

W11: A Case-driven workshop on intractable overactive bladder.

Workshop Chair: Jacques Corcos, Canada

20 October 2014 14:00 - 17:00

Start	End	Topic	Speakers
14:00	14:10	Introduction, definition, standardization "A Critical View and Future Perspectives"	<ul style="list-style-type: none"> • Marcus Drake
14:10	14:20	Questions	All
14:20	14:30	Case 1. Presentation of a new patient "How to conduct the first visit"	<ul style="list-style-type: none"> • Jacques Corcos
14:30	14:40	Questions	All
14:40	14:55	Case 2. The patient who took "all drugs": What can we expect from new and future drugs:	<ul style="list-style-type: none"> • Francisco Cruz
14:55	15:05	Questions	All
15:05	15:20	Case 3. The patient doesn't want anything "invasive" What can we offer?	<ul style="list-style-type: none"> • Elizabeth Shelly
15:20	15:30	Questions	All
15:30	16:00	Break	None
16:00	16:10	The best patient for Botox injection "How, when and who to inject?"	<ul style="list-style-type: none"> • Campeau Lysanne
16:10	16:20	Case 5. The best patient for Neuromodulation	<ul style="list-style-type: none"> • Jacques Corcos
16:20	16:30	Questions	All
16:30	16:40	Case 6. The worse case scenario "DHIC in the elderly"	<ul style="list-style-type: none"> • Marcus Drake
16:40	16:45	Questions	All
16:45	17:00	case discussion	All

Aims of course/workshop

Complicated cases of OAB are seen daily in urology and urogynaecology practice. Managing these cases is often challenging despite the multiplicity of treatment options available. A better understanding of the disease, a better management of the patient seen at his first visit, a better knowledge of new and future drugs, a better use of non invasive techniques, a better use of botulinum toxin and neuromodulation are many ways of improving our management of these difficult cases.

This workshop will re-visit all these approaches and will be driven by clinical cases to better illustrate these different approaches. Participants will be also invited to bring their difficult cases to be discussed by other attendees and by the panel of experts.

Overactive bladder; terminology

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 pathology¹. A correction was made when it was realized that the term “urge incontinence” had been used in the original definition². Another correction alludes to the use of the word “frequency”, which is actually a sign- the correct term for the symptom being “increased daytime frequency”³. Thus, the current wording of the definition is most appropriately phrased as; “overactive bladder syndrome (OAB) is characterized by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology”³.

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 confusion⁴. 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 strength⁵ 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^{6,7} 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 urgency¹. 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 be 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”⁸. 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 provoked¹. 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. Drake MJ. Do we need a new definition of the overactive bladder syndrome? ICI-RS 2013. *Neurourology and Urodynamics* 2014;33:622-4.
4. Blaivas JG. Overactive bladder and the definition of urgency. *Neurourol Urodyn* 2007;26:757-8; discussion 9-60.
5. 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.
6. Gulur DM, Mevcha AM, Drake MJ. Nocturia as a manifestation of systemic disease. *BJU Int* 2011;107:702-13.
7. 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.
8. 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

Find “The” outcome

- Get “THE” most bothersome symptom
- What the patient cannot do because of his OAB
 - Go to see a movie, play cards or golf
 - 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 →



MICTURITION CHART	
Time	Volume voided (ml)
07:00	150 ml
08:00	200 ml
09:00	180 ml
10:00	120 ml
11:00	100 ml
12:00	150 ml
13:00	180 ml
14:00	120 ml
15:00	100 ml
16:00	150 ml
17:00	180 ml
18:00	120 ml
19:00	100 ml
20:00	150 ml
21:00	180 ml
22:00	120 ml
23:00	100 ml
00:00	150 ml
01:00	180 ml
02:00	120 ml
03:00	100 ml
04:00	150 ml
05:00	180 ml
06:00	120 ml
07:00	100 ml

3-Treat the cause

Treat associated conditions

- Bladder outflow obstruction
- Stress UI

Treat reversible conditions

- Urinary Tract Infection
- Congestive Heart Failure
- Sleep apnea
- 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

6- Consider the use of alternative medication

- 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.
Neurorol Urodyn. 2009;28(1):40-6

6- Consider the use of alternative medication

- B3 agonist (Myrabegron) alone or with anticholinergics

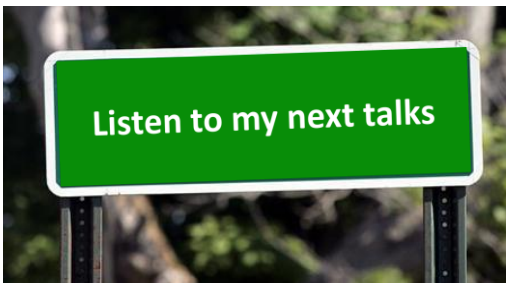
7- Intensify the follow up

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

If nothing works



If nothing works



Thank you

**Case 2. The patient who took “all
drugs”: What can we expect from new
and future drugs**

Francisco Cruz

Department of Urology
Hospital S. João & Faculty of Medicine of Porto

Porto, Portugal

Disclosures:

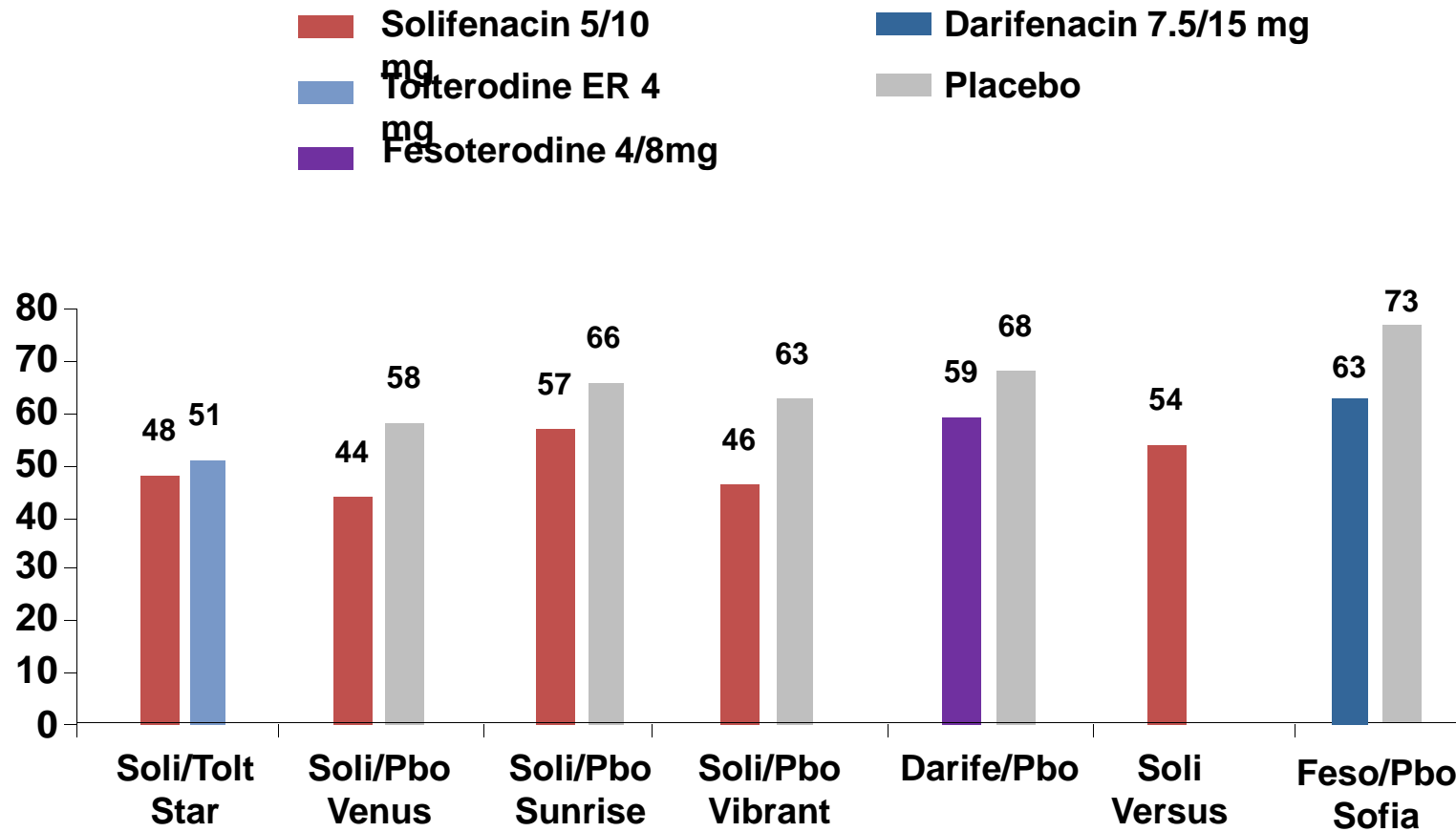
I received travel grants and honorarium as consultant, speaker or investigator from the following corporations:

Allergan, Astellas, Ipsen, Janssen-Cilag, Pfizer, Recordati,

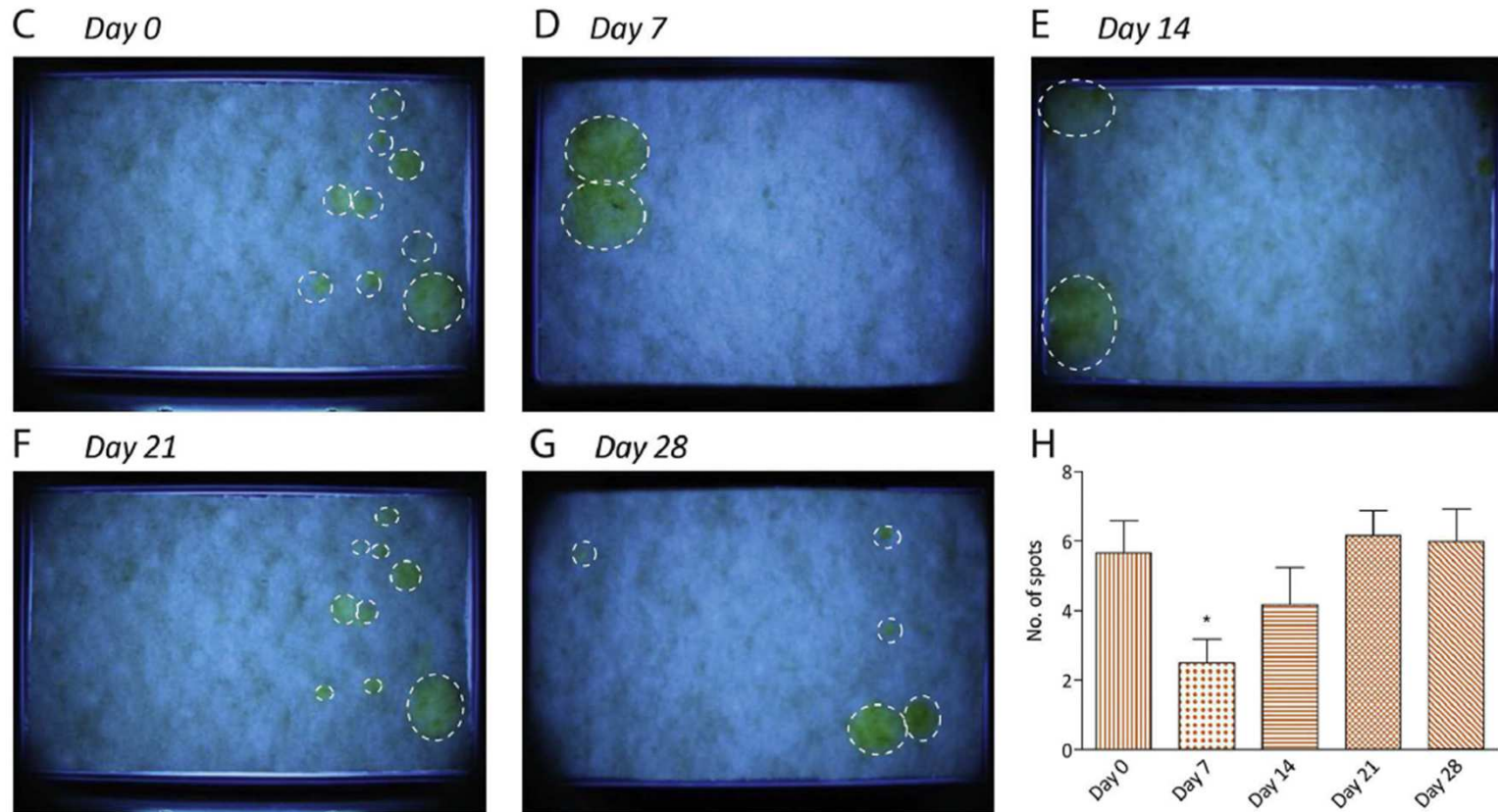
Reasons for failure

- Drug did not work (persistent urgency)
- Adverse effects
- Unrealistic expectations
- Failure to perceive benefit
- Compliance
- Other LUTS
- Wrong diagnosis

