W5: Management of "antimuscarinics resistant lower urinary tract symptoms" (former intractable OAB)

Workshop Chair: Jacques Corcos, Canada

26 August 2013 14:00 - 18:00

Start	End	Topic	Speakers
14:00	14:05	introduction	• Jacques Corcos
14:05	14:25	Why to change the name	• Marcus Drake
14:25	14:35	Questions	All
14:35	14:50	First visit management	• Jacques Corcos
14:50	15:00	Questions	All
15:00	15:10	new medication	• Francisco Cruz
15:10	15:30	Discussion	All
15:30	16:00	Break	None
16:00	16:15	Physical therapy	• Elise De
16:15	16:25	Questions	All
16:25	16:45	Botulinum toxin	• Brigitte Schurch
16:45	16:55	Questions	All
16:55	17:15	Neuromodulation	• Jacques Corcos
17:15	17:25	Questions	All
17:25	17:55	Case discussion	All
17:55	18:00	evaluations	All

Aims of course/workshop

This course has been modified compared to the one given in 2012. The participant will first be involved in the present terminology controversy around OAB. Then we will discuss the first visit of these patients and how to deal initially with this none-response to anticholinergics. New pharmacologic treatments will be presented including new available treatment as well as future prospects. The role of physical therapy and other "non invasive" techniques will be debated as well as different techniques of neuromodulation and the use of Botulinum toxin. Between each topic a 7 to 10 minutes will be left for discussion and questions.

Disclosure 2013

Speaker, investigator or consultant for the following pharmaceutical companies involved in the field of knowledge covered by this talk:

- Allergan
- Astellas
- Watson

Anticholinergics resistant overactive bladder

Jacques Corcos MD
Professor of Urology
McGill University

ICS 2013

OAB

- Frequency > 8/day
- Urgency
- Urge incontinence
- Nocturia > 1/night

Rovner and Wein. , 2002
Stewart 2001
Corcos et al 2006

Is OAB the right term ?
Is it an organ specific disease or the bladder is just the "victim " of other dysfunctions (brain, cord, peripheral nerves…)
All patients are not the same (i.e Prostate cancer)

18% of the population

Rovner and Wein. , 2002
Stewart 2001
Corcos et al 2006

Is OAB the right term ?
Is it an organ specific disease or the bladder is just the "victim " of other dysfunctions (brain, cord, peripheral nerves…)
All patients are not the same (i.e Prostate cancer)

Bladder is the reflect of the soul

Rovner and Wein. , 2002
Stewart 2001
Corcos et al 2006

Are patients with OAB well treated ?

- Only 13% of people with symptoms report having been diagnosed by a health care provider
- **64% of those with symptoms not currently being treated at all**

Only 8% seek treatment

- Consider that its part of aging
- Many with co-morbid problems and reluctant to add another pill

Harris (Kimberley-Clark) survey 2004
Muller N. Urol Nursing 2005; 25: 109-115

How Do we initially treat primary OAB?

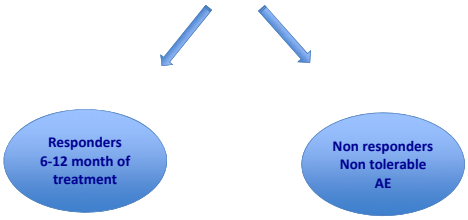
- History and physical
- Suggest changes in life style
  Medication, caffeine, soft drink, tobacco, alcohol etc.
- Start medication

No need for testing

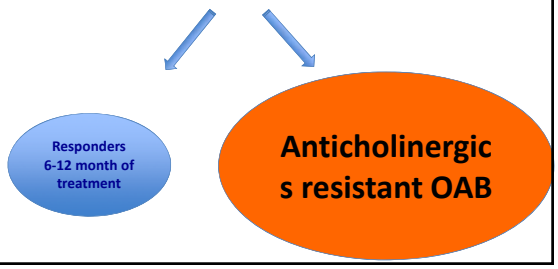
Medication

Oxybutinine based medication	Other antimuscarinics
Generic LA (Ditropan XL) (Uromax) Patches (Oxytrol) Gel (Gelnique)	Tolterodine (Detrol) Derafenacine (Enablex) Trospium (Trosec) Solifenacine (Vesicare) Fesoteridine (Toviaz)

Anticholinergic treatment



Anticholinergic treatment



How to manage these complex patients ?

- How to call this disease ? Is there one or several ? M Drake
- The first visit J. Corcos
- Is there still a place for physical therapy ? E. De
- The new and future medications F. Cruz
- Is Botulinum toxin "The" response ? B. Schurch
- Or is it neuromodulation ? J. Corcos
- Cases from real life

Interaction

Overactive bladder; Why to change the name?

Marcus Drake, Bristol Urological Institute, University of Bristol, UK

The overactive bladder (OAB) is a prevalent problem, with considerable effects on the quality of life of affected individuals and substantial health economic costs. The condition is symptom-based, and is defined by the International Continence Society (ICS) standardization committee as urgency, with or without urgency incontinence, usually with frequency and nocturia, if there is no proven infection or other obvious pathology [1]. A correction was made when it was realized that the term "urge incontinence" had been used in the original definition [2]. OAB is thus a syndrome in which several of the lower urinary tract symptoms (LUTS) relating to the storage of urine co-exist, with urinary urgency as the essential parameter.

The definition is well-established and constitutes the basis of diagnostic and treatment pathways, and the regulatory bodies' evaluation of pharmaceutical interventions. This limits the scope for redefining the condition, effectively meaning that any amendments need rather to be explanatory, for example a better matching to the patient description, or clinical categorization, rather than revisions.

Each element of the ICS definition can viewed critically, though such a process should be done from an evidence base, and such a base is not clear-cut in published literature. Within the definition of OAB, a strict requirement for a patient to report urgency can be a limitation. Two clear contexts where this applies are: 1. Those patients who void frequently or prophylactically to prevent the bladder ever getting to a volume at which urgency is perceived; 2. People with reduced afferent innervation or sensory pathways, notably neuropathic disease, where the sensation of urgency is lacking but for whom the urinary tract behaves overactively in other respects. In addition, placing the word "bladder" in the condition effectively obscures the fact that other process can generate a very similar symptom. For example, stimulation of urethral receptors gives an urgency sensation, such that people with stress urinary incontinence may present with urgency, and focusing on the urgency could lead to a misinterpretation of a bladder mechanism rather than the true basis of an outlet mechanism. The alternative ICS name of "urgency frequency syndrome" avoids this issue.

Urgency is the pivotal symptom, defined by the ICS as the complaint of a sudden compelling desire to void which is difficult to defer. However, there remains plenty of room for confusion [3]. For example, a normal "urge to void" is not synonymous with abnormal urgency; the ICS therefore suggested that the term "desire to void" is more appropriate for describing normal filling sensation. The wording of the definition of urgency can be disputed. "Complaint" implies that the patient complains about it, which may be hampered in patients who are reluctant to make a fuss. "Sudden" may be considered to exclude patients for whom urgency builds progressively with filling, and is rather a vague term for which there is no defined agreement. Difficulty deferring may also exclude some apparently relevant patients, as long-standing OAB may be associated with enhanced outlet strength [4] and consequently a better ability to delay voiding.

The symptom of "increased daytime frequency" is the complaint by the patient who considers that he/ she voids too often by day. In contrast the observation of frequency (the "sign") is a simple statement of how often somebody passes urine in the daytime (meaning when they are not trying to sleep). It is not clear which form of "frequency" the definition of OAB is referring to. There is no minimum number of voids included in the standardized definition. Many researchers consider this a weakness, and certainly clinicians are familiar with patients who perceive they void too often by day, but in reality they go infrequently when a bladder diary is completed. In effect the definition captures not only what the patient perceives about their condition, but also what they perceive about normal voiding frequency of others.

The symptom of nocturia is the complaint that the individual has to wake at night one or more times to void. No agreement has been reached for individuals with differing sleep patterns, such as night-shift workers. Furthermore, the multifactorial nature of nocturia [5,6] makes it an uncertain

factor in OAB. Certainly, diagnosing OAB in somebody whose main bothersome LUTS is nocturia is probably inappropriate and risks placing the patient into the wrong therapeutic pathway.

In many OAB patients, urgency incontinence occurs, defined as involuntary leakage of urine, accompanied or immediately preceded by urgency [1]. This standardized definition abandoned the requirement that the leakage should be a "social or hygienic problem" to be called incontinence, because considerable leakage can occur which in some individuals may not a problem to them- particularly in children and the elderly. In a prevalence survey, 69% of women had "any incontinence", but only 30% found this a "social or hygienic problem" [7]. All measures, for example "warning time" (between first sensation of urgency and eventual voiding) depend on the patients and the clinicians reaching a consensus as to the meaning of urgency. The ICS terminology committee excluded "for fear of leakage" in the new definition of urgency, mainly because many OAB patients don't leak. However, there are grounds to consider including "for fear of leakage" alongside the sudden compelling desire to void which is difficult to defer in the definition of urgency. Many OAB patients certainly feel as if they are going to leak, even if they say they never have, commonly expressing anxieties exemplified by; "when I want to go, I have to rush because I think I may wet myself." Hence "fear of leakage" is an important concept to patients.

Crucially, the current definition of OAB is based on symptoms; in contrast, detrusor overactivity (DO) is a urodynamic observation, characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked [1]. OAB and DO are thus not interchangeable terms, and the clinician must be specific in their use. Clinicians need to be clear on this, and when discussing urgency with patients.

In summary, specific wording of the definition of OAB is open to criticism, and the elements making up OAB (urgency, frequency, nocturia and incontinence) likewise have limitations, but the scope for revision is restricted by the need to avoid undermining the basis of therapy.

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:167-78.
2. Abrams P, Artibani W, Cardozo L, Dmochowski R, van Kerrebroeck P, Sand P. Reviewing the ICS 2002 terminology report: the ongoing debate. Neurourol Urodyn 2009;28:287.
3. Blaivas JG. Overactive bladder and the definition of urgency. Neurourol Urodyn 2007;26:757-8; discussion 9-60.
4. Kapoor D, White P, Housami F, Swithinbank L, Drake MJ. Maximum urethral closure pressure in women: normative data and evaluation as a diagnostic test. International Urogynecology Journal 2012;23:1613-8.
5. Gulur DM, Mevcha AM, Drake MJ. Nocturia as a manifestation of systemic disease. BJU Int 2011;107:702-13.
6. Weiss JP, Blaivas JG, Jones M, Wang JT, Guan Z. Age related pathogenesis of nocturia in patients with overactive bladder. J Urol 2007;178:548-51; discussion 51.
7. Swithinbank LV, Donovan JL, du Heaume JC, et al. Urinary symptoms and incontinence in women: relationships between occurrence, age, and perceived impact. Br J Gen Pract 1999;49:897-900.

What to do at the first visit

Jacques Corcos MD, FRCS(S)
McGill University

Anticholinergics resistant OAB

Doctor, I tried everything you recommended and **ALL** the drugs, nothing works !
Please help me !!!

Anticholinergics resistant OAB

Failed behavioral changes and medical treatment using known oral medications (anticholinergics, antispasmodics, antidepressants, sedatives, calcium channel blockers, β adrenergics agonists)

Anticholinergics resistant OAB

- Contra indications to medication
  NA Glaucoma, Constipation etc..
- Resistance to medication……Why ??

What "resistant means ? Are you using the right outcome ?

Direct activation of intracellular signaling by pathologic process

Altered membrane potential of smooth muscle cell

Lack of pharmacologic levels in bladder tissue

"Intractable" OAB: What to do ?
"The 7 rules" for successful management

1. Understand what really bother the patient
2. Reconsider diagnosis (SUI, IC)
3. Treat a reversible or worsening cause (i.e diuretics)
4. Changes in life style, when ? How? For how long ?
5. Reconsider same medication
6. Consider adding meds (DDAVP)
7. Intensify the follow up (nurse continence advisor)

1-What bother the patient: Clinical Efficacy

Combination of efficacy, tolerability, and compliance

- Efficacy:
  - Traditional OAB outcome measures
  – QoL
  – Global assessment of impact
  – Combinations
- Tolerability: side effects
- Compliance and persistence

1. Wein AJ. Urology 2003; 62 (Suppl 5B) 20-27

Clinical Significance of QOL Outcomes

- How much change in HRQOL is enough to evaluate the treatment or to consider one treatment better than another?
- Clinically meaningful change in HRQOL
  - **Minimal importance difference (MID)**
    - Smallest difference in the score of the domain of interest which patients perceive as beneficial (or harmful) which would mandate, in the absence of troublesome side effects or excessive cost, a change in patient's management
  - **How much is enough?**

Jaeschke R. et al. Control Clin Trials 1991; 12 (Suppl 4) 226S.
Guyatt GH. Et al. Mayo Clin Proc 2002; 77:371-383.

"The" outcome

- Get **"THE"** most symptom which bother the most
- What the patient cannot do because of his OAB
  - Go to see a movie
  - Go to sleep at friends/children
  - Walk the dog
  - Etc..
- Establish a "contract" with the patient
- Improve **this** complaint

2-Reconsider diagnosis

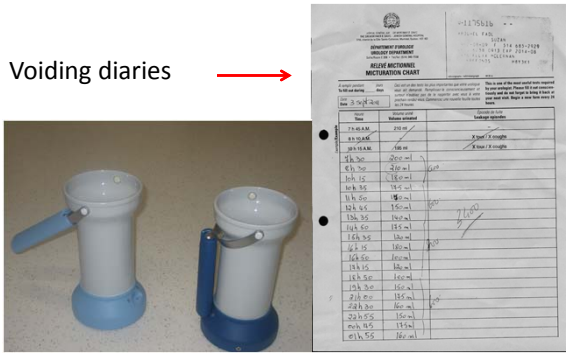
- Clinical evaluation
- Voiding diaries →

Frequency volume chart (FV-chart) ++

volume voided and the time of each micturition for 3 days

2-Reconsider diagnosis

Voiding diaries →



3-Treat a reversible cause

Treat associated conditions

- Bladder outflow obstruction
- Stress UI

Treat reversible conditions

- Urinary Tract Infection
- Congestive Heart Failure
- Diabetes
- Spinal stenosis

4- Behavioral management

Fluid management:

- Limit diuretics, caffeine, soda, alcohol
- Avoid to drink in evening

Schedules voids

- Regularly timed intervals
- Increase time between voids

Use pelvic floor

- Kegels, PFMT, vaginal cones

5-Reconsider same medication

- Why the patient stopped it ?
- Restart it at lower dose and slowly increase to maximum dosage
- Use mouth moisteners / gums / candies
- Use laxatives
- Consider use of tricyclic antidepressants associated to anticholinergics

6- Consider the use of DDAVP

- If nocturia is the main complaint
- DDAVP 0.1 to 0.2 mg (or 60-120 µg of Melt)
- Alone or with anticholinergics

Desmopressin, as a "designer-drug," in the treatment of overactive bladder syndrome.
Hashim H, Malmberg L, Graugaard-Jensen C, Abrams P.
Neurourol Urodyn. 2009;28(1):40-6

7- Intensify the follow up

- These patients need close monitoring
- Frequent visit if problem with medication
- Counselling and phone follow up by **nurses continence advisors**
- Hot lines

If nothing really works…..

