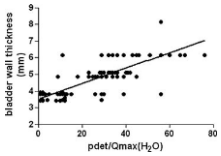
Relationship between diagnosis, detrusor pressure and BWT



A: stress incontinence
B: detrusor overactivity
C: bladder outlet obstruction

Linear association between detrusor pressure at maximum flow and BWT



Kuhn et al 2010

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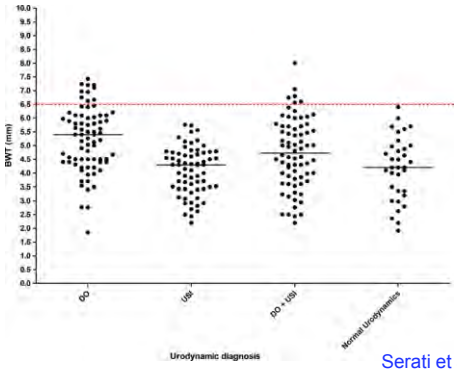

Serati et al 2010

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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

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Vascular Dysfunction

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Serum Markers of Metabolic Syndrome Elevated in OAB

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

  Yoshimura et al N&U 2012, Hsaio et al, Int Urogyne J 2012, Kupelian et al, BJU Int 2012, Chung et al, N&U 2011
- Other markers including B-type natriuretic peptide and adipokinin now being investigated

Yoshimura et al N&U 2012, Liu et al PloS ONE 2013

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CNS Dysregulation

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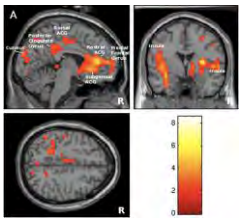
Characteristic Brain Response to Bladder Filling In OAB Patients



- 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

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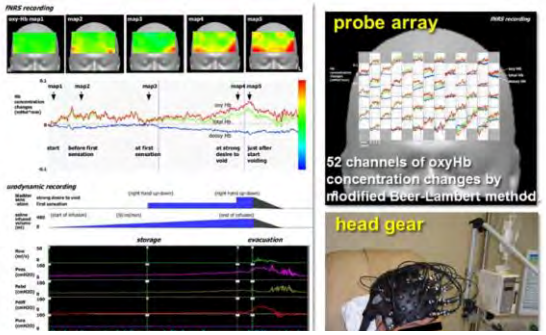
Near Infrared Brain Spectroscopy – Sakakibara et al, N&U 2014



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Urothelial Dysfunction

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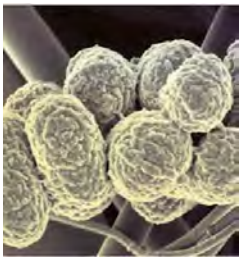
Urothelial Inflammation and Overactive Bladder

- 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



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Inflammatory Urinary Biomarkers

- Urinary NGF
- Urinary BDNF
- Urinary PGE2
- Urinary MCP1

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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
  Tolton et al, 2014

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Hypothesis Free Research
The Promise of 'Omics

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Family studies

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Family Studies - OAB

- Familial aggregation for urgency incontinence, and nocturnal enuresis
- An affected first degree relative confers 1.5-3.7 fold increased risk
  Diokno et al, 1990; Mushkat et al, 1995; Lapitan et al, 2001; Elia et al, 2002; Buchsbaum et al, 2002; Ertunc et al, 2004; Hannestad et al, 2004

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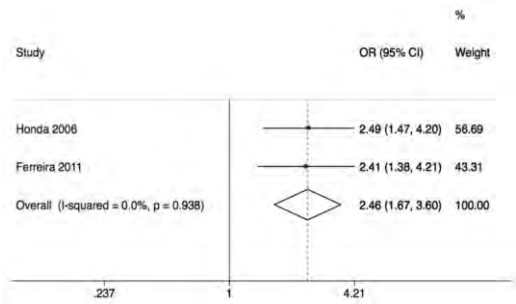
Beta 3 adrenoceptor- rs4994 and overactive bladder in women



- Venice Rating BAA – Moderate epidemiological credibility

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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"

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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

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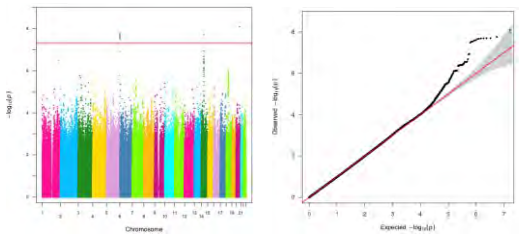
GWAS – Urge Incontinence