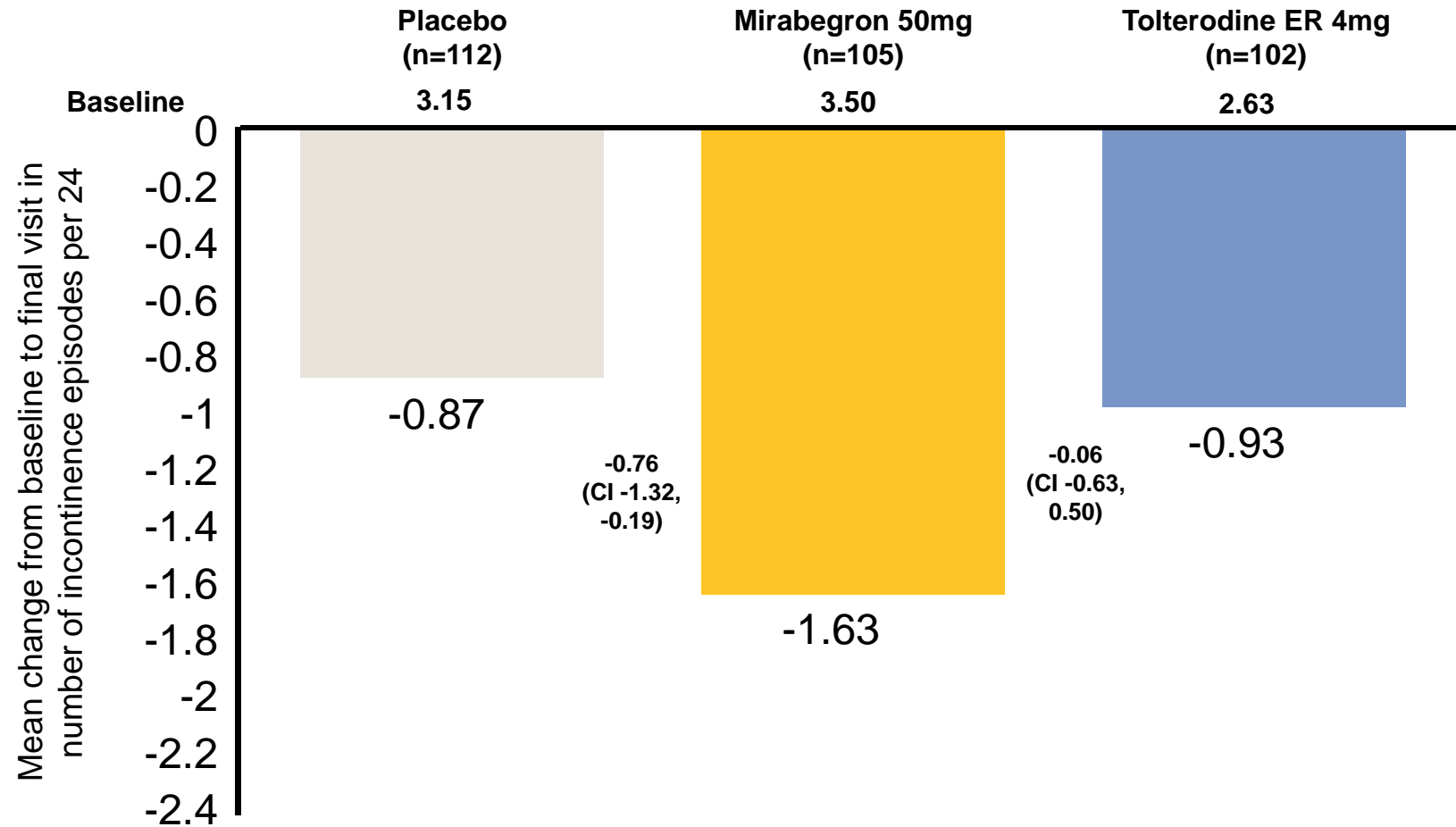
Initial dose is insufficient: Percentage of patients asking for dose escalation several trials



Antimuscarinics induce a shift from muscarinic to purinergic transmission in the rat bladder

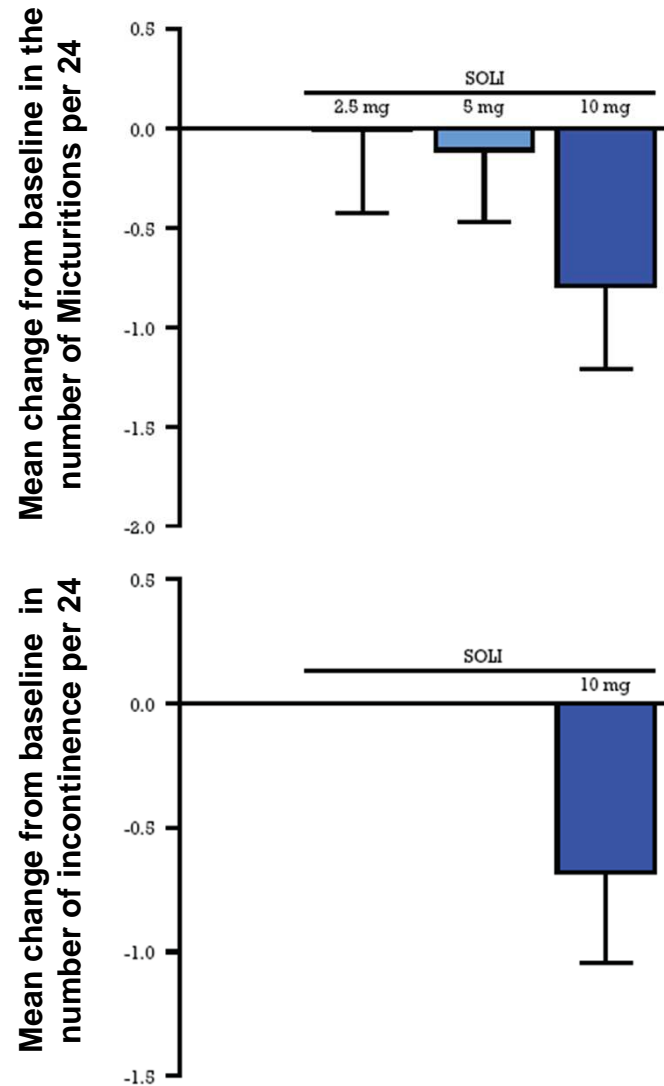


Post-hoc analysis (Study 046): Incontinence Prior AM medication with insufficient efficacy



Combination treatment with mirabegron and solifenacin Phase II study Symphony Study

SOLI = solifenacin.
MIRA = mirabegron

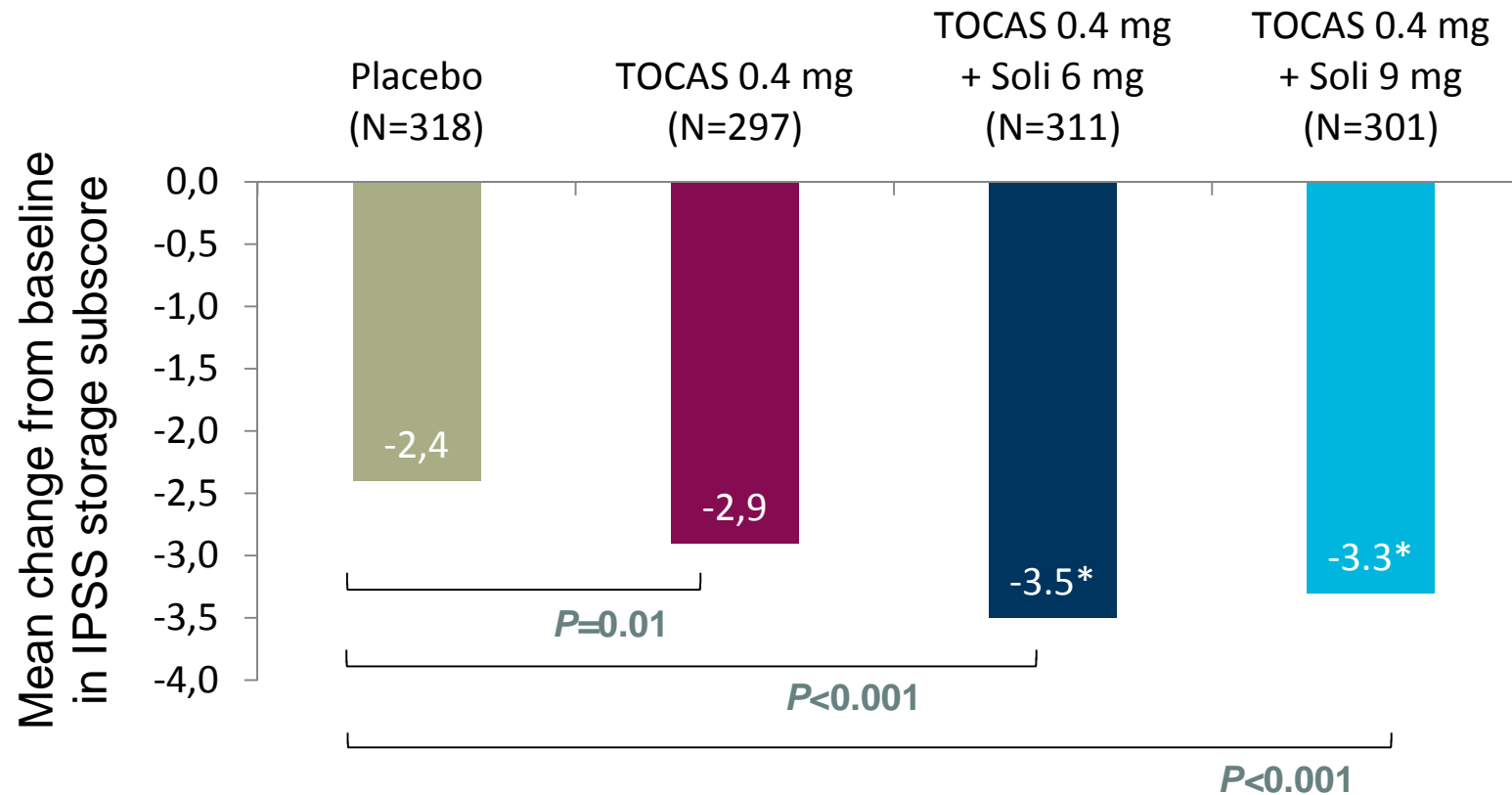


*

Adapted from Abrams, P et al. Poster presented at the Annual Congress of the AUA, 4–8 May 2013, San Diego,