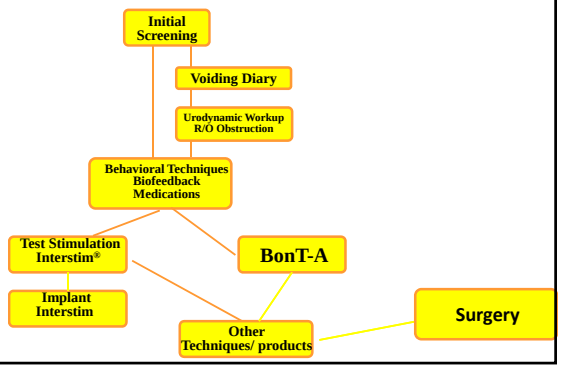
If nothing works ……

If nothing works ……

How to chose between these treatments ?

1. Availability of therapy
2. Patient's understanding of the long term treatment plan
3. Invasiveness of the procedure
4. Drug and technique related adverse effects
5. Drug efficacy
6. Cost

Management Algorithm for OAB



Thank you

Antimuscarinics and Mixed Action Drugs recommended for LUTS

Drug	Level of evidence	Grade of recommendation
Fesoterodine	1	A
Imidafenacin	1	B*
Oxybutynin	1	A
Propiverine	1	A
Solifenacin	1	A
Tolterodine	1	A
Trospium	1	A

International Consultation On Incontinence (ICI) Paris 2012 - Drug Treatment Committee (nr 8), in press
Karl-Erik Andersson, Christopher Chapple, Linda Cardozo, Francisco Cruz et al

New Pharmacotherapy or intractable OAB

Francisco Cruz

Department of Urology
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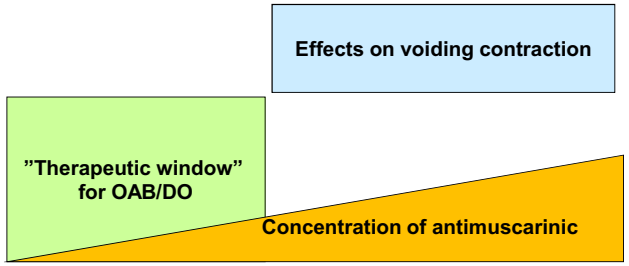
Porto, Portugal

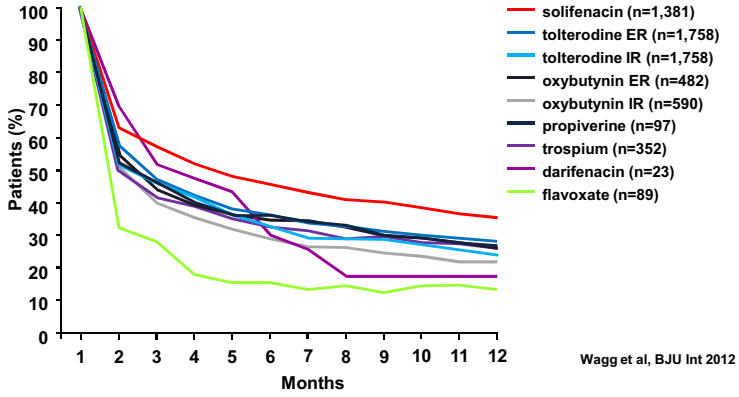
Rationale for Use of Antimuscarinics in OAB

- **Antimuscarinics have at herapeutic window that limits an increase in dose**



K-E Andersson, 2012

Reasons for abandoning antimuscarinic treatment



Wagg et al, BJU Int 2012

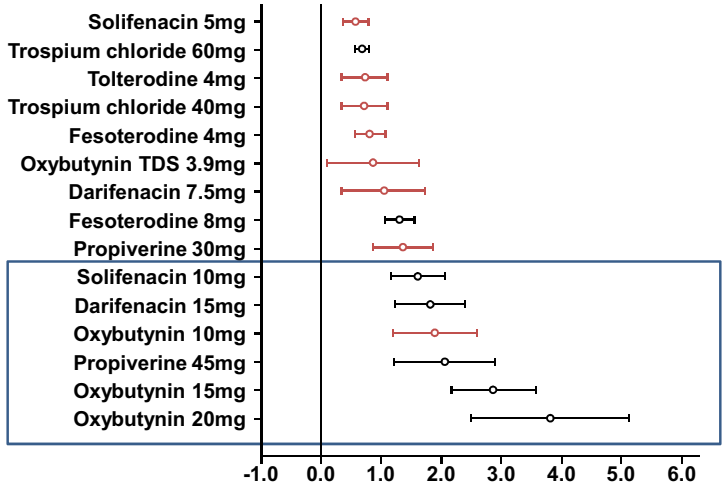
- **Low level of efficacy (41.3%)**
- **Adverse events (22.4%)**
- **Cost (18.7%)**

EAU Guidelines for Incontinence, 2012

New pharmacologic agents for LUTS coming into practice in the next 1-2 years

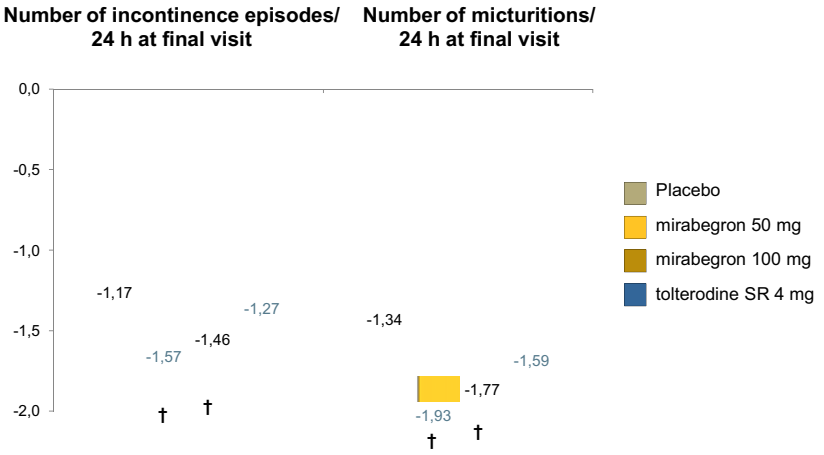
- Mirabegron (β3 AR agonist)
- Onabotulinum toxin type A
- PDE-5 inhibitors

Adverse Events of Antimuscarinics increase with dose escalation



Kessler *et al*, PLoS one. 2011; 6 (2): e16718

Efficacy of Mirabegron 50mg and 100 mg co-primary end-points

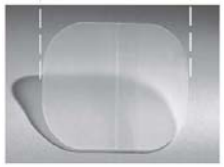


†Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment

Adapted from Khullar V et al. Eur Urol Suppl 2011;10:278-9(abs.886)

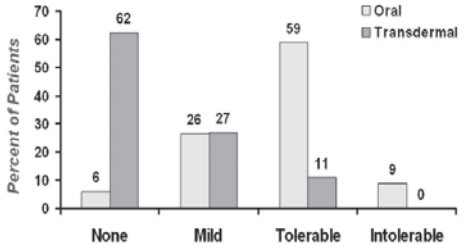
Trans-dermal route for oxybutynin

Patch



Gel

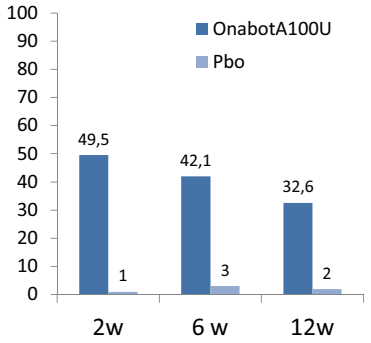
Dry mouth



Dmochowski et al, *J Urol*, 2002
Davila, GW, Clinical Interventions in Aging , 2006

IDO: Phase 3 OnabotA 100U vs Placebo Main Adverse Events

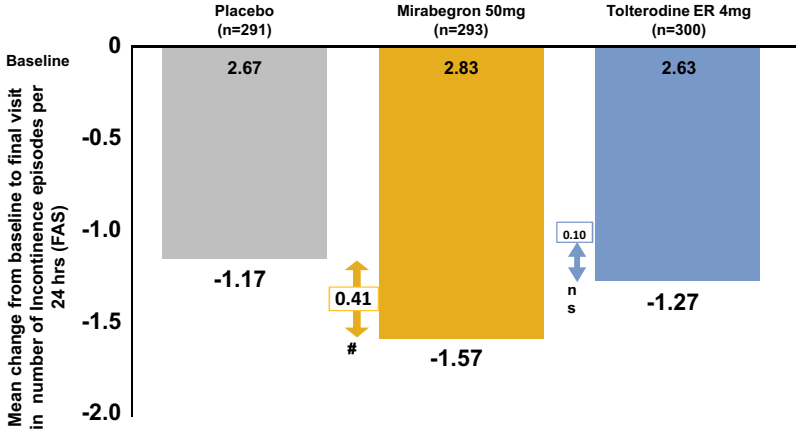
Mean post-void residual (ml)



	Onabot A 100U	Pbo
UTI	15%	5.9%
UR	5.4%	0.4%
CIC	6.1%	0%

Nitti et al, AUA 2012, Late Breaking News

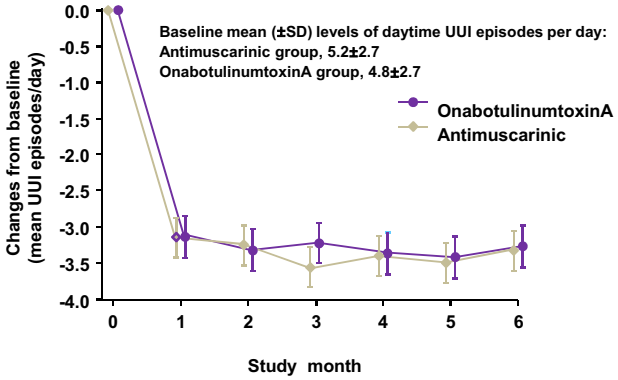
Mean number of incontinence episodes per 24h



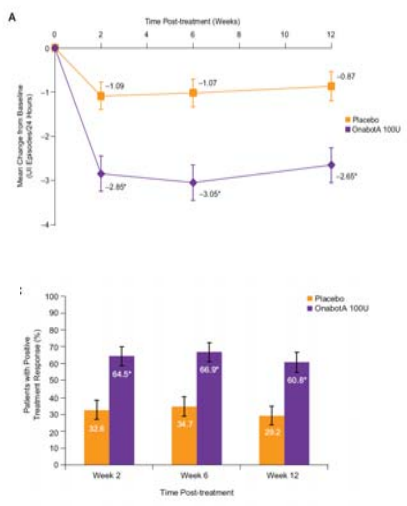
Adapted from Khullar V, et al. Eur Urol 2013; 63: 283–95

Statistically significant improvement versus placebo at the 0.05 level with multiplicity adjustments
ns: No statistically significant improvement versus placebo

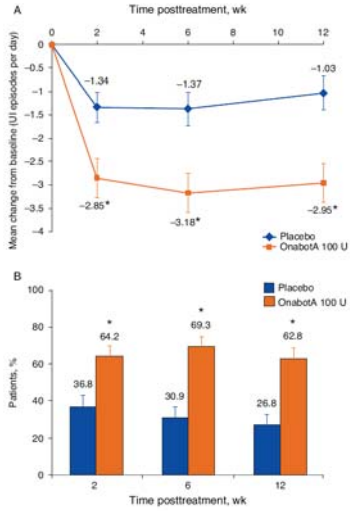
ABC trial: Antimuscarinics vs Botulinum Toxin Comparison



Pivotal phase 3 studies of onabot A 100 U in OAB



Nitti et al, J Urol 2012



Chapple et al, Eur Urol, 2013

New pharmacologic agents for LUTS coming into practice in the next 1-2 years

- Association of drugs with distinct mechanims of action

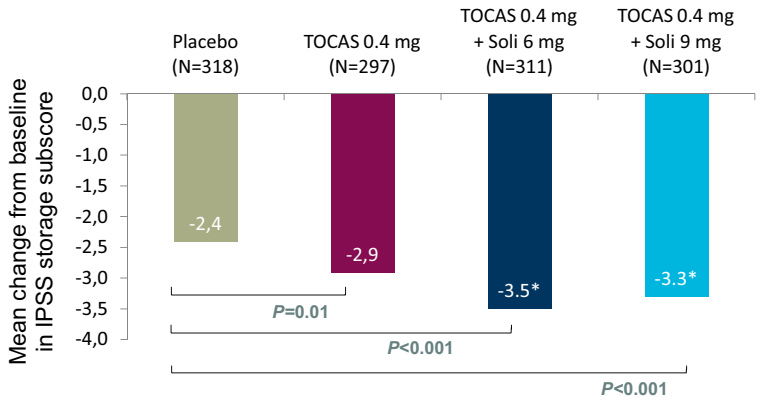
PDE-5 inhibitors and male LUTS

- Sildenafil, vardenafil and tadalafil improve IPSS in men (total, storage and voiding subscores)
- None of the PDE-5 inhibitors tested alone increased Qmax
- Tadalafil does not decrease detrusor contractility
- The longer half-life of Tadalafil favours its use

McVary et, al, *J Urol*, 2007
McVary et al, J Urol, 2007
Stief et al, Eur Urol, 2008
Dmochowski et al, J Urol, 2010
Liguori et al, J Sex Med, 2009

Antimuscarinics and male LUTS

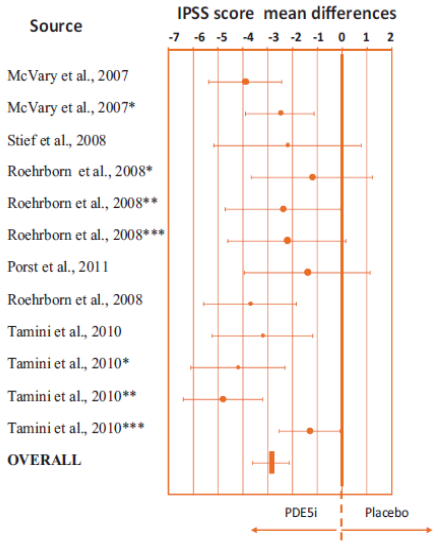
Combination therapy: more effective in improving storage LUTS than α_1-AR antagonist monotherapy