Cartwright et al, 2014

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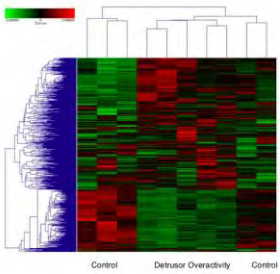
Bladder Transcriptomics



- 1115 differentially expressed genes in detrusor overactivity ($p<.001$)
- M3 muscarinic receptor most overexpressed gene Cartwright et al, 2012

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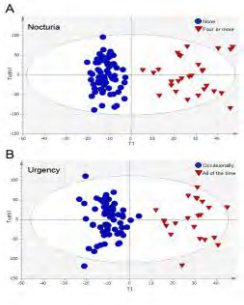
Urine Metabolomics

- 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



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OAB Biomarkers Summary

	Discovery	Validation	Implementation
Cystometry	√	X	√
Video-UDS	√	X	√
BWT	√	X	X
fMRI	√	√	Never!
Urinary Markers	√	?	?
'Omics	√	?	?

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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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Professor, Faculties of Medicine and Pharmacy
Université de Montréal, Quebec, Canada

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

2 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

966 articles removed
duplicates, editorial, comments, thesis

992 records screened

Article Screening and Assessment

992 records screened

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

239 full-text OAB treatment trials included

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; Nitti et al, BJU Int 2010; Malone-Lee & Al-Buheissi, BJU Int 2009)
  - 1 trial: vaginal estradiol (Cardozo 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
  (Abrams P et al, Br J Urol 1998; Blom MW et al, Curr Ther 1995; Digesu GA et al, Urology 2012; Rios LA et al, Neurourodyn 2007; Tarhan F et al, Urol Res 2004; Tincello DG et al, Eur Urol 2012; Ulshöfer B et al, Clin Drug Investig 2001; Zat'ura F et al, Eur Urol 2010)
- 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

Source	Pathophysiologic profile(s)	n	Intervention(s)	Urgency assessment	Efficacy outcome
Abrams et al. (1998)	Detrusor overactivity (DO)	293	Tolterodine 2mg bid or oxybutynin 5mg tid or placebo	Bladder diary	Oxybutynin significantly better than placebo. No difference between tolterodine and placebo.
Blom et al. (1995)	DO	16	Transdermal estradiol 0.05 mg alone or in combination with naproxen 250 mg bid or placebo	Bladder diary	Improvement with the combined transdermal estradiol plus naproxen combination only. No improvement with estradiol alone.
Zat'ura et al. (2009)	DO	135	Cizolirtine citrate 800 mg vs. oxybutynin 15 mg vs. placebo	Bladder diary	Cizolirtine and oxybutynin groups improved compared to placebo. No difference between cizolirtine and oxybutynin
Digesu et al. (2012)	DO	257	Oral elocalcitol 75 µg/d vs. 150 µg/d vs. placebo	Bladder diary	No difference between groups in intent-to-treat analysis
Rios et al. (2007)	DO	58	Intravesical resiniferatoxin 50nM 100ml vs. placebo	Bladder diary	Placebo superior to resiniferatoxin

Effectiveness of OAB treatment compared to placebo

Source	Pathophysiologic profile(s)	n	Intervention(s)	Urgency assessment	Efficacy outcome
Tarhan et al. (2004)	DO	31	Intravesical sodium nitroprusside 7.2mM solution vs placebo	Volume at strong desire to void	No improvement either within or between groups
Tincello et al. (2012)	DO refractory to antimuscarinic therapy	240	Botulinum toxin A 200 units vs. placebo injected into the bladder wall	Bladder diary and urgency severity scale	Significant improvement in urgency episodes and on urgency severity scale in botulinum group compared to placebo
Ulshofer et al. (2001)	DO	46	Trospium chloride 15 mg tid vs. placebo	Volume at strong desire to void	No significant difference in the change in volume between trospium chloride and placebo in intent-to-treat analysis.