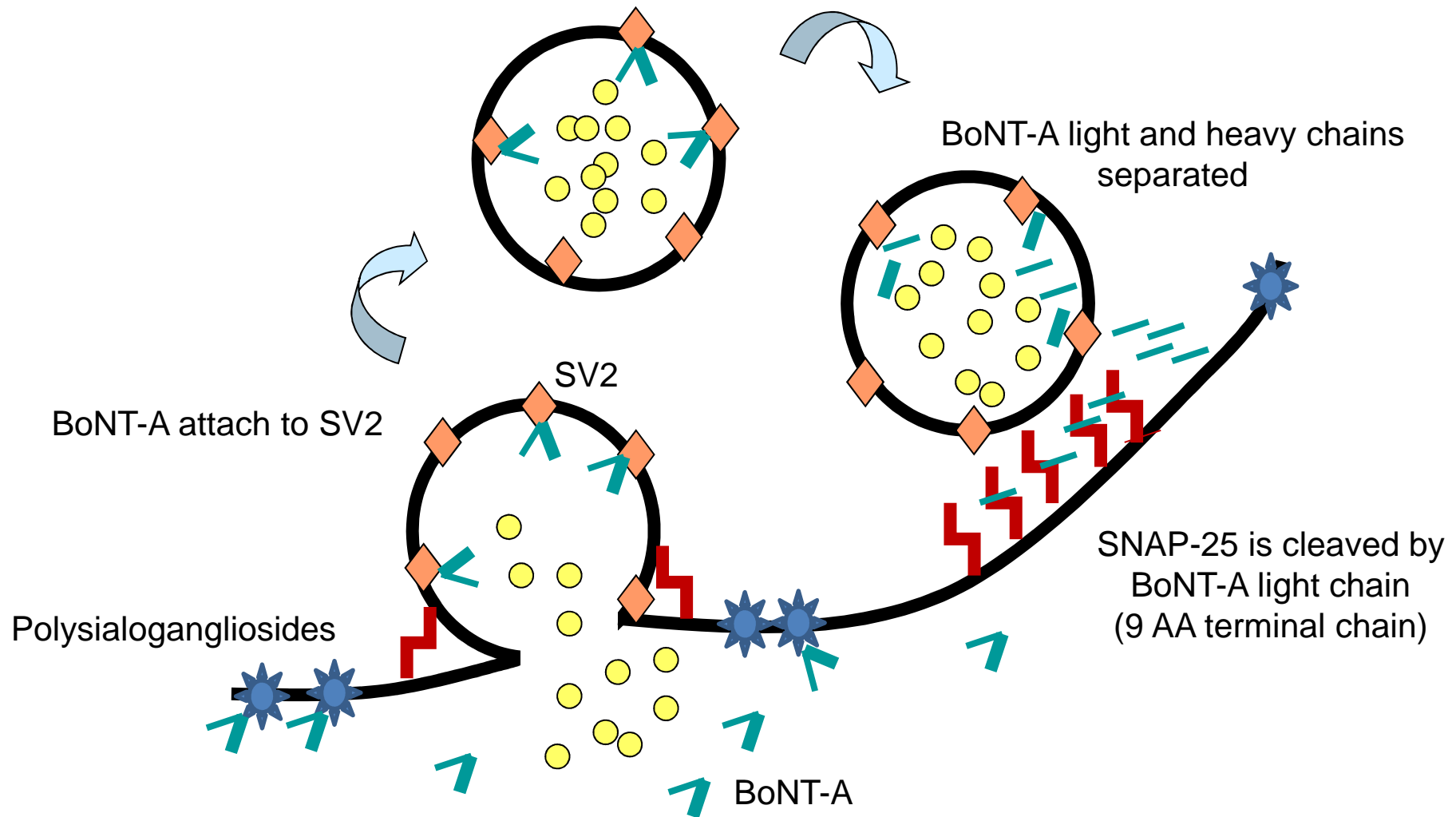
Antimuscarinics and α_1 -AR antagonists in male storage LUTS

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

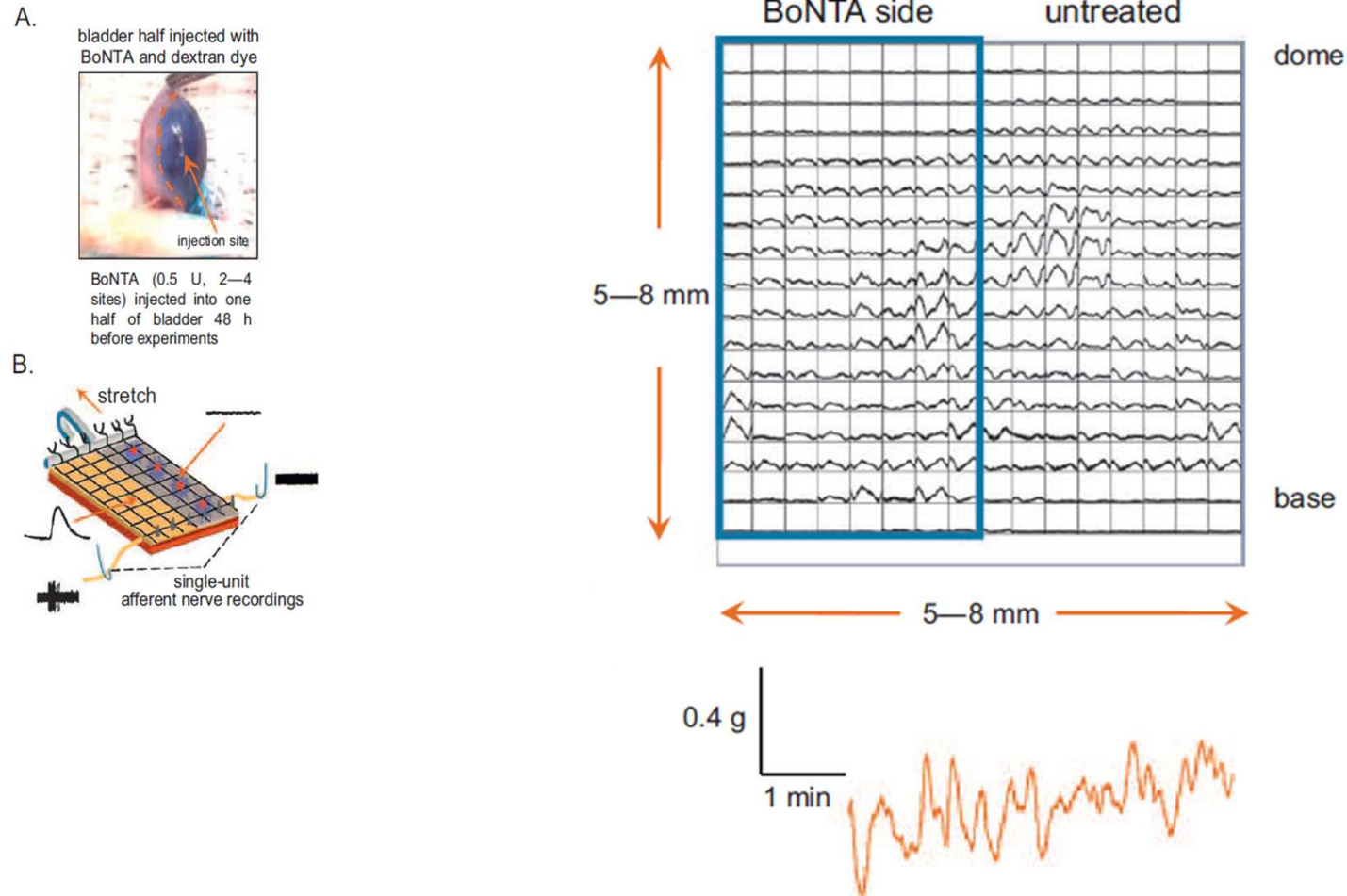


* Combination therapy (both doses) vs. Tamsulosin OCAS monotherapy: $P<0.05$

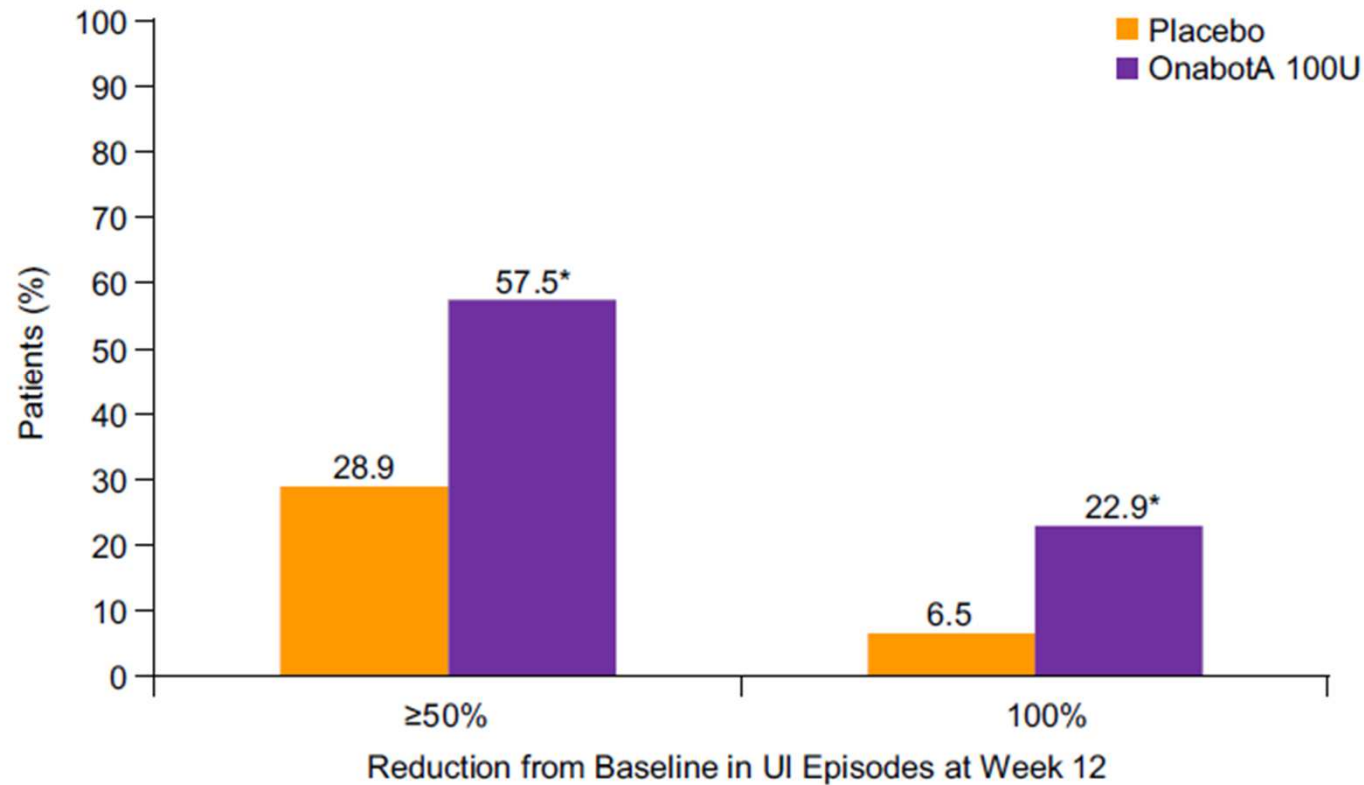
Mechanism of action of BoNT-A



Intrinsic contractile detrusor activity is not inhibited by BoNTA treatment in SCT or control mouse bladders