* Combination therapy (both doses) vs. TOCAS monotherapy: *P*<0.05

Drake M et al. Poster presented at EAU Congress 2012 (abs. 746)

Systematic review of PDE5 inhibitors in BPH-LUTS

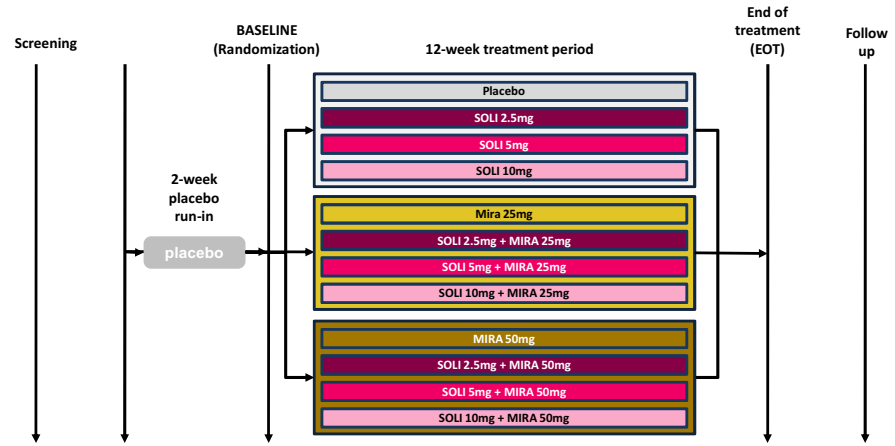


Gacci et al, Eur Urol, 2012

New pharmacologic principles for LUTS to be explored in the next 5-10 years

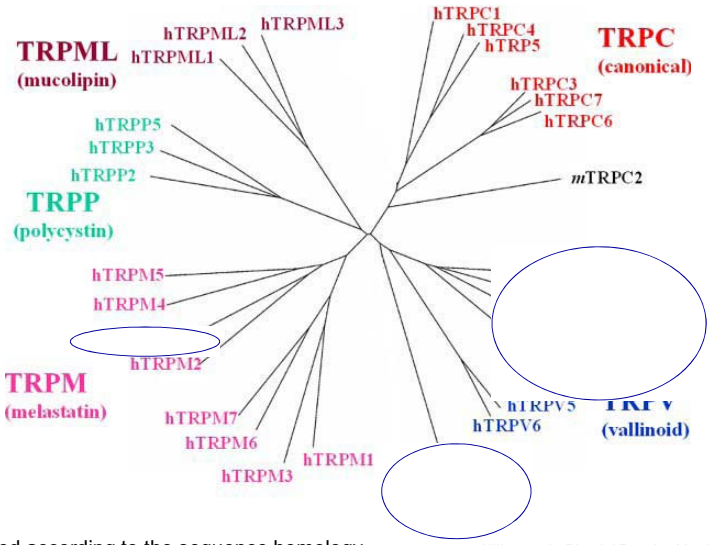
- TRPV1-TRPV4 antagonists
- Cannabinoid receptor manipulation
- Purinergic receptor antagonists
- Neurotrophic factors

Combination treatment with mirabegron and solifenacin Phase II study Symphony Study



SOLI = solifenacin. MIRA = mirabegron
Abrams, P et al. Poster presented at the Annual Congress of the AUA, 4–8 May 2013, San Diego, CA, USA No. 1958

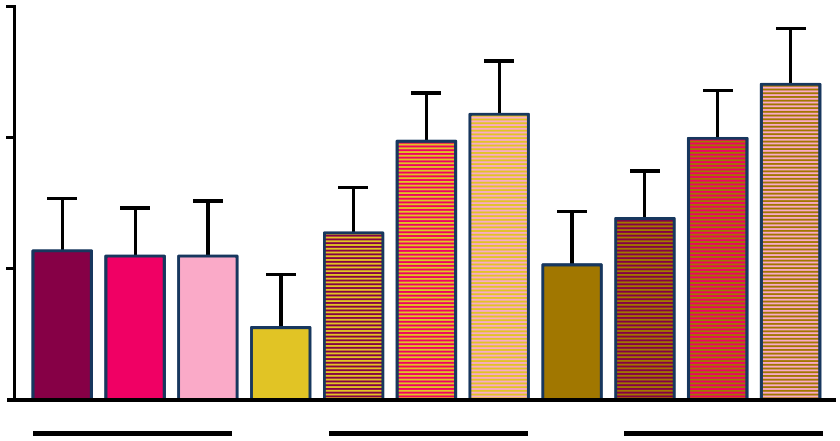
The TRP family



TRP are named according to the sequence homology

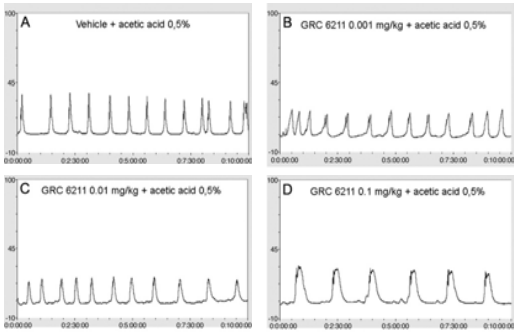
Nilius et al., Physiol Rev 87:165-217, 2007

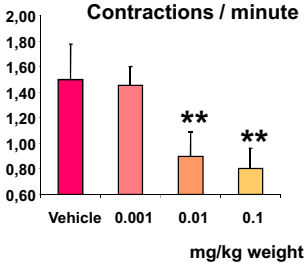
Change from baseline to EOT* in MVV per micturition Difference vs placebo



Abrams, P et al. Poster presented at the Annual Congress of the AUA, 4–8 May 2013, San Diego, CA, USA No. 1958

Effect of TRPV1 antagonist on rat cystometry with 0,5% acetic acid

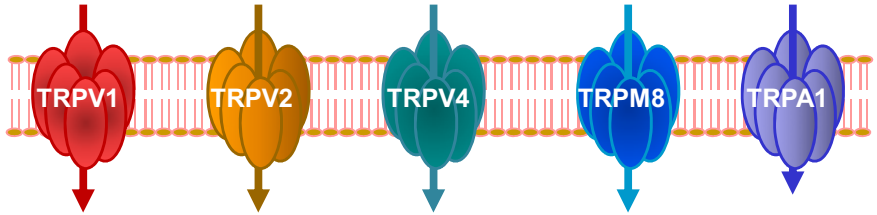




Antagonist: GRC 6211 (intestinal route)
Vehicle: 0.5% methylcellulose

Charrua et al, *J Urology*, 2009

The TRP family and the LUT

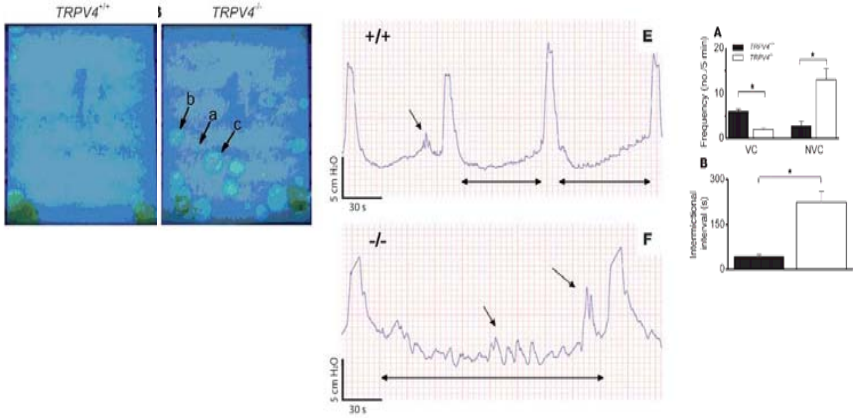


TRPV1	TRPV2	TRPV4	TRPM8	TRPA1
Noxious heat >43 ºC	Noxious heat >50 ºC	Innocuous heat >24 ºC	Innocuous cold (<25ºC)	Noxious cold (<17ºC)
Protons	THC	EETs	Menthol	Icilin
Vanilloids (Cap, RTX, olvanil)	2-APB	2-APB	Icilin	Acrolein
Endocannabinoids (AEA)	Stretch	Stretch	Cooling compounds	AITC
Polyamines	Urothelial tumorogenesis	4αPDD	PIP2	THC
		GSK1016790A	LPLs	Carvacrol, Thymol, Gingerol, Eugenol
		BAA	PUFAs (inhibition)	H2S

CAP (capsaicin) RTX (resiniferatoxin) AEA (anandanmide) THC (tetrahydrocannabinoid) 2-APB (2-aminoethoxydiphenyl borate) EET (epoxyeicosatrienoic acid) GSK1016790A (synthetic activator) 4αPDD (4α-phorbol 12,13-didecanoate) BAA (bisandrographolide A) PIP2 (phosphatidylinositol 4,5-bisphosphate) LPL (lysophospholipid) AITC (allyl isothiocyanate) CIN (cinnamaldehyde) H2S (hydrogen sulfide)

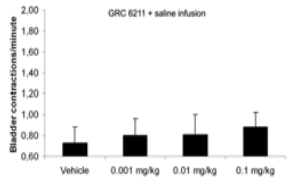
Avelino et al, Acta Physiol Scand, 2012, Skryma et al, Nature Rev urol, 2012

TRPV4 has a key role in normal micturition

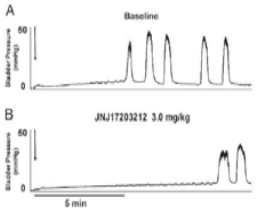


Gevaert T et al, JCI, 2007

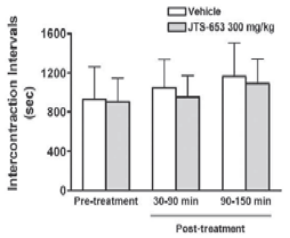
TRPV1 antagonists and bladder function in naive animals
GRC 6211 (1) , JNJ17203212 (2), JYL1421 (2), JTS 653 (3)



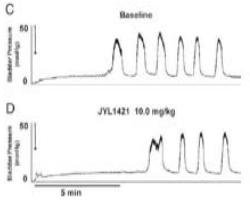
GRC 6211



JNJ17203



JTS 653

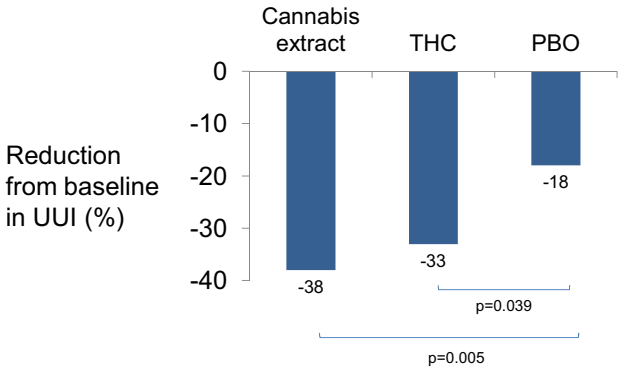


JYL1421

(1) Charrua et al, J Urol, 2009, (2): Cefalu et al, J Urol, 2009, (3) Kitagawa et al, J Urol, 2013

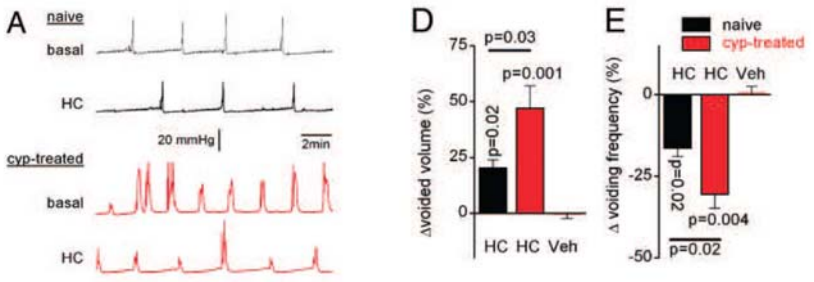
The effect of cannabis on urge incontinence in MS patients : CAMS-LUTS trial

630 MS patients with UUI randomized to cannabis extract, Delta(9)-tetrahydrocannabinol (THC) or placebo



Freeman RM et al. Int Urogynecol J Pelvic Floor Dysfunct. 2006

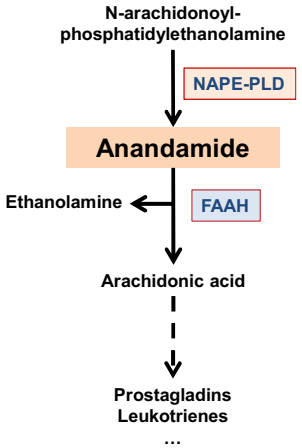
TRPV4 antagonist HC-067047 and DO in r

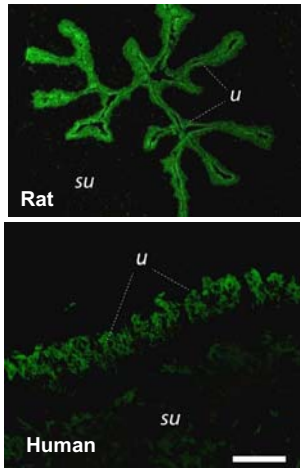


Cyp induced bladder inflammation

Everaerts et al., PNAS, 2010

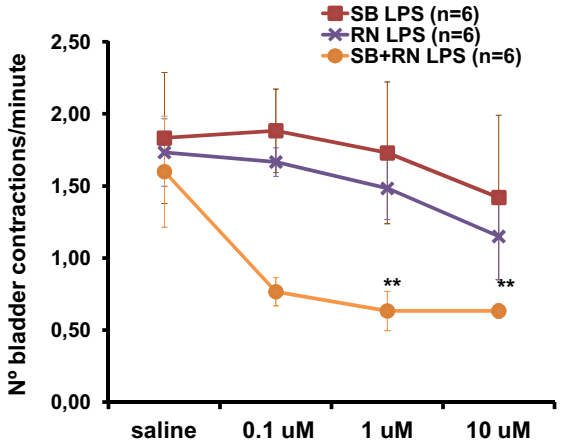
Anandamide pathway, an endo-cannabinoid receptor agonist