No difference between 2 different treatments in urgency outcomes

- 3 comparative trials
  (Zat'ura F, Eur Urol 2010; Junemann KP, Eur Urol 2005; Leung HY, BJU Int 2002)
- 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

No difference between 2 different treatments in urgency outcomes

Source	Pathophysiologic profile(s)	n	Intervention(s)	Urgency assessment	Efficacy outcome
Zat'ura et al. (2009)	DO	135	Cizolirtine citrate 800 mg vs. oxybutynin 15 mg vs. placebo	Bladder diary	Cizolirtine and oxybutynin groups improved compared to placebo. **No difference between cizolirtine and oxybutynin**
Junemann et al. (2005)	DO	201	Propiverine 15mg bid vs tolterodine 2mg bid	Bladder diary	Both groups improved, **no between group differences**
Leung et al. (2002)	DO	106	Tolterodine 2 mg bid vs. oxybutynin 5 mg bid	Bladder diary and VAS	No improvement in urgency either within or between groups on bladder diary. **No between group difference** on VAS in intent-to-treat analysis.

Similar effects of OAB conservative management interventions

- 1 conservative management trial (Burgio KL, JAMA 2002)
- Intervention : behavioural training with or without biofeedback vs. self-help booklet
- Main results :
  - All participants improved
  - No between group difference

Similar effects of OAB conservative management interventions

Source	Pathophysiologic profile(s)	n	Intervention(s)	Urgency assessment	Efficacy outcome
Burgio et al. (2002)	DO	222	Behavioural training with or without biofeedback vs. self-help booklet	Bladder diary	All groups improved, **no between-group differences**.

Similar improvement with pelvic floor muscle exercises vs oxybutynin

- 1 trial (Kafri R, Int Urogenycol 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

Similar improvement with pelvic floor muscle exercises vs oxybutynin

Source	Pathophysiologic profile(s)	n	Intervention(s)	Urgency assessment	Efficacy outcome
Kafri et al. (2007)	DO	44	Oxybutynin ER 5 mg/d vs. supervised and home-based pelvic floor muscle exercises	Bladder diary	Both groups improved, **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
  (Manecksha RP et al, Eur Urol 2012; Kuo HC, J Urol 2007; Kuo HC, Neurourodyn 2011)
- Population studied : OAB patients refractory to antimuscarinic trantment
- Main results : No between-group differences

No impact of botulinum toxin A site injection on treatment responses

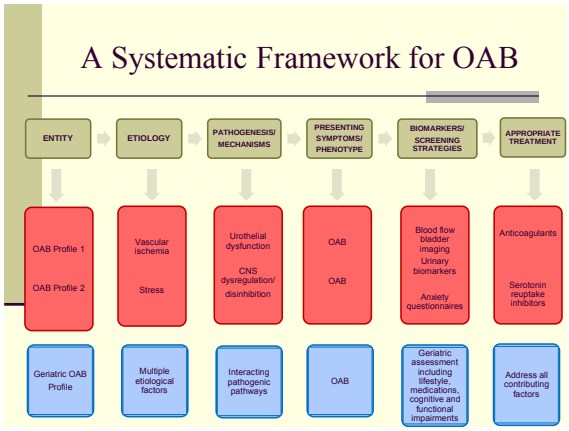
Source	Pathophysiologic profile(s)	n	Intervention(s)	Urgency assessment	Efficacy outcome
Manecksha et al. (2011)	DO refractory to antimuscarinic therapy	22	Trigone-including vs. trigone-sparing injection of botulinum toxin A 100 units	Overactive bladder symptom score	Both groups improved, between group difference in favour of the trigone-including group at 12 weeks but **not at 6 or 26 weeks**.
Kuo HC (2007)	DO refractory to antimuscarinic therapy	45	Detrusor vs. suburothelial vs. bladder base injection of botulinum toxin A 100 units	Bladder diary and urgency severity scale	Only bladder base group improved on bladder diary, **no between group differences**
Kuo HC (2011)	DO refractory to antimuscarinic therapy	105	Bladder body vs. bladder body/trigone vs. bladder base/trigone injection of botulinum toxin A 100 units	Bladder diary and urgency severity scale	All groups improved, **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
ENTITY
ETIOLOGY
PATHOGENESIS/ MECHANISMS
PRESENTING SYMPTOMS/ PHENOTYPE
BIOMARKERS/ SCREENING STRATEGIES
APPROPRIATE TREATMENT
OAB Profile 1
OAB Profile 2
Vascular ischemia
Stress
Urothelial dysfunction
CNS dysregulation/ disinhibition
OAB
OAB
Blood flow bladder imaging
Urinary biomarkers
Anxiety questionnaires
Anticoagulants
Serotonin reuptake inhibitors
Geriatric OAB Profile
Multiple etiological factors
Interacting pathogenic pathways
OAB
Geriatric assessment including lifestyle, medications, cognitive and functional impairments
Address all contributing factors