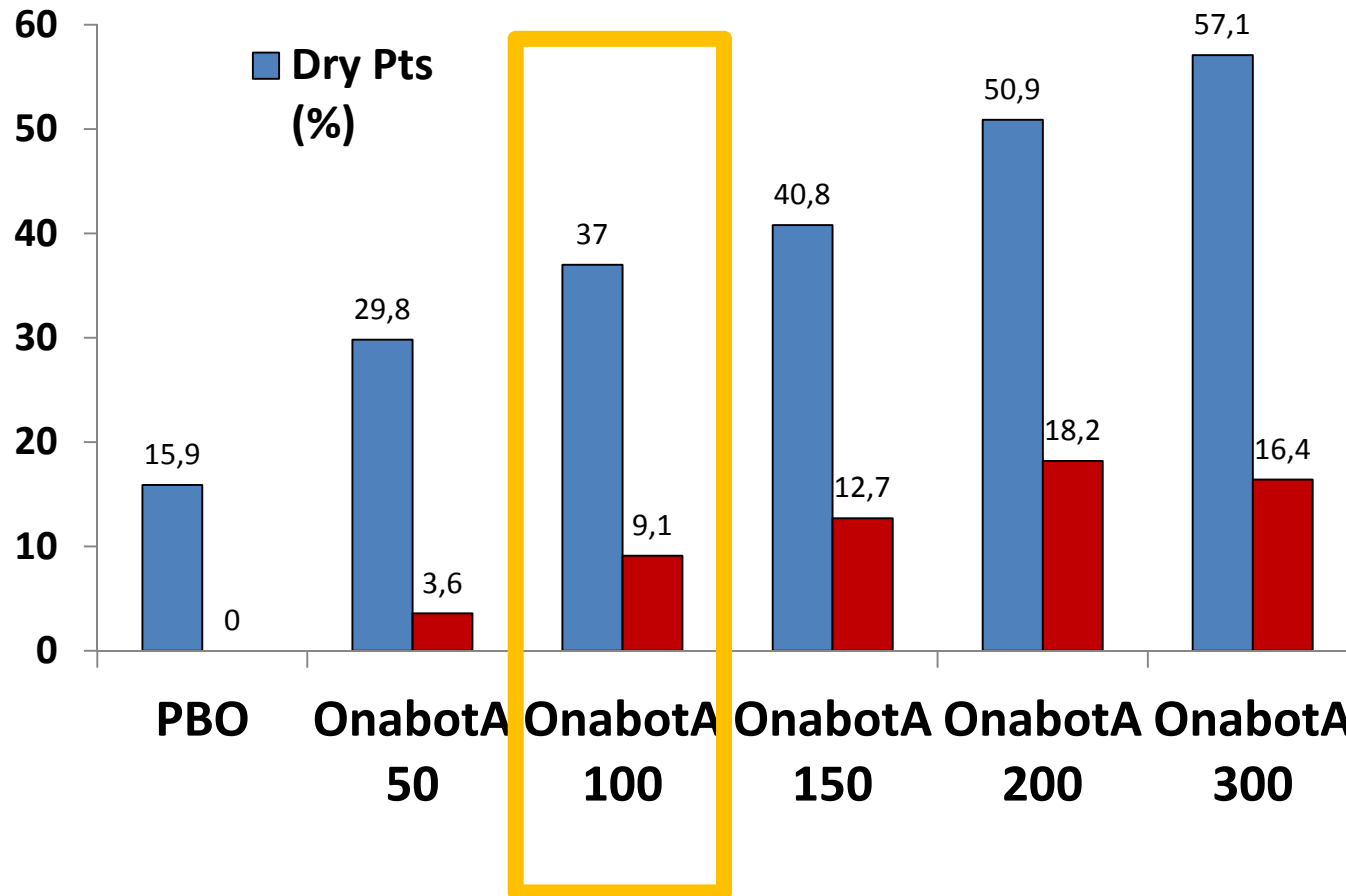
Reductions in urinary incontinence of Onabotulinum Toxin A 100 U versus placebo



Dry: no incontinence episodes in the 3 day Bladder diary preceding the 12-week time point.

Adapted from:
Nitti et al, J Urol, 2013

Dose-finding study of OnabotA in OAB



Data obtained at week 12

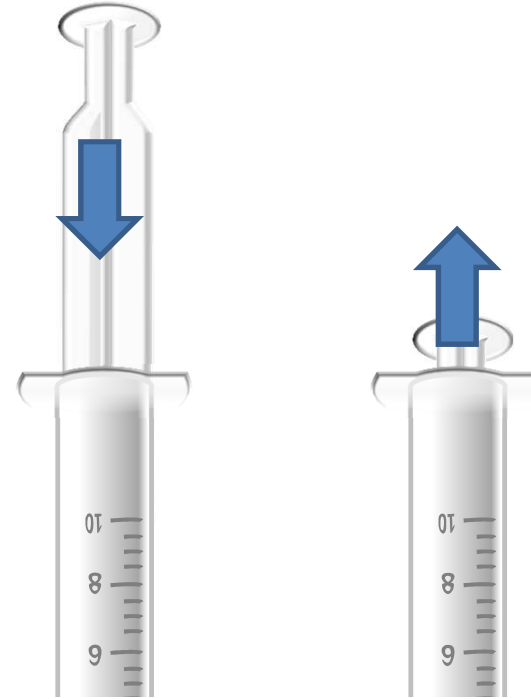
Dmochowski et al. J Urol, 2010

100 U reconstitution using one BOTOX[®] 100 U vial

1. Add 10 mL of 0.9% saline solution* to the 100 U vial.

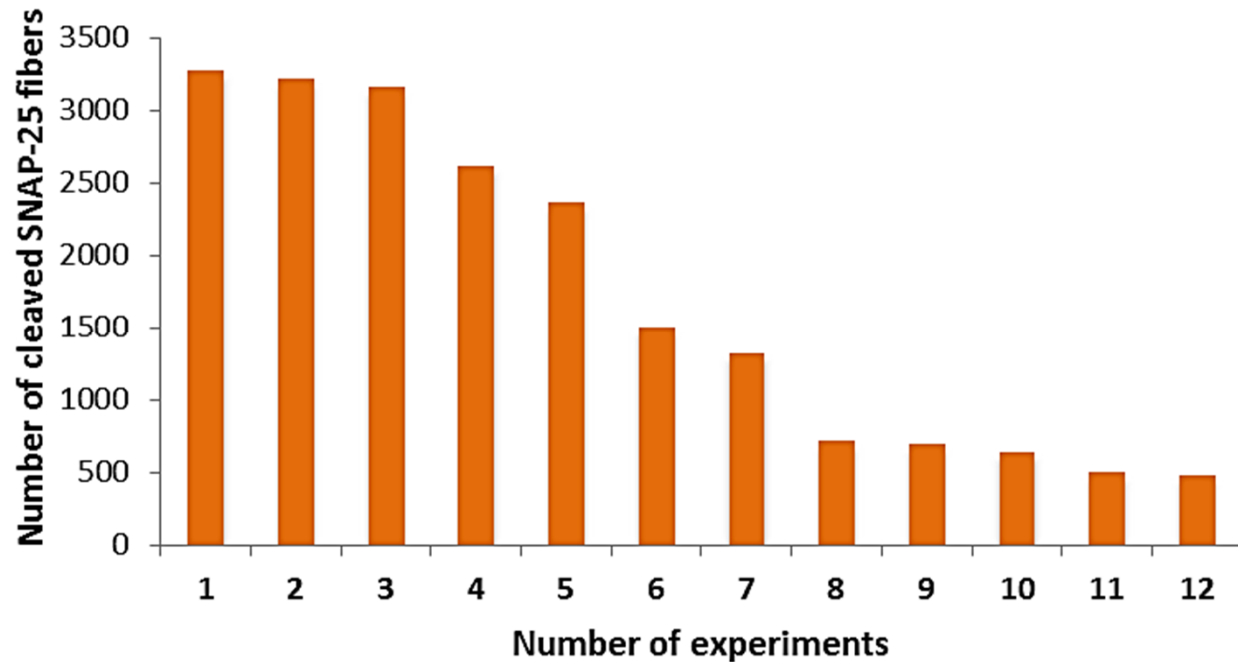
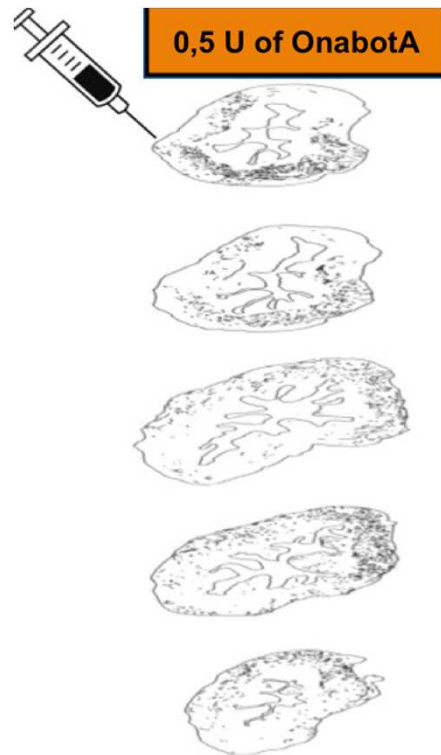
2. Mix gently

3. Draw 10 mL from the 100 U vial into the 10 mL syringe



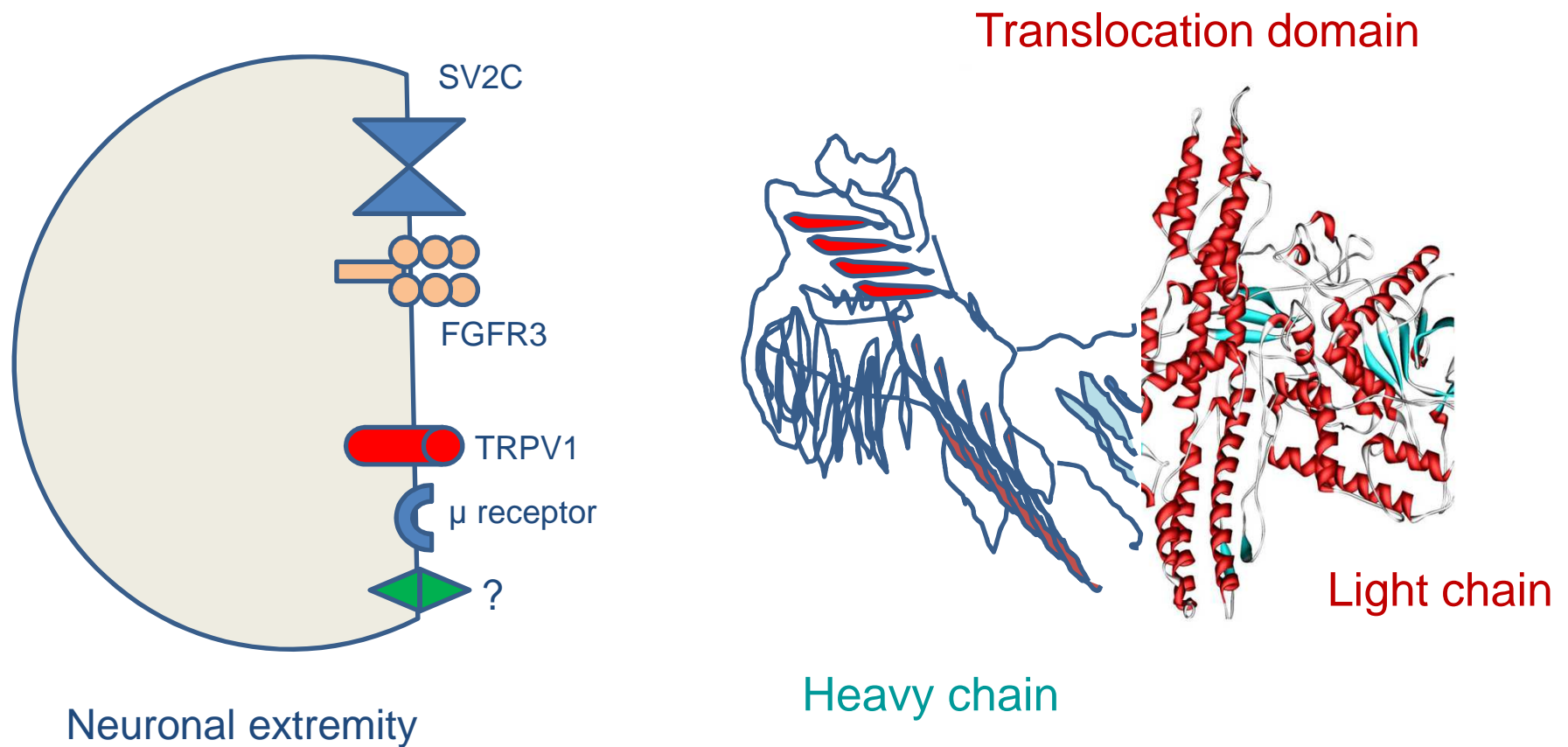
- Unreconstituted vials must be stored in the refrigerator at between 2°C and 8°C or in the freezer at $\leq -5^{\circ}\text{C}$
- After reconstitution, the vials may be stored in the refrigerator (2–8°C for up to 24 hours).
- BOTOX[®] should not be frozen after reconstitution
- BOTOX[®] should not be stored in the syringe