Strittmatter F et al, Eur Urol, 2011

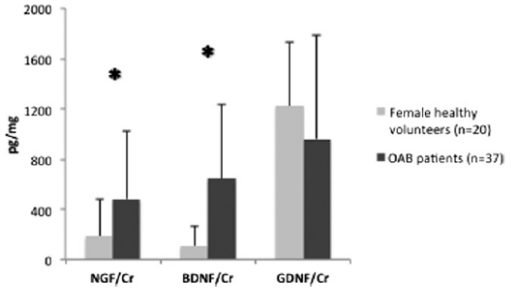
TRPV1-TRPV4 antagonist combination



RN1734 = TRPV4 antagonist
SB366791 = TRPV1 antagonist

Charrua et al, unpublished

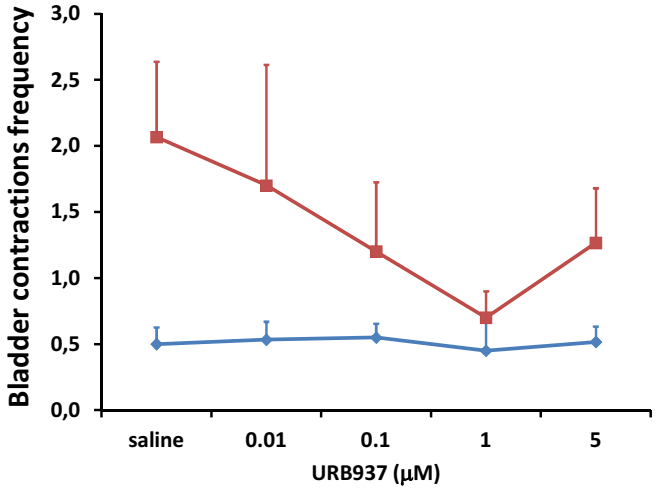
Urinary NGF/Cr and BDNF/Cr levels in female volunteers and OAB patients



TrKA/TrKB antagonists ⟷ NGF/BDNF sequestration

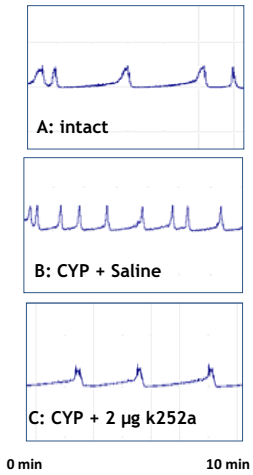
Antunes-Lopes T et al, *J Urol, 2013*

Commulative doses FAAH inhibitor (URB937) on inflammed (LPS) bladder function



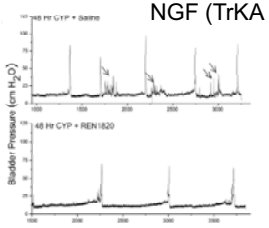
Charrua and Cruz, unpublished

TrK antagonists and neurotrophin sequestration in a rat model of cystitis

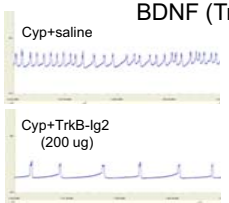


Frias B et al, *Neurourol Urodyn*, 2009 (abstract)

NGF (TrKA Ig2)

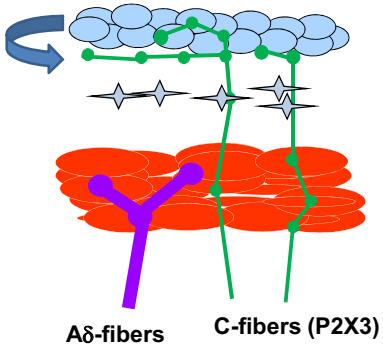


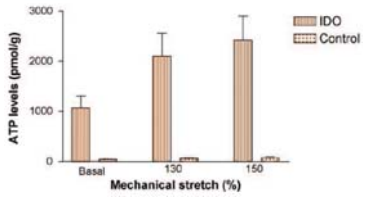
BDNF (TrKB Ig2))



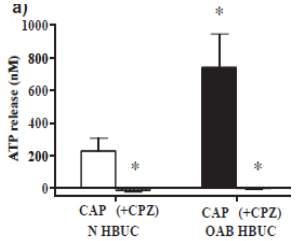
Hu, VY et al, J Urol, 2005
Pinto et al, Neuroscience, 2010

ATP release from urothelium of IDO bladders





Kumar et al, Eur Urol, 2010



Birder et al, Acta Physiol (Scand), 2013

Conclusions:

New developments in antimuscarinics may come from combinations or the discovery of new routes of administration

Mirabegron, Onabot/A and PDE5 inhibitors are the obvious candidates

Decisions about first-line drug, second-line drug and combination of drugs will be an important area of research

TRP antagonists, cannabinoid receptor manipulation, purinergic receptor antagonists and modulation of neurotrophic factors have promising animal data

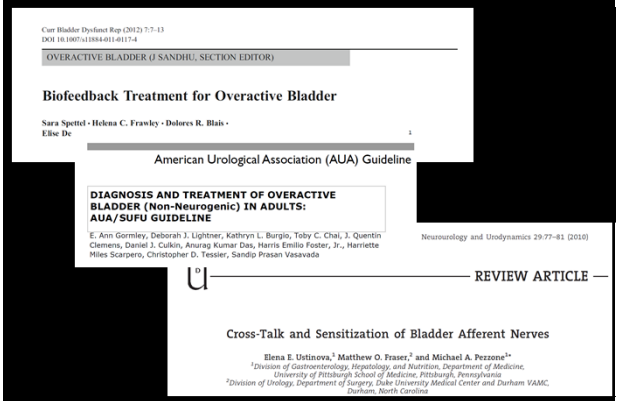
Pelvic Floor Rehabilitation in Refractory OAB

Biofeedback,
Electrical Stimulation,
and Physical Therapy

Albany Medical College

Elise De, M.D.
Assistant Professor Surgery
Division of Urology
Albany Medical College

Recommended Reading

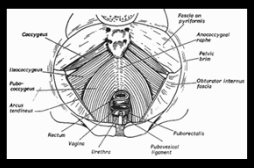


How is the Pelvic Floor Related

- OAB is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, *in the absence of urinary tract infection (UTI) or other obvious pathology.*[Haylen et al: Neurourol Urodyn. 2010;29(1):4-20.]
- Pelvic floor overactivity is described by the International Continence Society as "A situation in which the pelvic floor muscles do not relax, or may even contract when relaxation is functionally needed, for example during micturition or defecation."[Messelink et al: *Neurourol Urodyn.* 2005;24(4):374-380.]
- This dysfunction has been implicated clinically as an underlying factor in OAB as well as other diagnoses such as interstitial cystitis, irritable bowel syndrome, and chronic pelvic pain.[Shafik A: *Int Urogynecol J Pelvic Floor Dysfunct.* Dec 2000;11(6):361-376. Nickel et al: *J Urol.* Jul 2009;182(1):155-160.]

Symptoms

- Symptoms of:
  - Urgency
  - Frequency
  - Incontinence (urge, stress, or unawares)
  - Hesitancy
  - Incomplete emptying
  - Pelvic pain
  - Dyspareunia
  - Bowel complaints

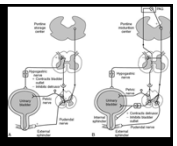


- Patients often present with refractory so-called idiopathic OAB with multiple failed therapies (hydrodistension, multiple medications, incontinence surgery, neuromodulation, laparoscopy or even hysterectomy).
- Treatment of the pelvic floor overactivity can provide significant relief of symptoms in patients otherwise written off as "bladder cripples".

Muscles lead to OAB?

- Pelvic floor muscle overactivity can lead to pelvic organ cross-sensitization and voiding, evacuation, and pain symptoms via cross-afferent stimulation in the pelvis. Ustinova EE, Fraser MO, Pezzone MA. Cross-talk and sensitization of bladder afferent nerves. Neurourol Urodyn. 2010;29(1):77-81.
- Reflexive pro- and anti-dromic pathways exist via peripheral dichotomizing afferents along the dorsal roots and via reflexive central pathways. These interactions have been demonstrated in varied species by multiple methods (immunohistochemical labelling studies, single-unit afferent recordings, etc). Ustinova et al. Neurourol Urodyn. 2010;29(1):77-81. Rudick et al Am J Physiol Regul Integr Comp Physiol. Sep 2007;293(3):R1191-1198. Malykhina AP. Neuroscience. Nov 9 2007;149(3):660-672.

Biofeedback



- Biofeedback is an umbrella term:
  - Communication to the patient regarding physiological variables.
  - Biofeedback may serve as an adjunct to other conservative therapies targeting muscle function:
    - Pelvic floor muscle training
    - Surface electromyography (sEMG)
    - Electrical stimulation
    - Cognitive behavioral techniques such as bladder training and urge suppression techniques.
- Basic concept:
  - Feedback should improve muscle awareness
  - Control may subsequently improve pelvic floor dysfunction
  - For OAB biofeedback can enhance voluntary inhibition of detrusor activity.
- Biofeedback is to be distinguished from digital massage or stretching of the muscles, which intervenes directly on muscle tone and pelvic alignment.

Electrical Stimulation

- Electrical stimulation:
  - Originally described by Caldwell in 1963 to address fecal and urinary incontinence [Caldwell K. Lancet. 1963;2:174–175.]
- Electrical stimulation involves creation of a passive contraction of the pelvic muscles, usually by transmission of an electric current via a vaginal or anal probe.

Pelvic Floor Muscle Training, Biofeedback and Electrical Stimulation

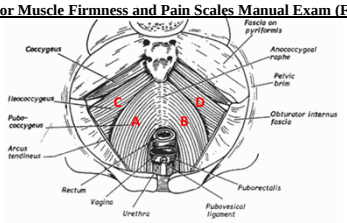
- "On-off" switch for the detrusor:
  - 50-80% reduction in urge and/or stress incontinence episodes
  - 15-50% dry rates in randomized controlled trials [Burgio 1998 and 2002].
  - Combination with anticholinergics benefit over either alone [Burgio 2000].
- Pelvic floor muscle dystonia:
  - Relaxation decreases input along S 2,3,4 and "cross talk" [Malykhina 2007]).
  - Biofeedback effective in 70% of women [Bendena 2007].
  - Men with chronic prostatitis and CPPS:
    - Biofeedback decreased the Chronic Prostatitis Symptom Index (NIH-CPSI)
    - 23.6 to 11.4, $p < 0.0001$ [Cornel 2005].

Pelvic Floor Physical Therapy

Digital massage or stretching of the muscles
Intervenes directly on muscle tone and pelvic alignment

- Weiss found that symptoms of urgency/frequency were reduced in 35 of 42 patients with manual therapy aimed at decreasing pelvic muscle tone tone.[Weiss et al: J Urol. Dec 2001;166(6):2226-2231.]
- Similar results were found by Lukban et al using myofascial release, joint mobilization, and home exercises. [Lukban et al: Urology. Jun 2001;57(6 Suppl 1):121-122]
- Research in this particular area of OAB management is hampered by a lack of data:
  - Incidence of pelvic floor muscle overactivity in women with OAB
  - Absence of a standardized means by which to measure it.
  - There is some research on pelvic muscle overactivity in chronic pelvic pain [Review: Westesson et al: Curr Urol Rep. Jul 2010;11(4):261-264.]

Pelvic Floor Muscle Firmness and Pain Scales Manual Exam (FiPS MANUAL):

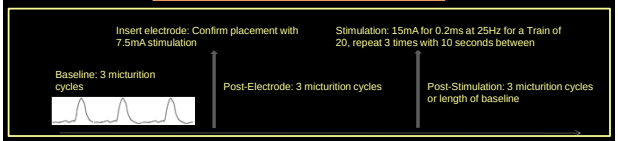


1. Palpable Firmness (A, B, C, D, as per image above): Examination is performed by identifying the muscle, then palpating a point overlying each of the four sites to be tested, the pubococcygeus and iliococcygeus sub-divisions bilaterally. The firmness evaluation will be performed using a 3-point scale.
   - o -1 [Underactive] = Less palpable resistance to pressure (comparable to mid-third of thenar eminence when at rest)
   - o 0 [Normal] = Resting compressibility of thenar eminence
   - o 1 [Overactive] = Compressibility of thenar eminence when thumb is apposed to 1st or 5th digit
2. Palpable Pain A, B, C, D (1-10 Likert): As the exam is performed manually by the examiner enough to indent the thenar eminence 7 mm when the 1st and 2nd digit are apposed, the patient rates pain on a scale of 0-10 for each site A to D during the exam.

Spettel, Frawley, Blais De: Curr Bladder Dysfunct Rep (2012) 7:7–13

17 Rabbits

Animal model: Needle tetanizing electrical stimulation



- Stimulation group (11 rabbits):
  - Baseline CMG of 3 micturition cycles
  - EMG electrode inserted by palpation, confirmed using a single stimulation of 7.5mA
  - Rest period of 5 minutes, additional 3 micturition cycles were recorded with both CMG and EMG.
  - Stimulation: 15mA for 0.2ms at 25Hz for a Train of 20, x 4 (10 second rest in between each)
  - Post-stimulation CMG with EMG was conducted for either 3 micturition cycles or, if unduly prolonged, the time of prior micturition intervals.
- Control group (4 rabbits):
  - Baseline CMG of 3 micturition cycles were recorded
  - Repeated for 3 cycles without any electrodes or stimulation
- Posterior Rhizotomy (2 rabbits):
  - Two additional rabbits received a posterior rhizotomy by cutting the dorsal sacral roots under the S3 vertebrae after baseline CMG and insertion of electrode into Pc.

Pelvic Floor Muscle Overstimulation:

- The results for rabbits with Pc stimulation could be divided into 3 groups based on their micturition pattern after stimulation.
  - Two rabbits **(Resilient Group)** were relatively unchanged overall in their micturition cycles after stimulation. The only difference between this group and the control without stimulation was the presence post-stimulation of unproductive contractions.
  - Two rabbits **(Overactive Group)** exhibited an overactive voiding pattern with lower capacity (mean -27ml +/- 9ml), a shortened interval between contractions (0.16 +/- 0.13), shorter duration of contraction (0.56 +/-0.43) and lower PVR after stimulation.
  - The majority (7) of the rabbits **(Dysfunctional Group)** exhibited a dysfunctional voiding pattern with larger capacity (17ml +/- 22ml), longer interval (2.27 +/- 2.01) and longer duration of contractions (1.63 +/-0.53) post-stimulation.

	Amplitude	Interval	Duration	Nonproductive Contractions
Control (4)	↔	↔	↔	None
Dysfunctional Bladder (7)	↔	↓	↑	Many
Overactive Bladder (2)	↔	↓	↓	Some
Resilient Bladder (2)	↔	↔	↔	Few

Rhizotomy:

- The two rabbits that underwent rhizotomy did not have a detrusor contraction after the dorsal roots were severed.
- Each bladder was filled until overflow incontinence occurred.
- Capacity increased from a baseline of 17 to 72cc in the first and 46 to 90cc in the second.
- This confirms that the reaction to electrical stimulation of the pubococcygeus muscle was not a field effect on the bladder.