Bladder nerve fibers positive for cleaved SNAP-25 in 12 mice injected in the same way by 1 single investigator



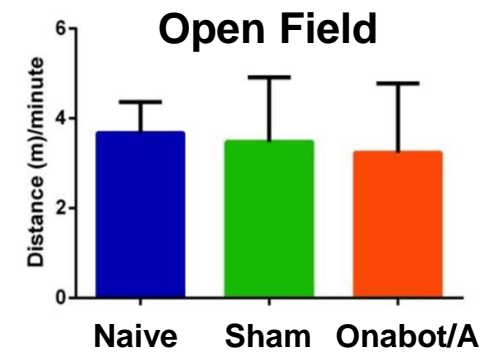
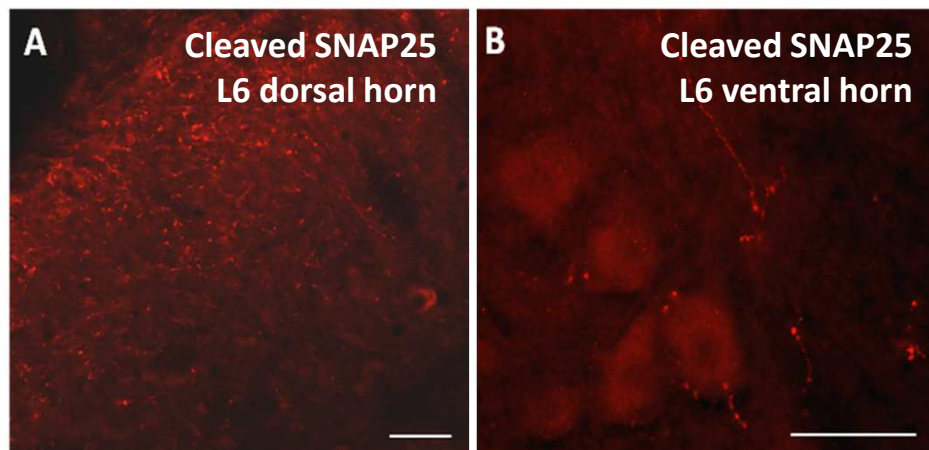
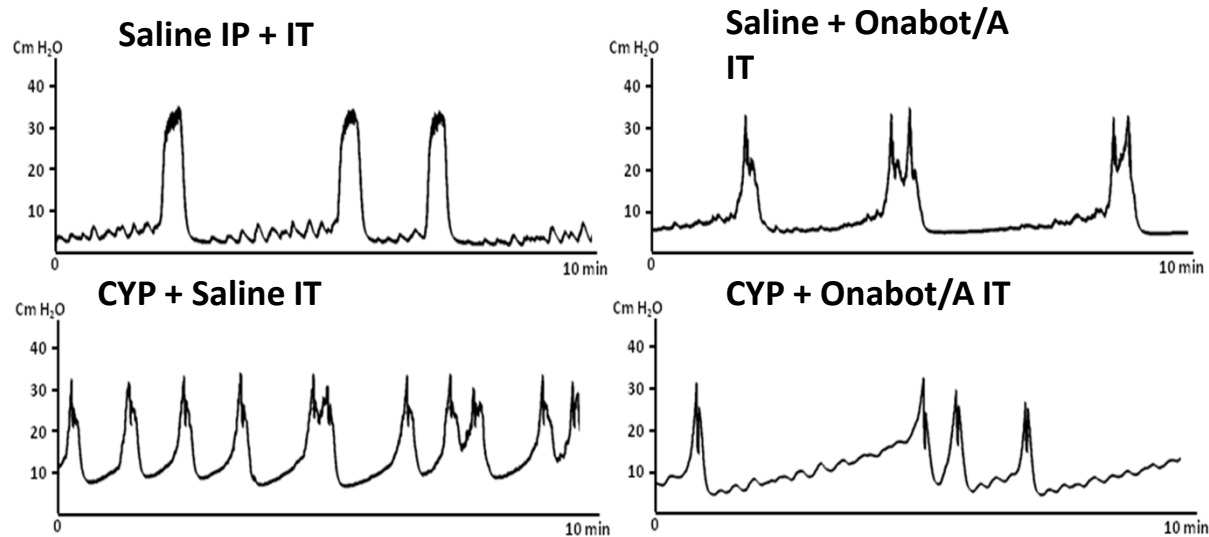
Same dose of OnabotA (0.5 U) and same volume of saline (10 μ L)

Crystal structure of botulinum neurotoxin type A and future recombinant toxins



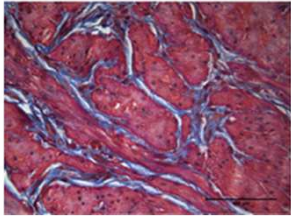
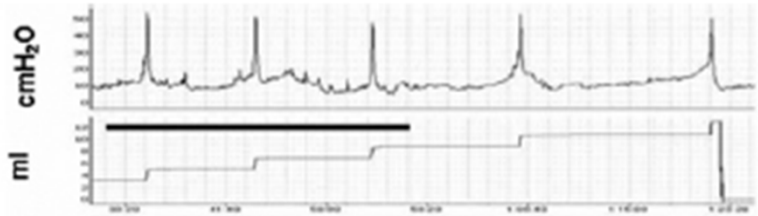
Adapted from: Lacy, D.B., Tepp, W., Cohen, A.C., DasGupta, B.R., Stevens, R.C. (1998) Crystal structure of botulinum neurotoxin type A and implications for toxicity. *Nat.Struct.Biol.* 5: 898-902

Intrathecal Onabot/A reduces urinary frequency induced by bladder inflammation without motor (hind limb) impairment

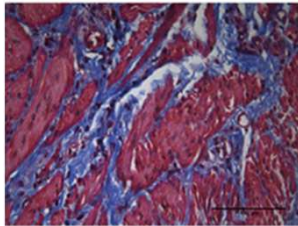
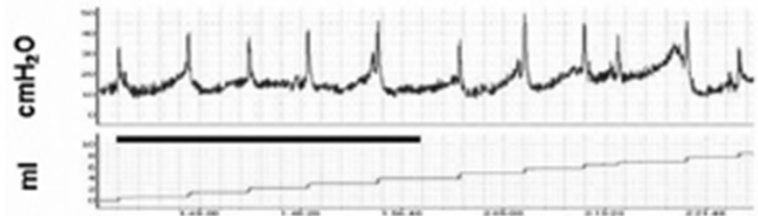


Bladder ischemia and bladder dysfunction

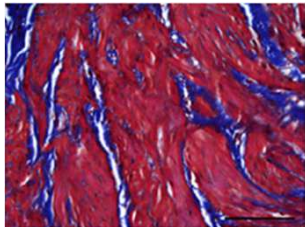
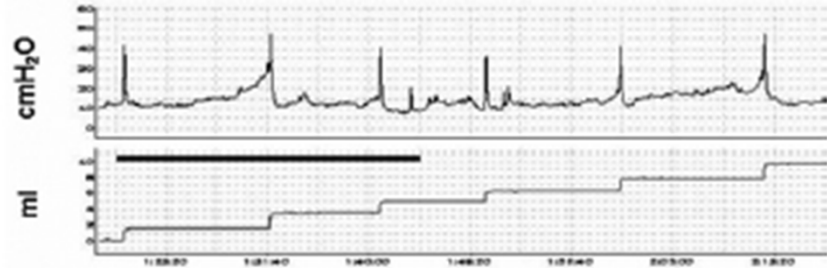
Control