Survival model: Needle and transvaginal electrical stimulation

- Needle tetanizing stimulation of the pubococcygeous muscle:
  - Prolonged interval between CMG contractions
    - 38 to 53 minutes (p=0.008 vs. pre-stimulation)
    - Mean increase of 15 minutes vs. 1 minute for control (p=0.022).
  - Needle stimulation led to voiding dysfunction in 7/9(78%) rabbits
  - Cage Parametes: Linear regression showed larger volumes and less frequent voids.
- Vaginal tetanizing stimulation:
  - Increased time to third contraction from 37 to 47 minutes (p=0.015 vs. pre-stimulation).
  - Transvaginal stimulation led to voiding dysfunction in 6/12(50%)
  - Little change in cage parameters was seen one day after vaginal stimulation.

Dobberfuhl, Spettel, Schuler, Levin, Dubin, De: A novel survival model of pelvic floor dysfunction after rabbit pelvic floor and transvaginal electrical stimulation. Submitted to NES-AUA May 2013

Curr Bladder Dysfunct Rep (2012) 7:7–13
DOI 10.1007/s11884-011-0117-4

Biofeedback Treatment for Overactive Bladder

Sara Spettel · Helena C. Frawley · Dolores R. Blais · Elise De

Published online: 6 January 2012

Abstract For several decades, biofeedback has been utilized to help patients gain control of urinary problems. First described in the 1950s, pelvic floor muscle training employing biofeedback techniques has re-emerged as many patients seek to improve their urinary symptoms without medications or invasive procedures. Developing evidence and clinical agreement suggest that the pelvic floor musculature plays an important and often overlooked role in the etiology of lower urinary tract symptoms. New techniques involving computerized visual feedback and electrical stimulation or magnetic stimulation seek to improve the efficacy of pelvic floor muscle exercises. However, findings from the literature for increased response to these exercises with intensity of biofeedback programs are conflicting. While they pose few risks or side effects, biofeedback programs are a time-consuming exercise for patients and providers. As we explore the promising role of pelvic floor rehabilitation in treatment of pelvic floor disorders, we must continue to assess the efficacy and cost-effectiveness of biofeedback as an adjunct to pelvic floor muscle exercises.

Keywords Biofeedback · Treatment · Overactive bladder · Urinary incontinence · Pelvic floor · Pelvic floor muscle exercises

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Introduction

Overactive bladder (OAB) is a common clinical scenario, affecting an estimated 16% of both men and women in the United States and increasing in prevalence with age [1, 2]. OAB is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology [3]. A unique challenge in the treatment of OAB is the heterogeneity of potential etiologies, obligating empiric and often multimodal and long-term therapy. This article discusses one of the more widely used but incompletely studied treatments of OAB: the use of biofeedback.

Biofeedback is an umbrella term referring to any communication to the patient regarding physiologic variables. With reference to pelvic floor treatments, it may serve as an adjunct to other conservative therapies targeting muscle function, such as pelvic floor muscle training, surface electromyography (EMG), electrical stimulation, and cognitive-behavioral techniques such as bladder training and urge suppression techniques. The basic concept is that with feedback, improved muscle awareness and control may subsequently improve pelvic floor dysfunction and, in the case of OAB, assist modulation of urinary symptoms through enhanced inhibition of detrusor activity. It is to be distinguished from digital massage or stretching of overactive

pelvic floor muscles, which intervene directly on muscle tone and pelvic alignment.

Biofeedback techniques have been used for decades in multiple specialties. The application for urinary symptoms was first popularized by Dr. Arnold Kegel in the 1950s for stress incontinence. Although the term *Kegel exercises* is often used as shorthand for tightening of the external sphincter, his original studies involved supervised sessions with a vaginal probe [4]. Much of the early interest in biofeedback was for stress incontinence, as the concept of isolating and strengthening the external sphincter was easily accepted by patients and physicians.

Beyond strengthening bladder outlet resistance, the exact mechanisms for biofeedback as a therapy for OAB are more elusive. Potential mechanisms include neural sensitization, relaxation of stimulating input from overactive levators, and conscious manipulation of known neural feedback pathways (to decrease detrusor contractions and modulate other pelvic organs [eg, the rectum]).

The objective of this article is to review the current literature, discussing the latest understanding of mechanisms in the treatment of OAB with biofeedback and suggesting future directions. The first section is an overview of the different interventions for urinary symptoms referred to as biofeedback and a discussion of potential mechanisms. The second section discusses biofeedback as a first-line therapy in OAB, as an adjunct or alternative to medications. The third section discusses related concepts: biofeedback in patients with increased pelvic floor muscle tone. The fourth section discusses the use of electrical and magnetic stimulation.

Treatments Falling Within the Purview of Biofeedback, and Mechanisms of Action

The term biofeedback can refer to a range of interventions, from simple behavioral strategies to multichannel information with electrical stimulation of muscles. The basic premise is that patients receive visual or auditory feedback for the pelvic floor muscle (or, less commonly, detrusor) at a resting state and during volitional contractions. A seminal paper on electrostimulation by Godec et al. [5] presented a rationale for use in OAB based on the observation that electrical stimulation of a pelvic muscle contraction causes detrusor muscle inhibition (see the article by de Groat [6] for a review of the neurologic basis for the OAB). In addition, an early study of biofeedback in children noted that some children were able to inhibit the detrusor contractions without increasing sphincter activity when receiving visual feedback on their bladder pressures [7]. Biofeedback has an extensive history of use in pediatric voiding disorders, which is beyond the scope of this article (for a review of biofeedback in children, see a 2010 article by Palmer [8]).

Types of biofeedback programs include the following:

- Manual (digital) palpation or EMG identification of muscles. Manual palpation or EMG identification provides patients with instantaneous feedback regarding contractions; this helps patients better identify contractions and teaches them how to achieve a correct contraction through the concept of operant conditioning. Surface EMG identification is provided using vaginal or anal probes or perineal electrodes that transmit signals to a computer, resulting in visual or auditory feedback of the contraction. Original biofeedback equipment used simple sounds or graph paper, whereas newer programs offer more complex visuals or animations to enhance the learning effect.
- Uroflowmetry and detrusor pressures. The use of a urine flow rate or detrusor pressure provides additional feedback during a micturition cycle. This is similar to the components of a urodynamic pressure flow test. Patients with significant Valsalva voiding or with failure to relax their external urinary sphincter during voiding are taught muscle relaxation. This type of biofeedback is the most common type employed for children diagnosed with dysfunctional voiding.
- Behavioral strategies. When directed at OAB symptoms, biofeedback sessions commonly include a significant focus on voiding strategies and lifestyle modifications. Several of the "control" groups in studies discussed compare teaching behavioral strategies with and without the use of biofeedback to identify contraction and relaxation. Once proper muscle group isolation is achieved, the next phase of therapy involves muscle manipulation. Exercises involving strengthening, relaxation, and urge control are taught, and patients practice during rest as well as real life situations (eg, contraction while coughing or bending over, and relaxing during voids). Patients commonly have a set of exercises of varying load or duration to perform at regular intervals during the day. Importantly, there is no single exercise protocol for all patients with urinary complaints, as some exercises increase outlet resistance, whereas others relax the levator muscles (and thereby the S2, S3, and S4 afferents).
- Electrical and magnetic stimulation. Originally described by Caldwell [9] in 1963 to address fecal and urinary incontinence, electrostimulation involves the creation of a passive contraction of the pelvic muscles, usually by transmission of an electric current via vaginal or anal probe. A review article by Fall and Lindstrom [10] describes two potential methods of action. The first is stimulation of pudendal nerve afferents, resulting in detrusor inhibition through central reflexes. The second mechanism hypothesizes stimulation of efferent nerves, resulting in enhancement of pelvic floor and urethral

sphincter musculature tone and induction of detrusor inhibition through the guarding reflex. Other research supports the concept of low-frequency pudendal nerve stimulation activation of spinal interneurons that release inhibitory neurotransmitters [11]. Supporters of this approach compare it in concept with more invasive methods of neuromodulation such as implanted sacral nerve stimulators (for a review of neuromodulation in OAB, see the 2011 article by Le and Kim [12].) Extracorporeal magnetic stimulation is similar in concept, using a magnetic field to create the electrostimulation to adjacent nerves [13]. This is usually done by having patients sit in a chair, with manipulation of position and intensity to stimulate various pelvic nerves and muscles for contraction.

A common theme in the description of biofeedback for OAB is that patients need to be motivated and to understand the expectations for continuous practice away from office sessions. The premise of mechanism involves resetting the way in which the patient uses the pelvic floor muscles and responds to sensations. For therapy to be effective, patients must have volitional control over their muscles. Depending on the completeness of the lesion, patients with a neurological cause of OAB are less likely to be helped than others. Although both men and women can have OAB, the vast majority of research for biofeedback in OAB includes only females.

Biofeedback as First-Line Therapy

In the absence of obvious pathology leading to OAB symptoms, such as bladder outlet obstruction, malignancy, or infection, biofeedback-assisted pelvic floor muscle training is an option for first-line treatment. Although anticholinergic medications are effective for a large number of patients, a significant percentage will discontinue due to side effects or the experience of refractory symptoms. In some studies, cessation is as high as 60% after 90 days [14]. Many patients and their providers are attracted to biofeedback as an alternative to continuous medical therapy or as a means by which to maximize response.

An influential 1998 study by Burgio et al. [15], to whom we owe much of the current research in biofeedback, randomly assigned 197 women with urge incontinence to 8 weeks of biofeedback-augmented pelvic floor muscle training, anticholinergics, or placebo. They found superior improvement in incontinence and satisfaction scores in women undergoing biofeedback compared with those receiving anticholinergics [15]. A follow-up study found in a crossover design that women who added biofeedback or drug therapy to their treatment experienced increased improvement in symptoms versus either treatment alone after 8 weeks [16]. This led to the hypothesis that anticholinergic medications and biofeedback, which have different mechanisms of action, could work synergistically to ameliorate OAB symptoms.

A study of this hypothesis, again by Burgio et al. [17], randomly assigned 64 patients to anticholinergic medication with or without concurrent biofeedback and found no difference between the groups at 6 and 12 months. Importantly, the study individually titrated the anticholinergic medication with proactive management of side effects, finding a mean 88.5% reduction in incontinence episodes in the "control" group—leaving little room for improvement with biofeedback.

A larger multicenter trial, the BE-DRI (Behavior Enhances Drug Reduction of Incontinence) trial, randomly assigned 307 women with urge incontinence to 10 weeks of anticholinergic therapy with or without biofeedback, followed by discontinuation of all therapy [18]. The primary outcome at 8 months was the ability to discontinue the anticholinergic medication while maintaining a 70% or greater reduction in frequency of incontinence episodes. The investigators found no difference in the primary outcome (40% maintained improvement after discontinuation in each group) but did note improved patient satisfaction and perceived improvement in those receiving biofeedback [19]. The authors noted that the women had biofeedback sessions concurrently while taking anticholinergic medication, and discussed the possibility that "combined intervention did not allow the transfer of learned continence skills to the new sensory context after drug therapy was discontinued" [19]. In addition, the 12-month follow-up of the BE-DRI study found that those who received biofeedback reported the rates of regular participation in the exercises declined from 81% during interventions to 32% at 1 year [20]. These studies highlight a potentially significant drop-out rate for both medications and pelvic floor muscle exercises.

A comprehensive systematic review and cost-effectiveness modeling of the effectiveness of conservative therapies for women with stress urinary incontinence showed that more intensive pelvic floor muscle training with biofeedback (vs no treatment) was superior (OR, 12.3) [21]. The same comparison and modeling has not yet been undertaken for pelvic floor muscle training plus biofeedback for OAB.

A 2011 Cochrane review of verbal feedback or device-assisted biofeedback for any type of urinary incontinence concluded that feedback or biofeedback may provide benefit in addition to pelvic floor muscle training in women with incontinence [22]. However, the authors concluded it was not clear whether it was the biofeedback that provided the additional benefit, or whether the effect could be attributed to some other difference between the groups under study,

such as a difference in contact time with the health professional.

One of the largest trials to address different types of behavioral training in OAB randomly assigned 222 patients to interventions with behavioral training using a self-help booklet or clinic behavioral training with or without manual biofeedback (verbal feedback based on vaginal palpation) [23]. They found improvements in all groups but no significant differences among groups. One of the main criticisms of biofeedback is that it requires a significant time commitment from the patient in addition to the health care resources required. In contrast, a 12-week study of 103 women by Wang et al. [24] randomly assigned patients to pelvic floor muscle training at home without any device or to biofeedback-assisted training twice a week in clinic with or without electrical stimulation and found higher subjective reduction rates for OAB for patients receiving biofeedback in clinic. In our clinical experience, some patients are capable of identifying specific muscles and following the behavioral modifications on their own, while some require a more formal program with the intensity of therapy tailored to the individual patient.

An interesting recent trial evaluated the use of biofeedback in women younger than 40 years old with recurrent UTIs [25•]. The study randomly assigned patients to no intervention or one of two separate types of biofeedback. It found a significant difference in culture-proven UTIs between patients who received biofeedback and those who did not. This study had the unique feature of an additional objective outcome variable, the UTI, as opposed to the patient-reported outcomes highly influenced by the "placebo" behavioral interventions. It is likely that dysfunctional voiding predisposes patients to UTIs by altering voiding pressure and completeness of emptying, with overlap with the OAB population.

The majority of studies examining biofeedback demonstrate improvement in outcomes, but conflicting results have been reported regarding improvement versus the control intervention. Importantly, patient satisfaction scores with biofeedback are often higher in these comparison studies, even with no significant difference in voiding symptoms. Tadic et al. [26] specifically examined the psychological burden of urge incontinence following an 8-week session of biofeedback-assisted pelvic floor exercises. They found significant patient-reported improvements in psychological outcomes compared with the patients' baselines at the end of the 8-week session, especially in women with a history of depression.

Our clinical experience with biofeedback (vaginal sensor-assisted visual feedback for pelvic floor muscle contraction and electrostimulation) in OAB has been predominantly positive in properly selected patients. One group in particular that has benefitted is patients in whom pelvic floor muscle overactivity can be appreciated on physical examination. However, if the patient has significant pain on palpation of the levator complex or a fearful response to intercourse or physical examination, Thiele massage or another form of relaxation is often required prior to efforts toward exercises and self-modulation of pelvic muscle tone. These patients also comprise a significant number of the patients referred for "refractory" OAB and recurrent UTI with variable cultures, with or without pelvic pain symptoms. Sometimes these patients will have tried a form of biofeedback unsuccessfully (eg, Kegel training without attention to relaxation of muscles). Unfortunately, evaluating the pelvic floor musculature is not a commonly taught component of the speculum examination, and many patients who could benefit from therapy directed at their pelvic floor remain unrecognized.

Biofeedback Pelvic Floor Overactivity

Pelvic floor overactivity is described by the International Continence Society as "a situation in which the pelvic floor muscles do not relax, or may even contract when relaxation is functionally needed, for example during micturition or defecation" [27]. This dysfunction has been implicated clinically as an underlying factor in OAB as well as other diagnoses, such as interstitial cystitis, irritable bowel syndrome, and chronic pelvic pain [28, 29]. The role of the pelvic floor musculature in normal function of the lower urinary tract is incompletely understood; the visceral and somatic interplay of structures in the pelvis is highly complex. Our own experience with a rabbit animal model of pelvic floor overactivity demonstrated changes in cystometric variables that were analogous to those seen in humans with OAB and dysfunctional voiding (unpublished data). Other studies have shown that pelvic floor muscle overactivity can lead to pelvic organ cross-sensitization and voiding, evacuation, and pain symptoms via cross-afferent stimulation in the pelvis [30•]. Reflexive pro- and antidromic pathways exist via peripheral dichotomizing afferents along the dorsal roots and via reflexive central pathways. These interactions have been demonstrated in varied species by multiple methods (eg, immunohistochemical labeling studies, single-unit afferent recordings) [30•, 31, 32].

Patients with pelvic floor muscle overactivity can present with OAB symptoms with or without other pelvic floor complaints (pain, dyspareunia). These patients often present with refractory, so-called idiopathic OAB with multiple prior failed therapies, and intervention on the pelvic floor can yield dramatic improvements. It is not uncommon to see patients with extensive histories, including hydrodistention, multiple failed medications, incontinence surgery, neuromodulation, laparoscopy, or even hysterectomy for pelvic symptoms, who have never undergone a pelvic floor muscle

examination. Unfortunately, there is currently no validated, reproducible examination by which to characterize pelvic floor muscle overactivity at rest. Nevertheless, assessment should be performed, and our clinical examination is outlined in Table 1. Treatment of the pelvic floor overactivity can provide significant relief of urinary and pain symptoms in patients otherwise written off as "refractory."

The literature regarding patients with pelvic floor dysfunction spans several disciplines. Some of the more successful studies using biofeedback come from the gastrointestinal literature for syndromes analogous to the urinary system, such as fecal incontinence, dyssynergic defecation, and levator ani syndrome [33–35] (see the article by Koh et al. [36] for review of biofeedback for gastrointestinal disease).

Several authors have studied the risk factors for patients who do not respond to biofeedback. Yoo et al. [37] reported that the only significant variable in those requiring no further therapy after biofeedback in their series of 84 women was change in amplitude of tonic pelvic floor contraction. The authors noted "women who increased tonic PFMT (pelvic floor muscle tone) contraction strength after 4 weeks of training derived the most benefit from treatment, which indicates that this group could be a prime target for biofeedback-assisted PFMT" [37]. The authors did not comment on the any differences in baseline pelvic floor tone, but this study suggests that women with baseline overactive pelvic floor tone would not be able to increase their amplitude of contraction and thus would be less likely to respond to this type of biofeedback. In a secondary review of previously described trials, Burgio et al. [23] found that the predictor of success for urge incontinence after biofeedback was original severity of urge incontinence and previous treatment [38]. Importantly, although these trials included a pelvic examination and controlled for pelvic organ prolapse, they did not formally examine or remark on pelvic muscle overactivity. A 2004 systemic review of clinical trials of pharmacologic and behavioral therapy found no consistent predictors of failure of urge incontinence treatment, again not evaluating pelvic musculature as a variable [39].

The effects of treatment of overactive pelvic floor musculature on OAB have been reported in small series. A small intervention study of 52 women at our institution using transvaginal biofeedback and electrical stimulation for women with pelvic floor overactivity, identified by clinical examination as described previously, resulted in a significant reduction in urinary urgency and frequency [40]. Weiss [41] found that symptoms of urgency/frequency were reduced in 35 of 42 patients with manual therapy aimed at decreasing pelvic muscle tone. Similar results were found by Lukban et al. [42] using myofascial release, joint mobilization, and home exercises. Research in this particular area of OAB management is hampered by a lack of data regarding the distribution of the phenomenon of pelvic floor muscle overactivity in women with OAB and the absence of a standardized means by which to measure it (for review of pelvic muscle overactivity in chronic pelvic pain, see Westesson and Shoskes [43].)

Electrical and Magnetic Stimulation

Electrical and magnetic stimulation have been postulated as therapies to improve the response to traditional biofeedback. As discussed previously, an electrical stimulation is created by an internal probe or external magnetic field with passive contraction of pelvic floor muscle. Several studies of electrical stimulation have shown improvement in OAB symptoms, though the degree of improvement and designs varied considerably [44]. For example, Yamanishi et al. [45] reported their experience with 60 male and female patients randomly assigned to twice-daily sham or pelvic floor electrostimulation. The patients who received electrical stimulation had increased satisfaction and bladder capacity. One of the better-designed studies by Brubaker et al. [46] randomly assigned 121 women at several centers to sham or twice-daily home pelvic floor electrical stimulation for 8 weeks. Although the study was limited by a heterogeneous incontinence population, they reported an improved response rate for OAB, almost 50%, as opposed to no difference for stress incontinence. The clinical applicability of these studies is an important issue, as twice-daily treatment with vaginal probes is time consuming and expensive.

Three studies randomly assigning patients to biofeedback with electrical stimulation or drug therapy found no statistical difference among groups, but improvement with biofeedback

Table 1 Pelvic floor muscle overactivity (firmness) manual examination

•Examination of the levator complex can be performed by inserting the finger into the vagina or rectum, then angling 45° to the left and right.
•In our clinical practice, levator tone is assessed as follows:
••The proximal (pubococcygeus) muscle and distal (iliococcygeus) muscles can be felt separately bilaterally.
••As a reference, normal firmness is equal to the resting compressibility of thenar eminence; decreased is less, whereas increased firmness would be equivalent to the compressibility of the thenar eminence when the thumb is opposed to the first (moderate) or fifth (severe) digits.
••Pain can be assessed at each point using a Likert scale.

was again equal to that of drug therapy (Franzen et al. [47] randomly assigned 61 patients to electrical stimulation or tolterodine for 7 weeks; Arruda et al. [48] randomly assigned 64 patients to oxybutynin, electrical stimulation, or pelvic floor exercises for 12 weeks; and Ozdedeli et al. [49] randomly assigned 35 patients to electrical stimulation or trospium hydrochloride for 6 weeks). However, not all the literature for electrical stimulation is positive. A 2010 study by Voorham-van der Zalm et al. [13] examining biofeedback with magnetic stimulation found no benefit in terms of symptom improvement and is one of the few studies to note an adverse effect in some patients, a change the authors attributed to increased resting tone of the pelvic floor muscles after treatment. In our clinical experience, patients with overactive pelvic floor muscles who undergo electrical stimulation therapy can experience pain; these patients must undergo physiotherapy for relaxation first. Again, we stress that a clinical assessment of the pelvic floor muscles before initiating any therapy for OAB, including biofeedback or electrostimulation, is crucial.

Conclusions

Biofeedback in its many forms as an adjunct to pelvic floor muscle exercises has been used to treat OAB symptoms for decades but is a highly individualized therapy. Behavioral intervention and pelvic floor muscle training should be considered for all patients with OAB. As studies have shown, however, a significant number of patients' symptoms may improve with behavioral modification and self-directed exercises without the need for additional visits or equipment. For patients who have difficulty locating or modulating their mechanisms of control, the benefit of visual or audio input associated with common applications of biofeedback can be significant. While conceptually promising, the clinical applicability of electrical stimulation over other types of biofeedback is still uncertain. For many patients referred as refractory or who present with pelvic floor muscle overactivity, directed therapy to these muscles followed by training for coordinated use and relaxation can offer dramatic relief for OAB symptoms and other related pelvic floor disease.

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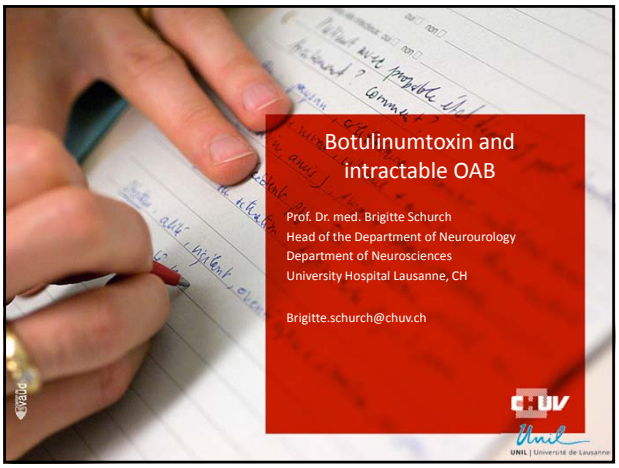
Botulinumtoxin and intractable OAB
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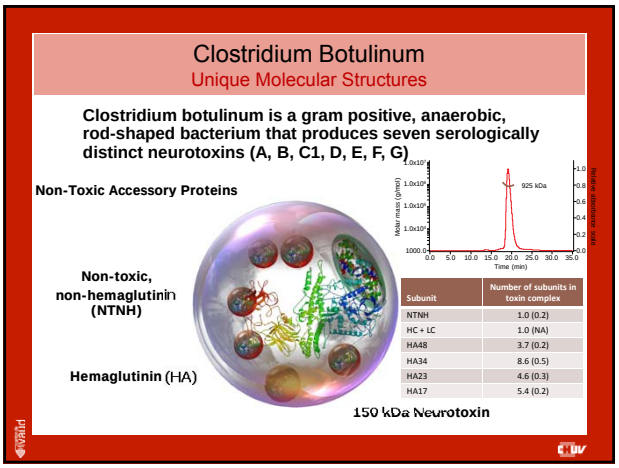
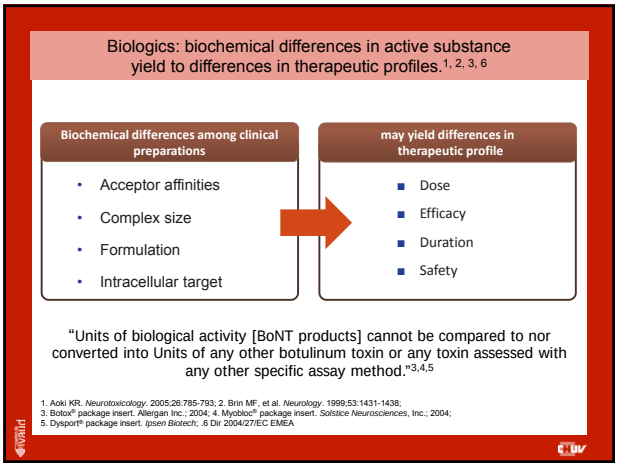
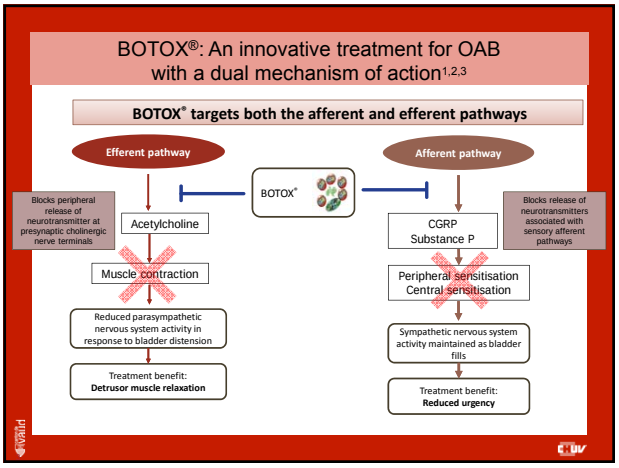
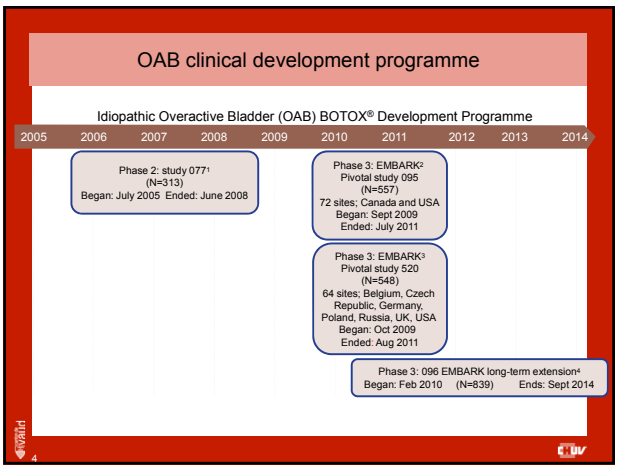
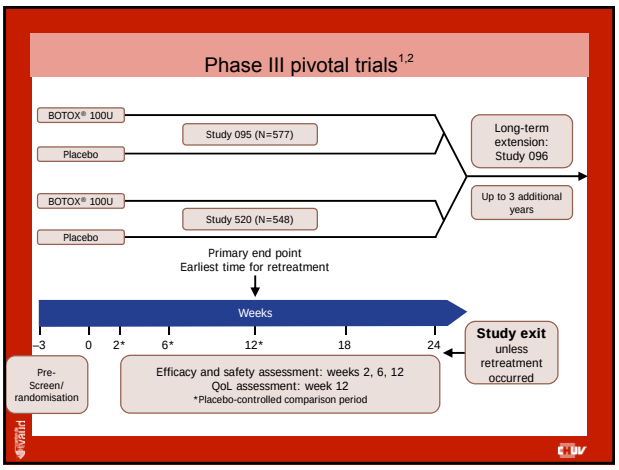

Clostridium Botulinum
Unique Molecular Structures
Clostridium botulinum is a gram positive, anaerobic, rod-shaped bacterium that produces seven serologically distinct neurotoxins (A, B, C1, D, E, F, G)
Non-Toxic Accessory Proteins
Non-toxic, non-hemaglutinin (NTNH)
Hemaglutinin (HA)
925 kDa
Time (min)
Subunit
Number of subunits in toxin complex
NTNH 1.0 (0.2)
HC + LC 1.0 (NA)
HA48 3.7 (0.2)
HA34 8.6 (0.5)
HA23 4.6 (0.3)
HA17 5.4 (0.2)
150 kDa Neurotoxin


Biologics: biochemical differences in active substance yield to differences in therapeutic profiles.1, 2, 3, 6
Biochemical differences among clinical preparations
Acceptor affinities
Complex size
Formulation
Intracellular target
may yield differences in therapeutic profile
Dose
Efficacy
Duration
Safety
"Units of biological activity [BoNT products] cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method."3,4,5
1. Aoki KR. Neurotoxicology. 2005;26:785-793; 2. Brin MF, et al. Neurology. 1999;53:1431-1438;
3. Botox® package insert. Allergan Inc.; 2004; 4. Myobloc® package insert: Solstice Neurosciences, Inc.; 2004;
5. Dysport® package insert. Ipsen Biotech; 6 Dir 2004/27/EC EMEA