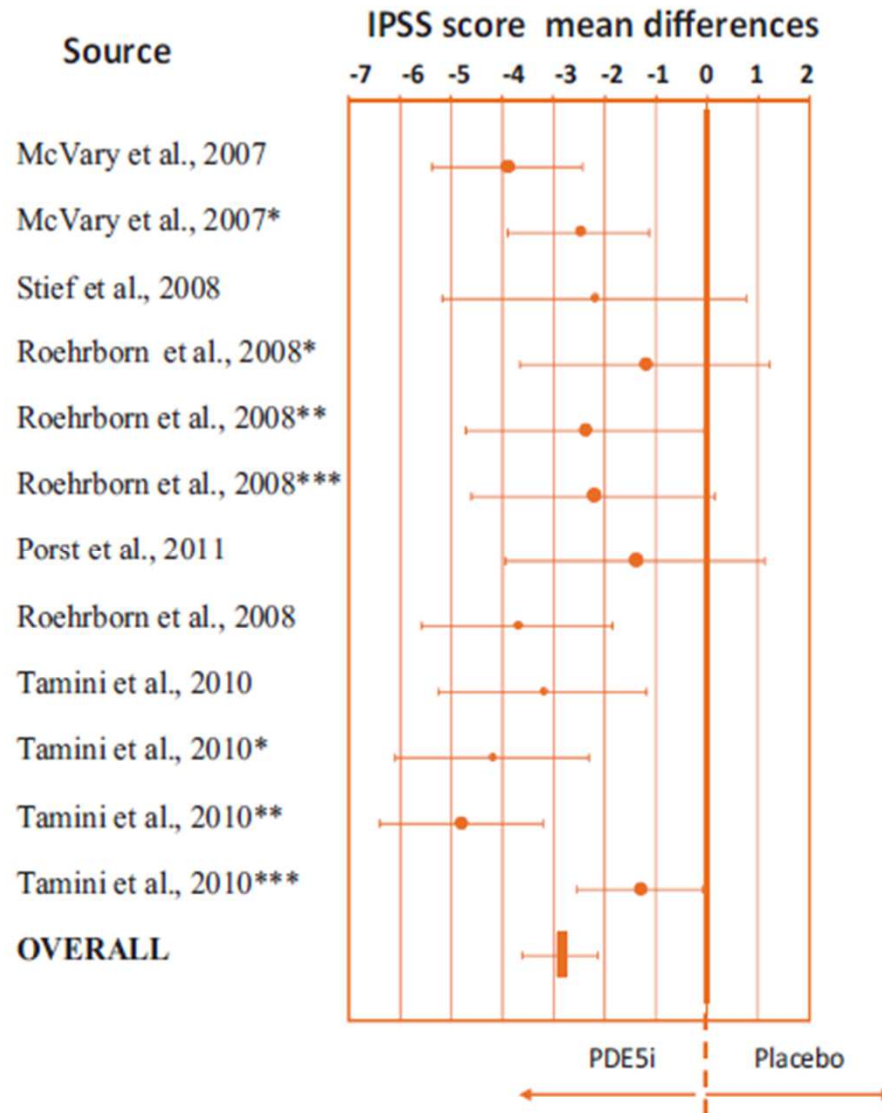
AI



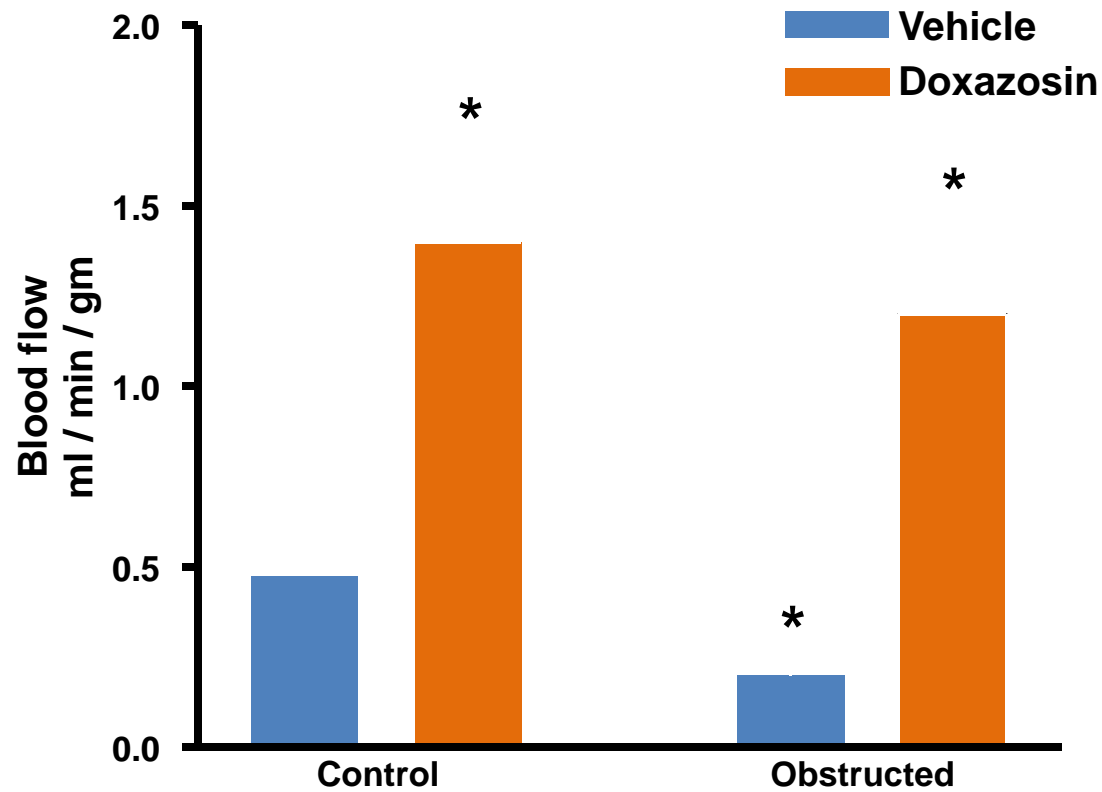
AI-tadalafil



Systematic review of PDE5 inhibitors in male LUTS

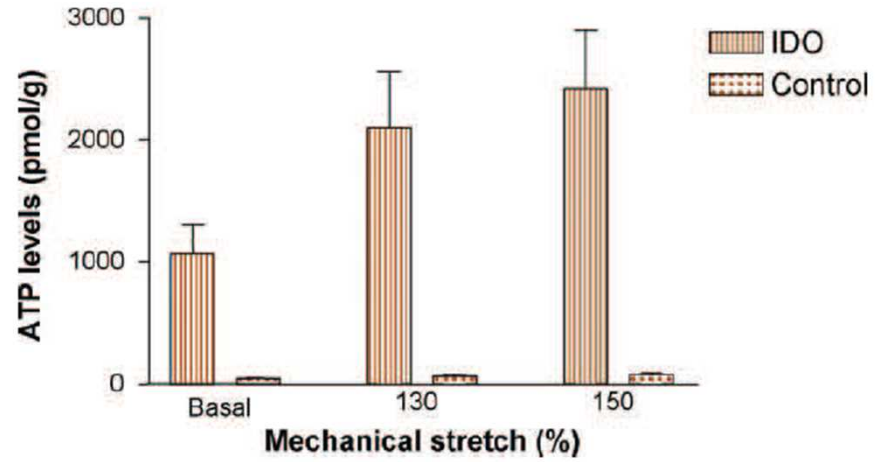
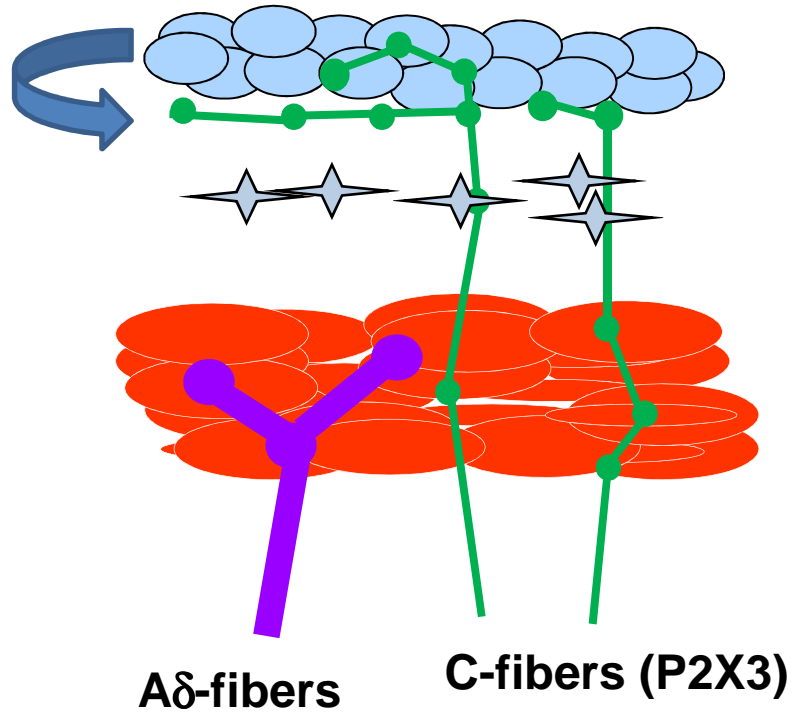


α_1 blockers increase blood flow in rat bladders obstructed by urethral ligation



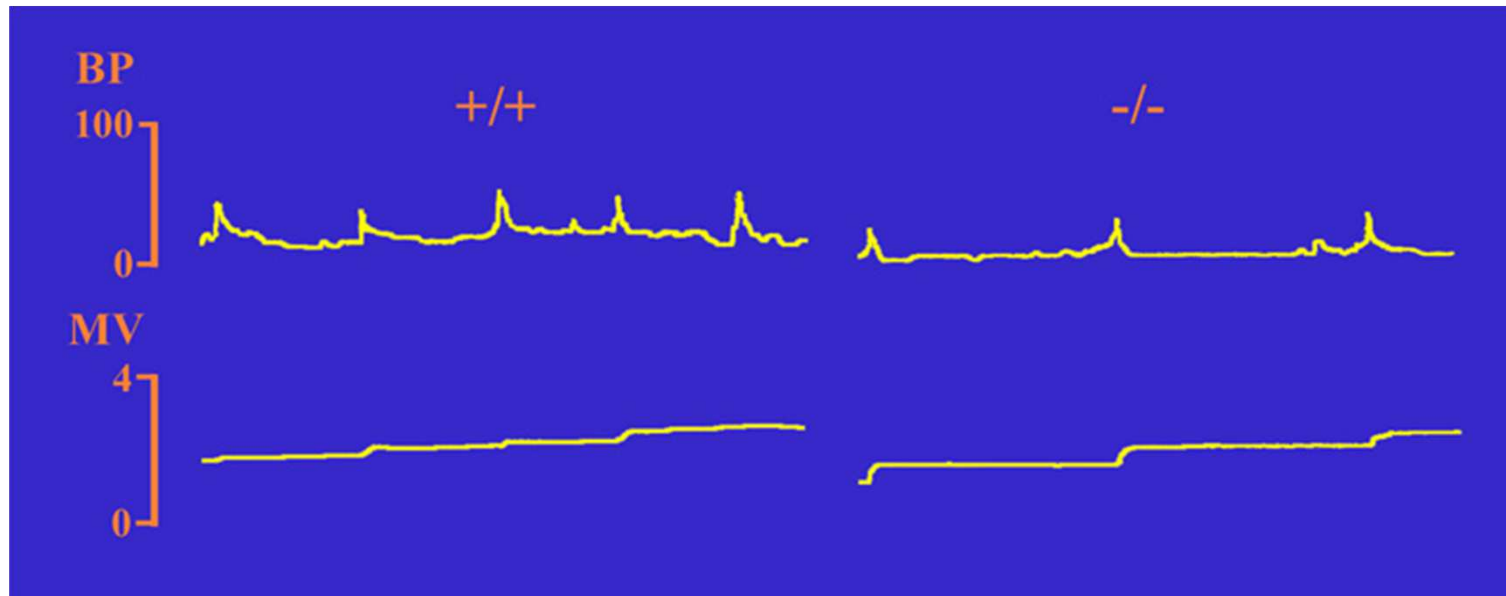
Effect of doxazosin on bladder blood flow of control and obstructed rats

ATP release from urothelium of IDO bladders

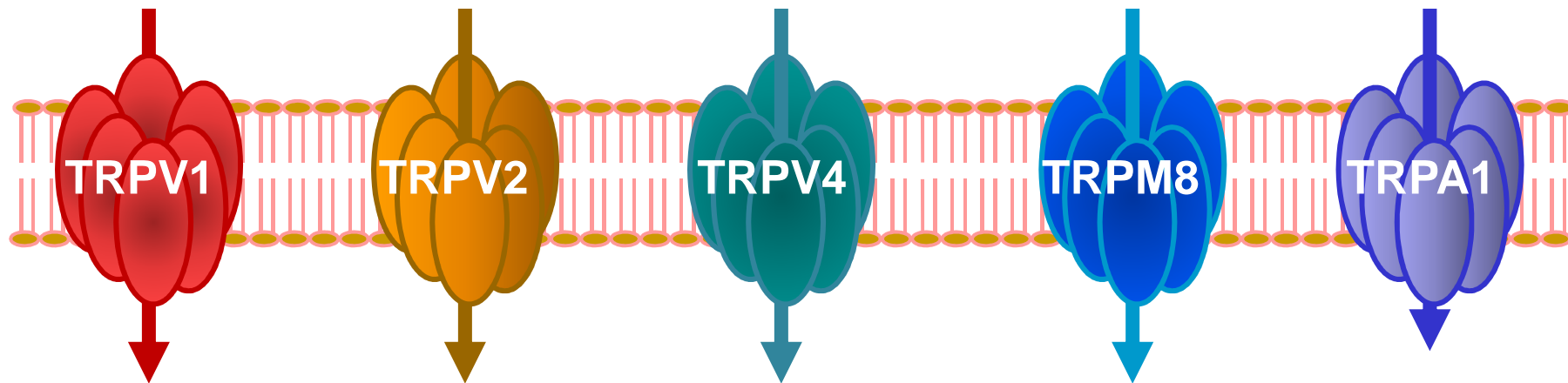


Kumar et al, Eur Urol, 2010

Bladder Function in P2X₃-deficient Mice



The TRP family and the LUT



Noxious heat >43 °C
 Protons
 Vanilloids
 (Cap, RTX, olvanil)
 Endocannabinoids
 (AEA)
 Polyamines

Noxious heat >50 °C
 THC
 2-APB
 Stretch
 Urothelial
 tumorigenesis

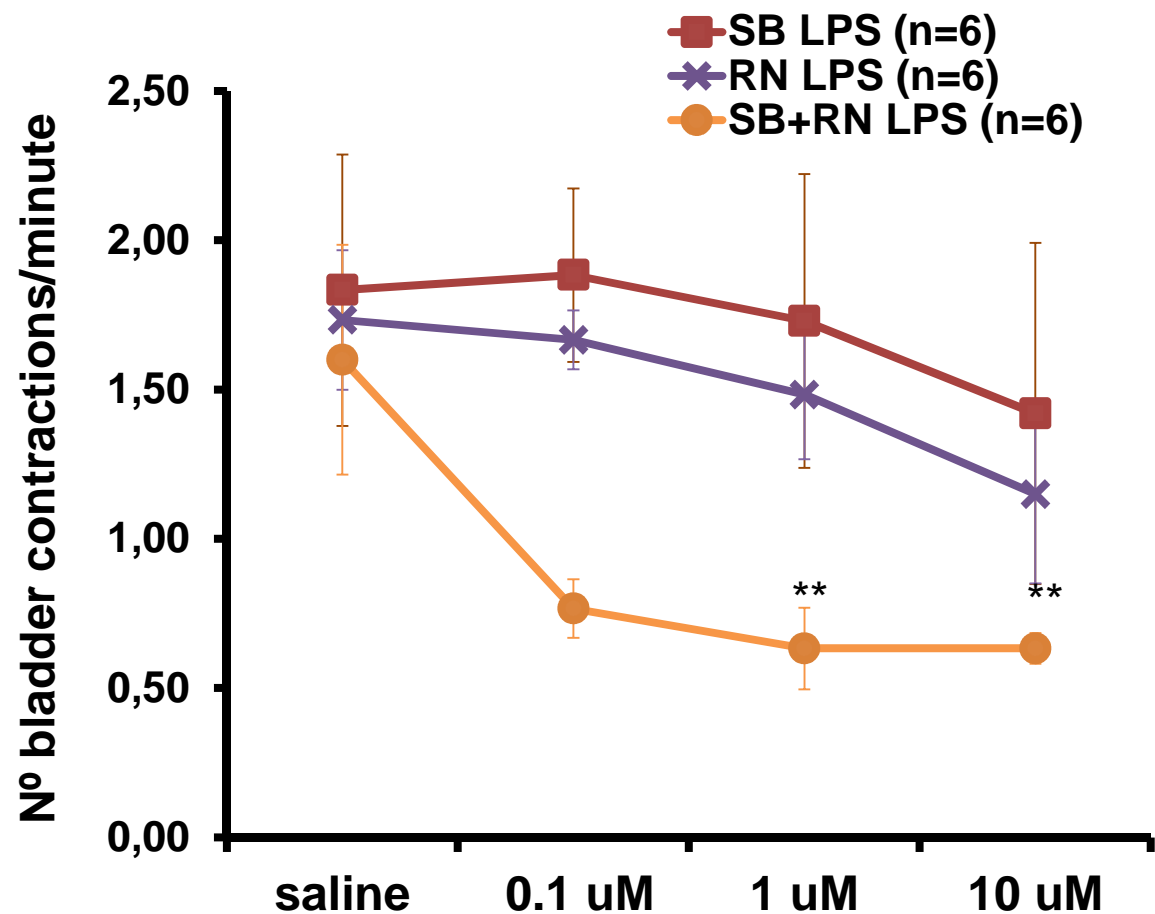
Innocuous heat >24
 °C
 EETs
 2-APB
 Stretch
 4αPDD
 GSK1016790A
 BAA