BOTOX®: An innovative treatment for OAB with a dual mechanism of action1,2,3
BOTOX® targets both the afferent and efferent pathways
Efferent pathway
Afferent pathway
BOTOX®
Blocks peripheral release of neurotransmitter at presynaptic cholinergic nerve terminals
Acetylcholine
Muscle contraction
Reduced parasympathetic nervous system activity in response to bladder distension
Treatment benefit: Detrusor muscle relaxation
CGRP
Substance P
Blocks release of neurotransmitters associated with sensory afferent pathways
Peripheral sensitisation
Central sensitisation
Sympathetic nervous system activity maintained as bladder fills
Treatment benefit: Reduced urgency


OAB clinical development programme
Idiopathic Overactive Bladder (OAB) BOTOX® Development Programme
2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Phase 2: study 077¹ (N=313) Began: July 2005 Ended: June 2008
Phase 3: EMBARK² Pivotal study 095 (N=557) 72 sites; Canada and USA Began: Sept 2009 Ended: July 2011
Phase 3: EMBARK³ Pivotal study 520 (N=548) 64 sites; Belgium, Czech Republic, Germany, Poland, Russia, UK, USA Began: Oct 2009 Ended: Aug 2011
Phase 3: 096 EMBARK long-term extension⁴ Began: Feb 2010 (N=839) Ends: Sept 2014


Phase III pivotal trials1,2
BOTOX® 100U
Placebo
Study 095 (N=577)
BOTOX® 100U
Placebo
Study 520 (N=548)
Long-term extension: Study 096
Up to 3 additional years
Primary end point
Earliest time for retreatment
Weeks
–3 0 2* 6* 12* 18 24
Study exit unless retreatment occurred
Pre-Screen/ randomisation
Efficacy and safety assessment: weeks 2, 6, 12
QoL assessment: week 12
*Placebo-controlled comparison period

Inclusion criteria of Phase III pivotal studies

- **Population of OAB patients**
  - ≥3 urinary urgency incontinence (UUI) episodes in 3-day diary
  - ≥8 micturitions/day
  - Post-void residual urine ≤100 mL
  - Inadequately managed by anticholinergics
    - Washout period 2 weeks
    - No anticholinergic use permitted during the trial

Phase III pivotal studies: studies endpoints

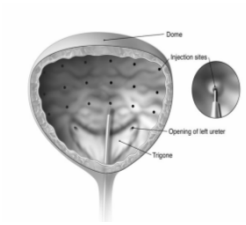
Endpoint	Measure
Primary	• Number of urinary incontinence episodes • Proportion of patients with positive treatment response on the Treatment Benefit Scale
Secondary	• Number of urgency episodes • Number of micturition episodes • Volume voided per micturition • I-QOL total summary score • KHQ domains (role limitations and social limitations)

Phase III pivotal studies: treatment paradigm

Patients randomised in a 1:1 ratio:
- BOTOX® 100 U; or
- placebo

Administered via:
- Rigid or flexible cystoscope
- 20 intradetrusor injections, sparing trigone
- 0.5 mL per site
- Optional instillation of local anesthesia and/or sedation

Re-treatment permitted:
- BOTOX® 100 U permitted after ≥ 12 weeks
- After two incontinent episodes
- PVR >200 mL
- Patient request



Demographics

Parameter	BOTOX® 100 U (N=557)	Placebo (N=548)
Age (years)	60.6	60.1
Sex Male Female	 11.0% 89.0%	 13.5% 86.5%
Race Caucasian Non-caucasian	 89.8% 10.2%	 92.0% 8.0%
BMI*	29.9	30.9

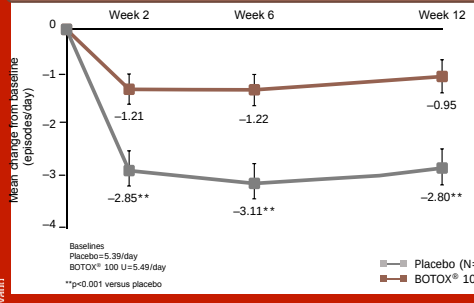
- Groups were well balanced with no significant differences between treatment groups

Baseline characteristics

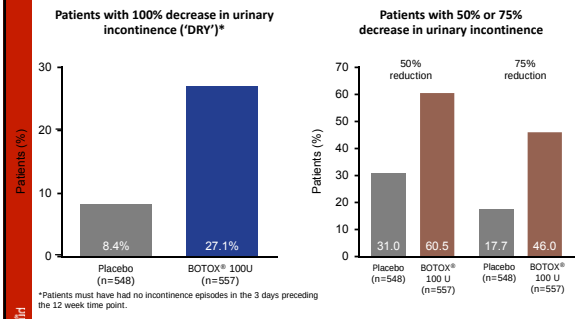
Parameter	BOTOX® 100 U (N=557)	Placebo (N=548)
Duration of OAB (years)	6.04	6.14
Number of prior anticholinergics used (mean)	2.4	2.5
Urinary incontinence episodes (per 24 hrs)	5.49	5.39
Urgency episodes (per 24 hrs)	8.82	8.31
Micturition episodes (per 24 hrs)	11.99	5.39
Nocturia episodes (per 24 hrs)	2.17	2.04
Volume voided per micturition (mL)	150.37	156.89

Urinary Incontinence episodes (UI) at follow-up

At week 12, BOTOX® led to a 51% reduction from baseline in UI episodes versus 18% with placebo (p<0.001)



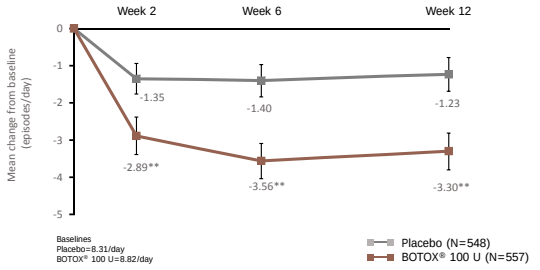
Significant reduction in urinary incontinence versus placebo



*Patients must have had no incontinence episodes in the 3 days preceding the 12 week time point.

Significant decrease in daily urgency episodes versus placebo

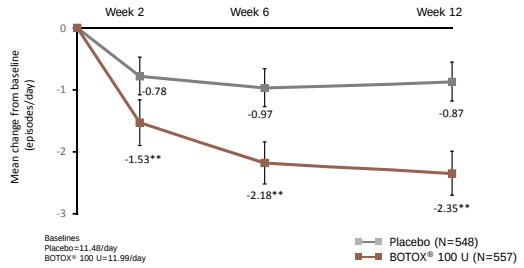
At week 12, BOTOX® led to a 37% reduction from baseline in daily urgency episodes versus 15% with placebo (p<0.001)



**p<0.001 vs placebo

Significant decrease in daily micturition frequency versus placebo

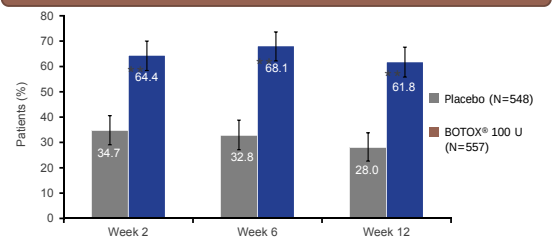
At week 12, BOTOX® led to a 20% reduction from baseline in daily micturition frequency versus 8% with placebo (p<0.001)



**p<0.001 vs placebo

Over 60% of BOTOX® patients were 'greatly Improved' or 'improved'

Significantly more BOTOX® patients reported their symptoms as 'Greatly Improved' or 'Improved'



**p<0.001 vs placebo

Median time to patient request for re-treatment is about 6 months

The median duration of response following BOTOX® treatment, based on patient request for re-treatment, was 166 days (~24 weeks)

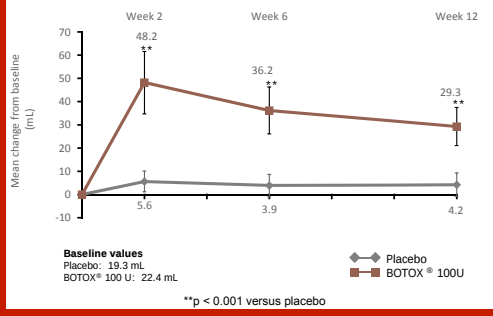
Definitions for adverse events

	Phase III pivotal studies
Urinary tract infection	Bacteriuria count of $>10^5$ CFU/mL **and** leukocyturia of >5/hpf
Urinary retention	Elevated PVR ≥200 mL requiring CIC CIC to be initiated either: ▪ if PVR between ≥200 mL and <350 mL and patient has associated symptoms that require CIC ▪ PVR ≥350 mL (regardless of symptoms)

Most common adverse events are urinary tract infection and dysuria

Adverse event ≥ 3%	First 12 weeks		Any time in treatment cycle 1	
	BOTOX® 100 U (N=552)	Placebo (N=542)	BOTOX® 100 U (N=552)	Placebo (N=542)
Urinary tract infection	99 (17.9%)	30 (5.5%)	141 (25.5%)	52 (9.6%)
Dysuria	50 (9.1%)	36 (6.6%)	60 (10.9%)	38 (7.0%)
Urinary retention	31 (5.6%)	2 (0.4%)	32 (5.8%)	2 (0.4%)
Bacteriuria	24 (4.3%)	11 (2.0%)	44 (8.0%)	19 (3.5%)
Haematuria	17 (3.1%)	16 (3.0%)	18 (3.3%)	18 (3.3%)
Residual urine volume	17 (3.1%)	1 (0.2%)	19 (3.4%)	2 (0.4%)
Sinusitis	12 (2.2%)	2 (0.4%)	18 (3.3%)	6 (1.1%)
Leukocyturia	11 (2.0%)	2 (0.4%)	18 (3.3%)	2 (0.4%)

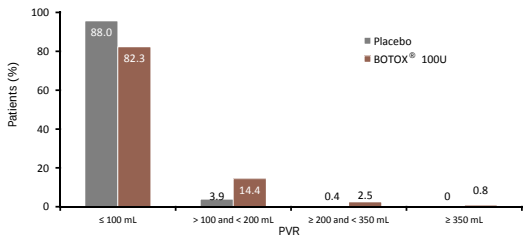
Urinary retention was higher with BOTOX® versus placebo



**p < 0.001 versus placebo

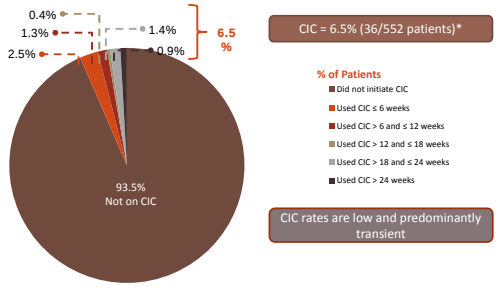
Majority of BOTOX®-treated patients had PVR ≤100 mL

- **Patients with absolute PVR at different thresholds at week 12**



PVR = post-void residual

Majority of patients do not require CIC



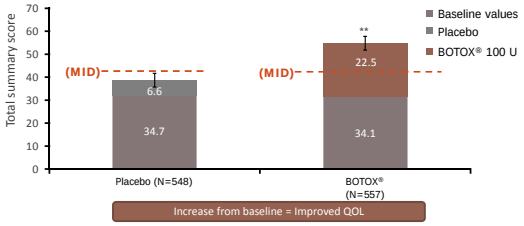
CIC = clean intermittent catheterization; PVR = post void residual

Low incidence of treatment discontinuation due to adverse events

Parameter	095 Study			520 Study		
	BOTOX® 100 U	Placebo	Total	BOTOX® 100 U	Placebo	Total
Randomized (N)	280	277	**557**	277	271	**548**
Discontinued						
Any reason						
Full Tx cycle 1	31 (11.1%)	34 (12.3%)	**65 (11.7%)**	20 (7.2%)	24 (8.9%)	**44 (8.0%)**
1st 12 wks	13 (4.6%)	21 (7.6%)	**34 (6.1%)**	11 (4.0%)	16 (5.9%)	**27 (4.9%)**
Due to AEs						
Full Tx cycle 1	5 (1.8%)	4 (1.4%)	**9 (1.6%)**	6 (2.2%)	1 (0.4%)	**7 (1.3%)**
1st 12 wks	4 (1.4%)	2 (0.7%)	**6 (1.1%)**	4 (1.4%)	1 (0.4%)	**5 (0.9%)**

Clinically significant improvements in I-QOL total summary score versus placebo

Change from baseline in I-QOL total summary score at week 12

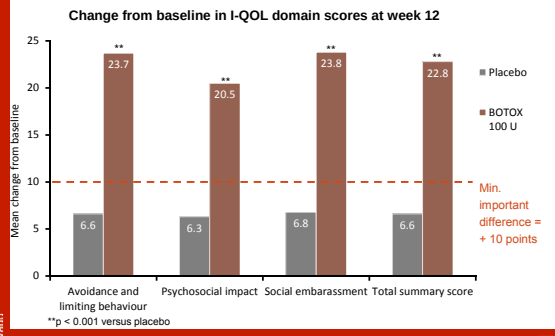


Increase from baseline = Improved QOL

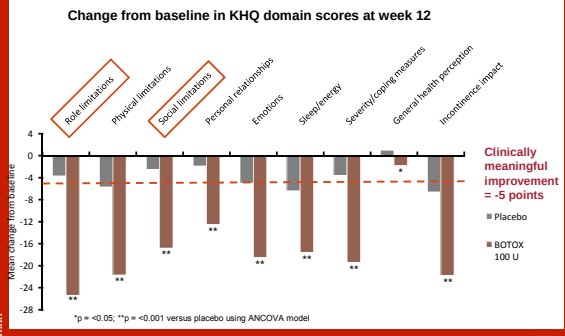
Minimally important difference (MID) = 10 point increase from baseline

**p<0.001 vs placebo

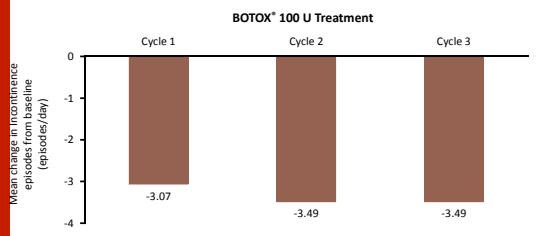
Clinically meaningful improvements in all I-QOL domains



Significant improvements in key domains affected in OAB



Long lasting efficacy predictably maintained with future treatment cycles



Consistent tolerability profile following repeat injections: long term follow-up study