Innocuous cold
 (<25°C)
 Menthol
 Icilin
 Cooling compounds
 PIP2
 LPLs
 PUFAs (inhibition)

Noxious cold
 (<17°C)
 Icilin
 Acrolein
 AITC
 THC
 Carvacrol, Thymol,
 Gingerol, Eugenol
 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)

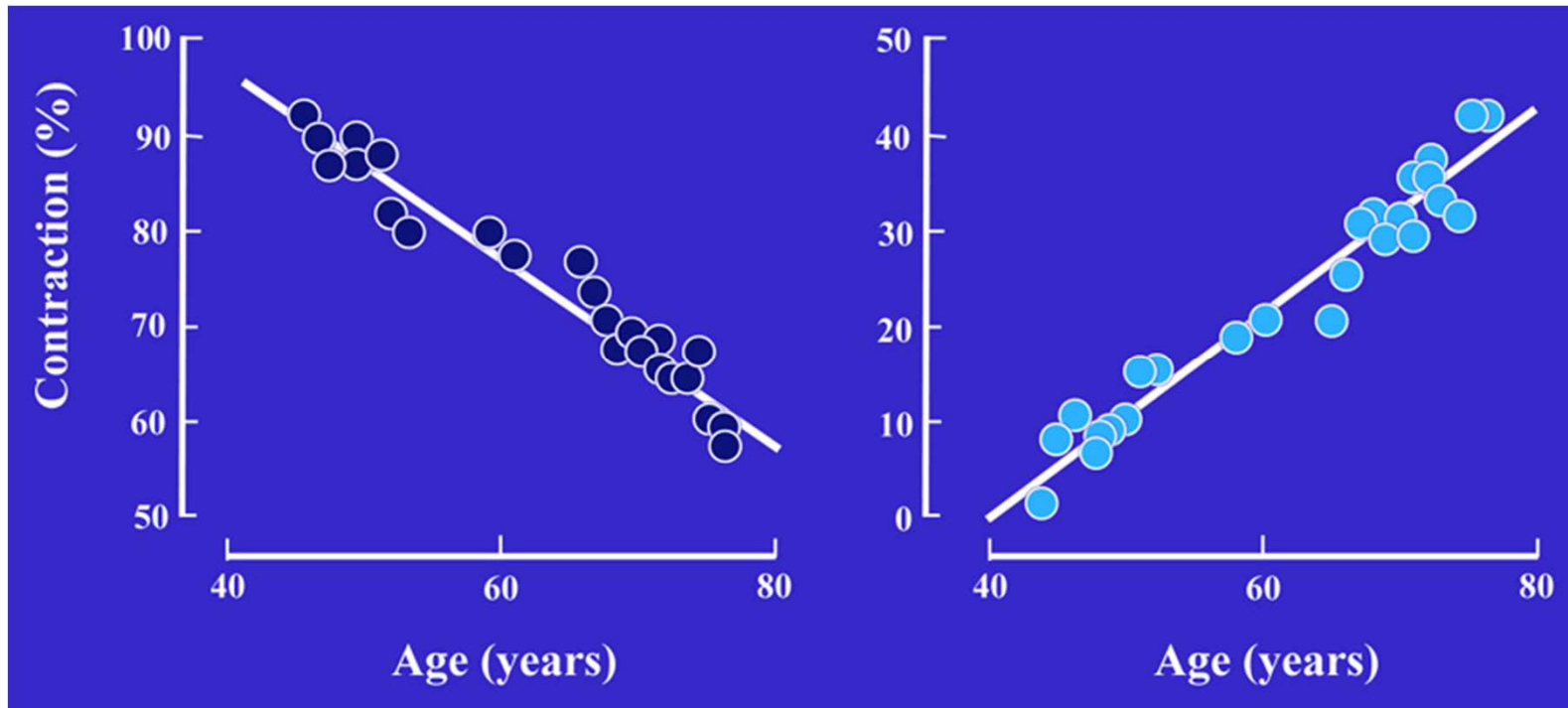
TRPV1-TRPV4 antagonist combination



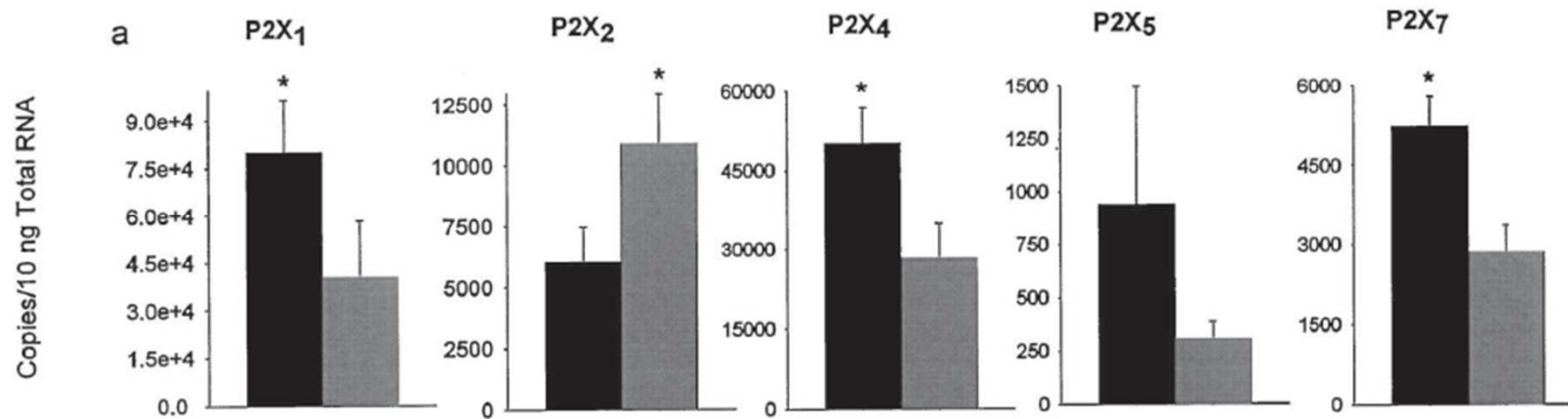
RN1734 = TRPV4 antagonist
SB366791 = TRPV1 antagonist

Activation of the ageing human bladder

- Cholinergic transmission vs age
- Purinergic transmission vs age



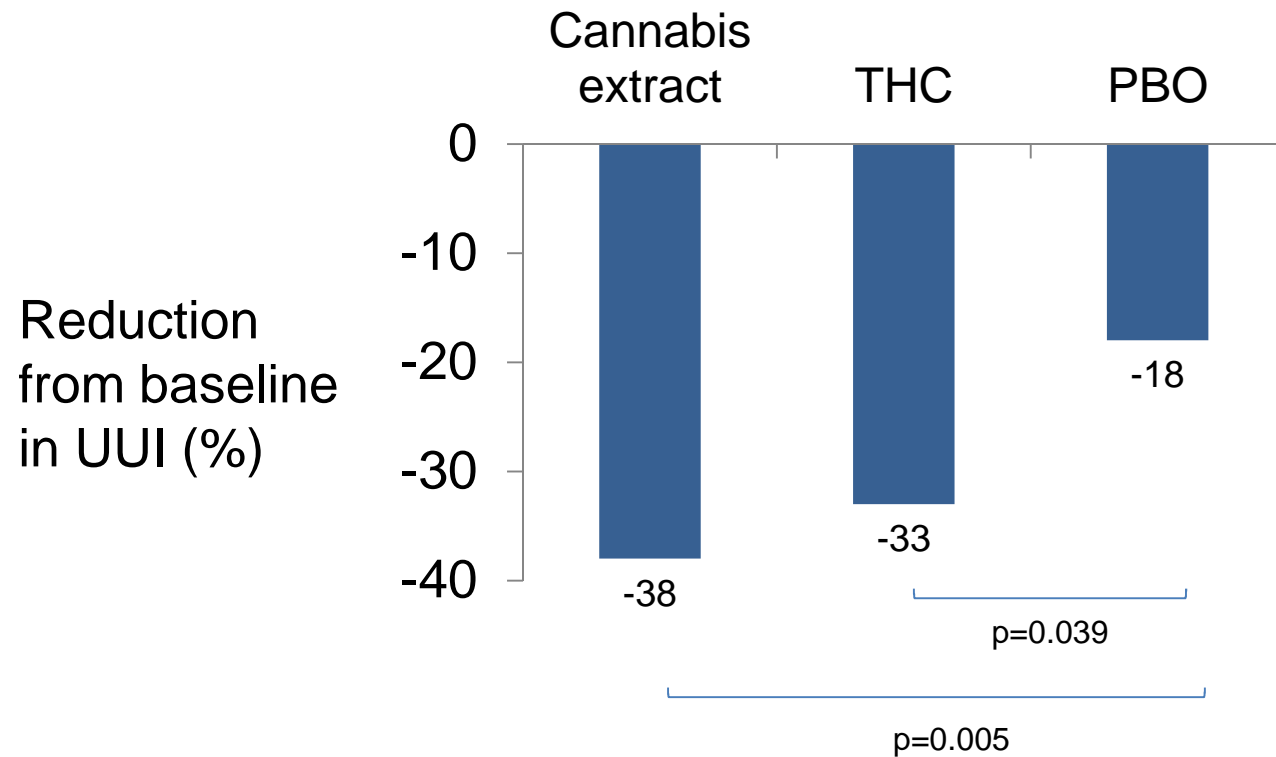
Altered expression of P2X receptors in female IDO