	1st BOTOX® (N=814)	2nd BOTOX® (N=546)	3rd BOTOX® (N=253)	4th BOTOX® (N=88)
Overall incidence of adverse events (%)				
	65.6	58.4	51.0	52.3
Incidence of individual adverse events ≥ 5% in any cycle (%)				
UTI	25.2	21.8	19.4	18.2
Dysuria	8.8	7.1	4.0	3.4
Bacteriuria	6.9	6.4	2.4	3.4
PVR, urinary retention and use of CIC				
Mean change in PVR (at week 2, mL)	45.8	44.4	53.4	62.7
Urinary retention (%)	4.1	3.1	2.8	3.4
Patients using CIC (%)	4.7	3.8	4.3	5.7

Summary

- BOTOX® 100 U significantly improves OAB symptoms in patients who had inadequate response to anticholinergic therapy
- BOTOX® 100 U significantly improves quality of life for patients with OAB
- BOTOX® 100 U has a favourable tolerability profile
  - Discontinuation rates less than 2%
- Sustained efficacy and tolerability over repeated BOTOX® treatments

Neuromodulation and lower urinary tract

Jacques Corcos MD, FRCS(S)
McGill University
Montreal, Canada

ICS Barcelone 2013

Bladder Neuro control

- Old history: 1863 **Giannuzi** :hypogastric and pelvic nerves are involved in dog bladder contraction
- 1878, **Saxtorph** proposed intravesical stimulation for urinary retention

Recent history

- In 1958, Katona transurethral electrical stimulation.
- In 1975 Katona reported 420 patients >>314 achieved micturition control.
- In 1982, Madersbacher : 30 patients >>17 bladder control (10 dry)
- 1982 Emil A. Tanagho and Richard Schmidt

Recent history

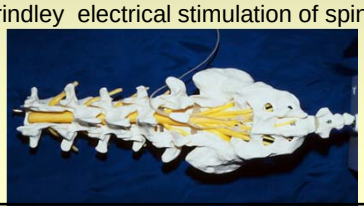
- In 1958, Katona transurethral electrical stimulation.
- In 1975 Katona reported 420 patients >>314 achieved micturition control.
- In 1982 [illegible] 17 bladde
- 1982 E [illegible] midt

Bladder pacemaker:
scientific basis and clinical future
Urology december 1982
Vol XX number 6

Bladder neuro control

- **Neuromodulation** Schmidt and Tanagho
- **Neurostimulation** Brindley

1972, Brindley electrical stimulation of spinal roots.



The paradox of Neuromodulation

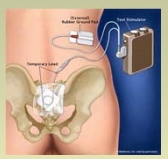
Works as well in patients with
Refractory overactive bladder
Than in patients with
Unexplained urinary retention

Selecting Patients for InterStim™ Therapy

- Initial Screening
- Voiding Diary
- Urodynamic Workup
- Behavioral Techniques
- Medication
- Test Stimulation
- Peripheral nerve evaluation or First stage implant
- Implant InterStim System

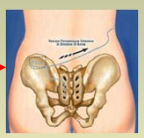
Procedure Flows

Test with PNE



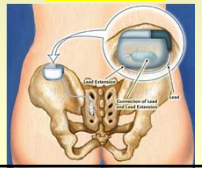
If inconclusive

Staged Implant

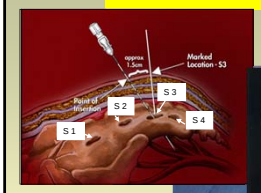


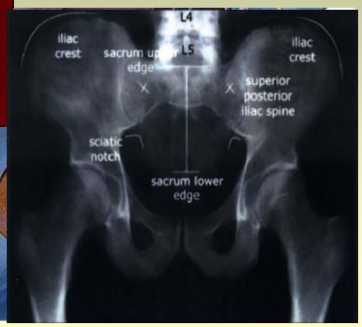
If conclusive

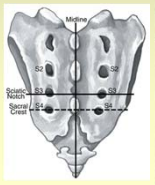
- Stage 2

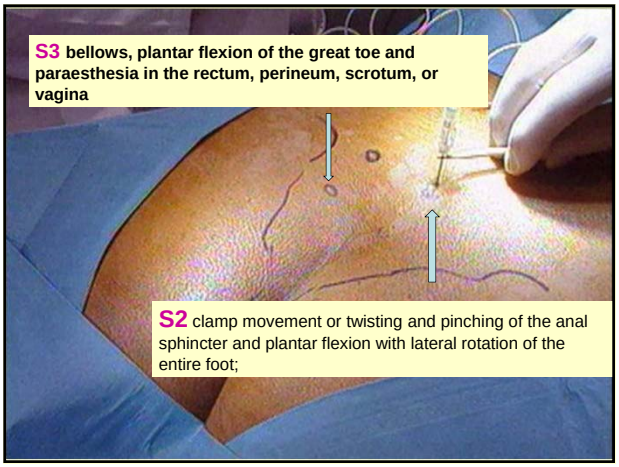


Peripheral nerve evaluation Testing for Motor & Sensory Responses



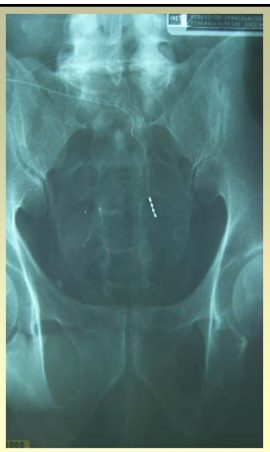






S3 bellows, plantar flexion of the great toe and paraesthesia in the rectum, perineum, scrotum, or vagina

S2 clamp movement or twisting and pinching of the anal sphincter and plantar flexion with lateral rotation of the entire foot;

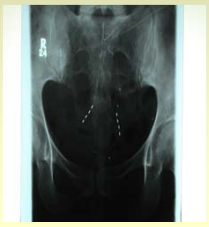


Benefits of Test Stimulation

- Locate & identify sacral nerves
- Verify neural integrity
- Allow the patient to feel the stimulation
- Assess viability of sacral nerve stimulation on voiding behavior
- Help physician & patient make an informed choice about the long-term therapeutic value in a low cost/minimally-invasive manner

Bilateral SNS

- Indications:
  - Pelvic pain (unless lateralized)
  - Severe U/F not responding to unilateral SNS



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UNILATERAL VERSUS BILATERAL SACRAL NEUROMODULATION IN PATIENTS WITH CHRONIC VOIDING DYSFUNCTION

W. A. SCHEEPENS, R. A. DE BIE,* E. H. J. WEIL AND Ph. E. V. VAN KERREBROECK
From the Department of Urology, University Hospital Maastricht and †Department of Epidemiology, Maastricht University, Maastricht, The Netherlands

- **Randomized Cross over study design; N = 33**
- **Patients with refractory UI, UF and UR**
- **Only Test Stimulation**
- **Voiding diaries before and during evaluation period**

- **RESULTS: Significant improvements in majority of pt's (test)**
- **No statistically significant improvement due to bilateral stimulation**
- **2 pt's with urinary retention started voiding to completion during bilateral stimulation only**

PNE +Implant v/s 2 stage procedure

42 patients

- 33% failed in PNE+
- 14% Failed 2 stage procedure

Everaert K et al. European Urology 45 (2004) 649–654

2 stages implants

- **1st stage:** implantation of permanent electrode

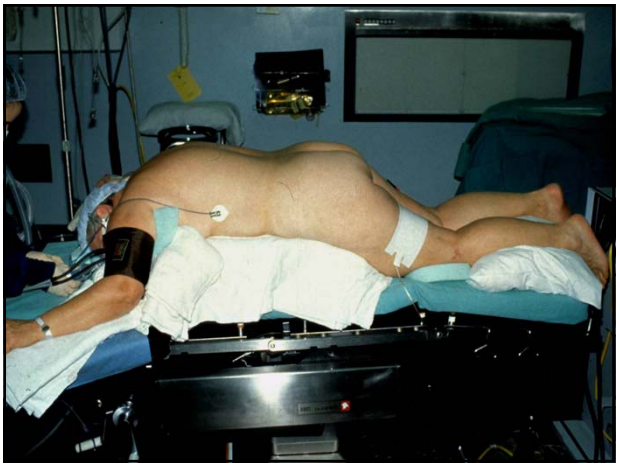
  ↓

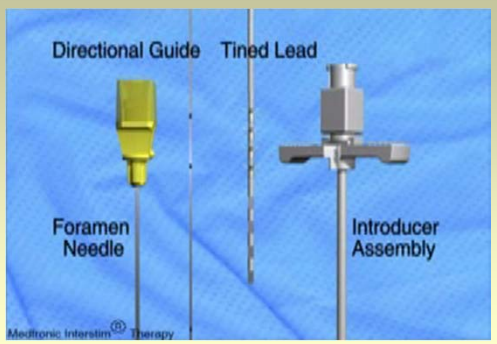
  Evaluation of results

  ↓

  If conclusive

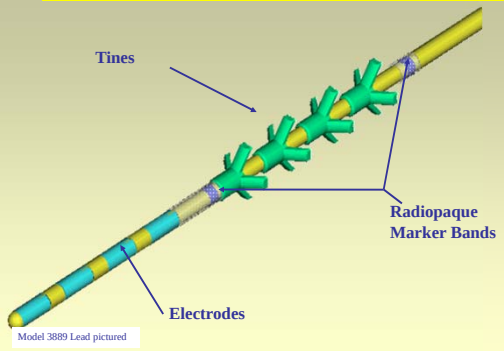
- **2nd stage:** implantation of neuromodulator unit

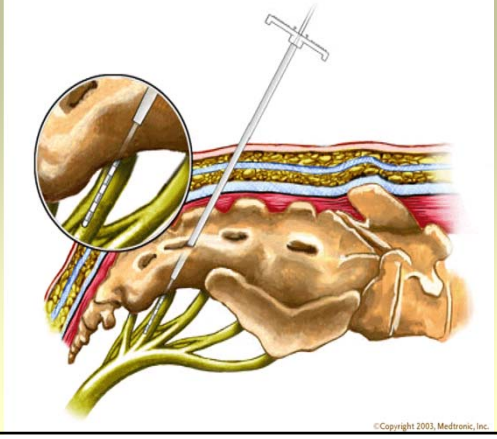


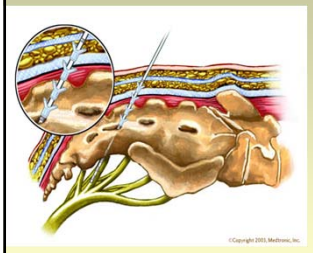


22-May-08
JBG

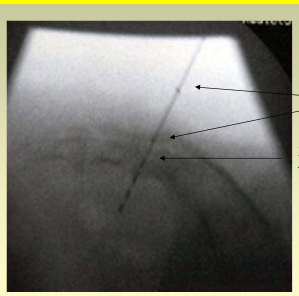
Tined Leads Model

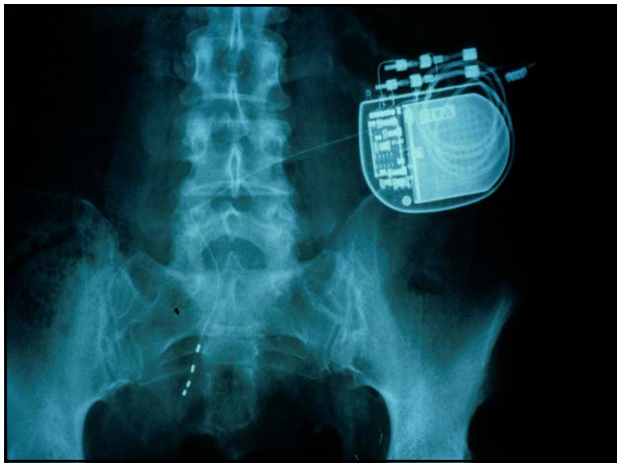






Lead placement





InterStim II Neurostimulator and Lead

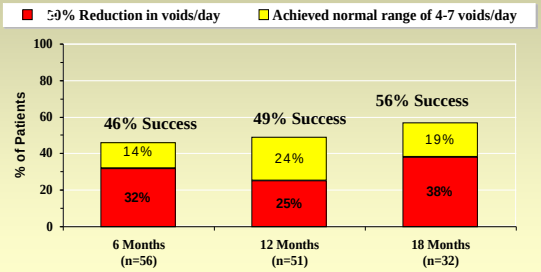
- Smaller implantable stimulator (~50% smaller)
- No need for lead extension (reduced procedure time and complication)

Refractory OAB

Clinical results

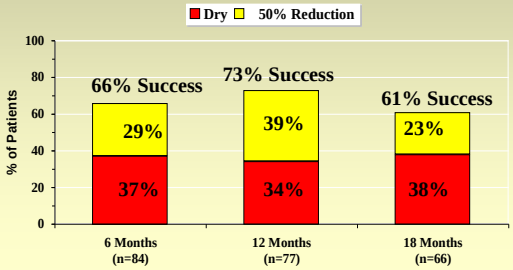
Urgency-Frequency

Number of Voids/Day



Urge Incontinence

Any Leaking Episodes



Long Term results > 64 months

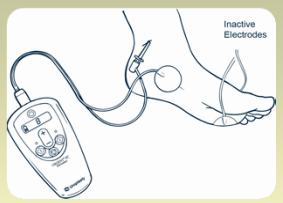
- **Urge /Frequency**
  - "good results"….. 61 % van Voskuiilen et al 2004
  - "good results "… 52 % Bosch & Groen 2002
  - Satisfied patients….54% at 12 years Elhilali , Corcos

Revisions and complications

- The explantation/revision rates ranged between 20 and 30% in most studies.
- Most common reported complications are
  - IPG site pain
  - Revision of lead
  - Infection at IPG site.

Tibial nerve neuro-modulation

Tibial Nerve Stimulation



- Tibial nerve sends afferents through the sacral nerve plexus
- Studied since the 1980's for the treatment of OAB
- Until recently there were no controlled trials

Tibial nerve Neuro stim.

http://www.youtube.com/watch?v=0drKILgxhiM

Percutaneous Tibial Nerve Stimulation for the Long-Term Treatment of Overactive Bladder (29 patients 36-month FU)
Peters et al J.Urol 2013

- Median of 1.1 treatments per month after a 14-week treatment tapering protocol.
- 77% (95% CI 64-90) patients maintained moderate or marked improvement.
- Compared to baselinemedian voids per day 12.0 (IQR 10.3-13.7) to 8.7 (IQR 7.3-11.3)
- night voids 2.7 (IQR 1.7-3.3) to 1.7 (IQR 1.0-2.7)
- urge incontinence/d f3.3 (IQR 0.7-6.0) to 0.3 (IQR 0.0-1.0)
- (all p <0.0001)

Conclusions

- Efficacy of SNM and PTNS in "desperate" cases
- Place of these techniques in comparison to Botox still debated
- High rate of secondary complications and patient's rejection with SNM
- Has to be available in a modern urological practice

Notes