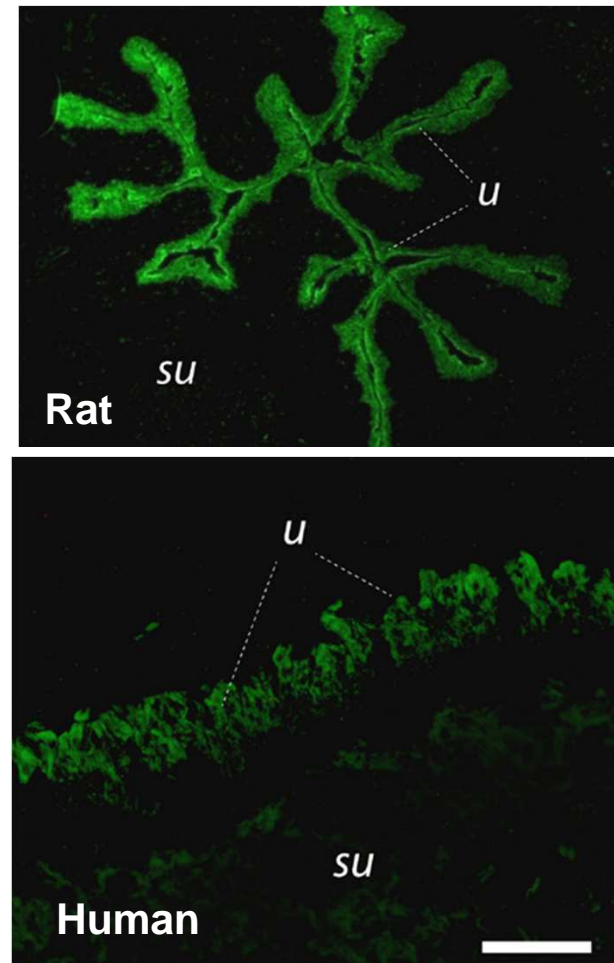
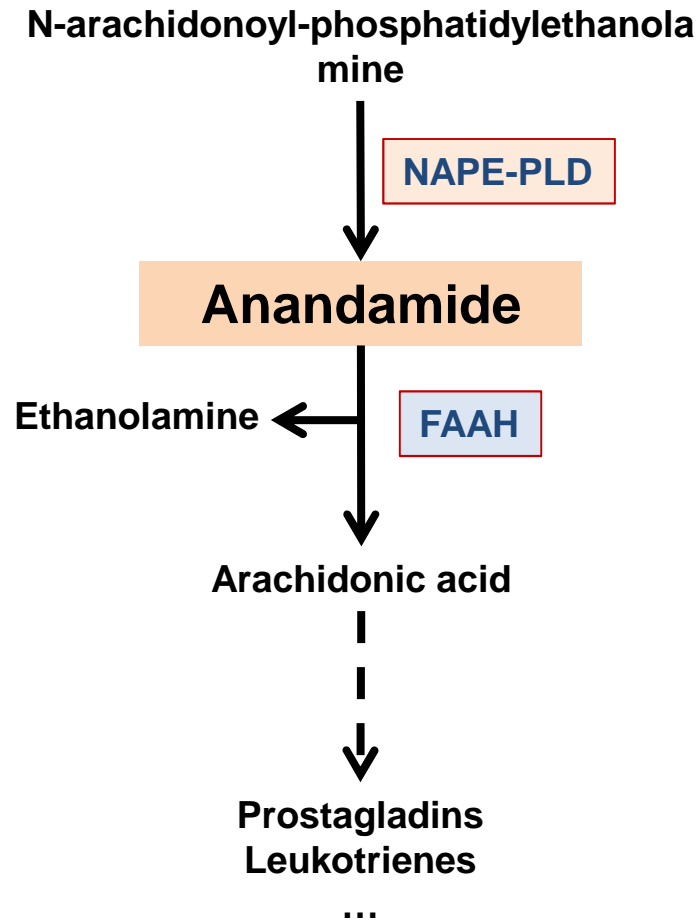
In IDO patients \pm 50% of detrusor contractions are mediated by a purinergic mechanism

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

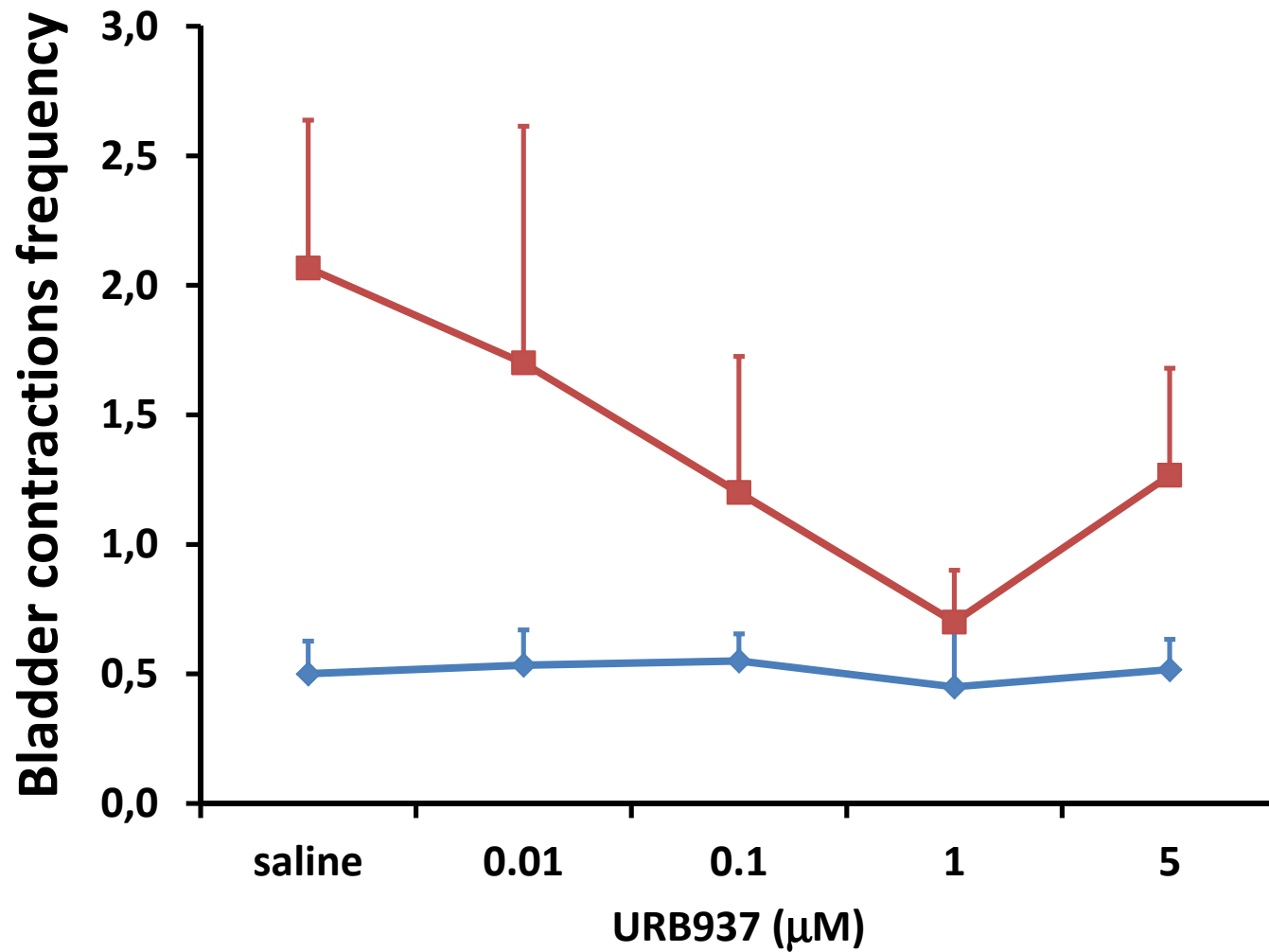
630 MS patients with UUI randomized to cannabis extract, Delta(9)-tetrahydrocannabinol (THC) or placebo



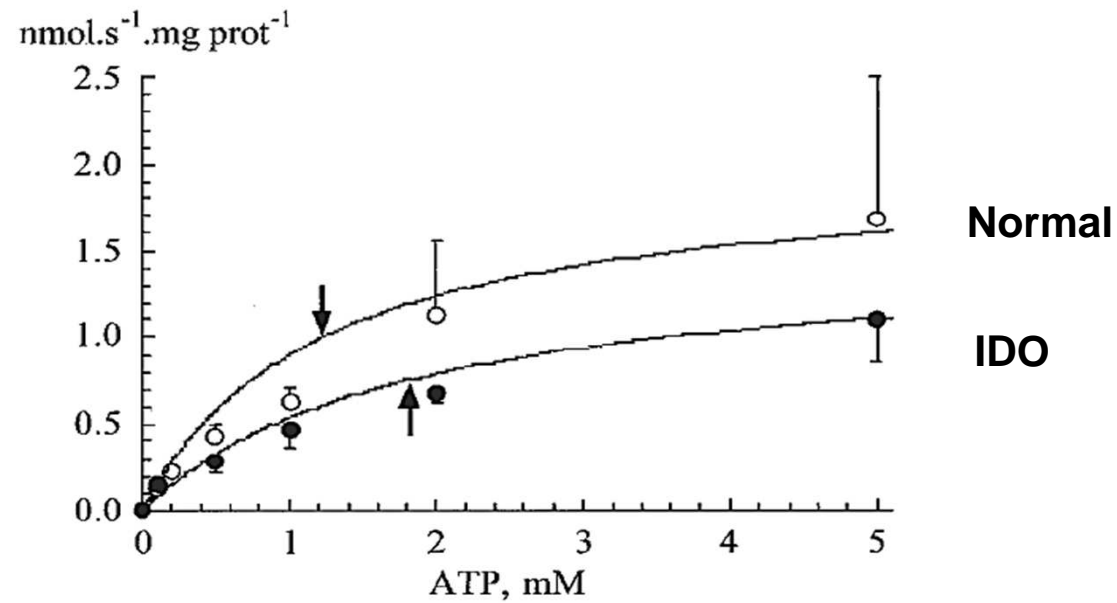
Anandamide pathway, an endo-cannabinoid receptor agonist



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



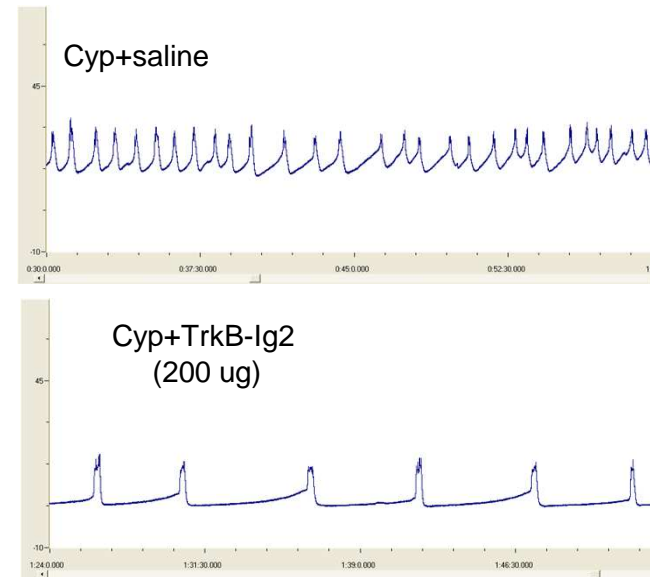
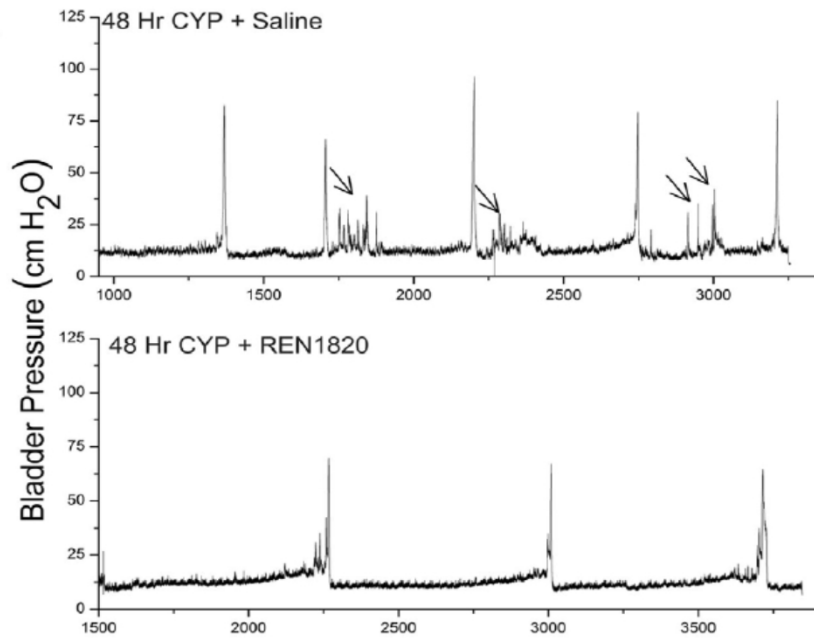
EctoATPase activity in normal and in IDO detrusor



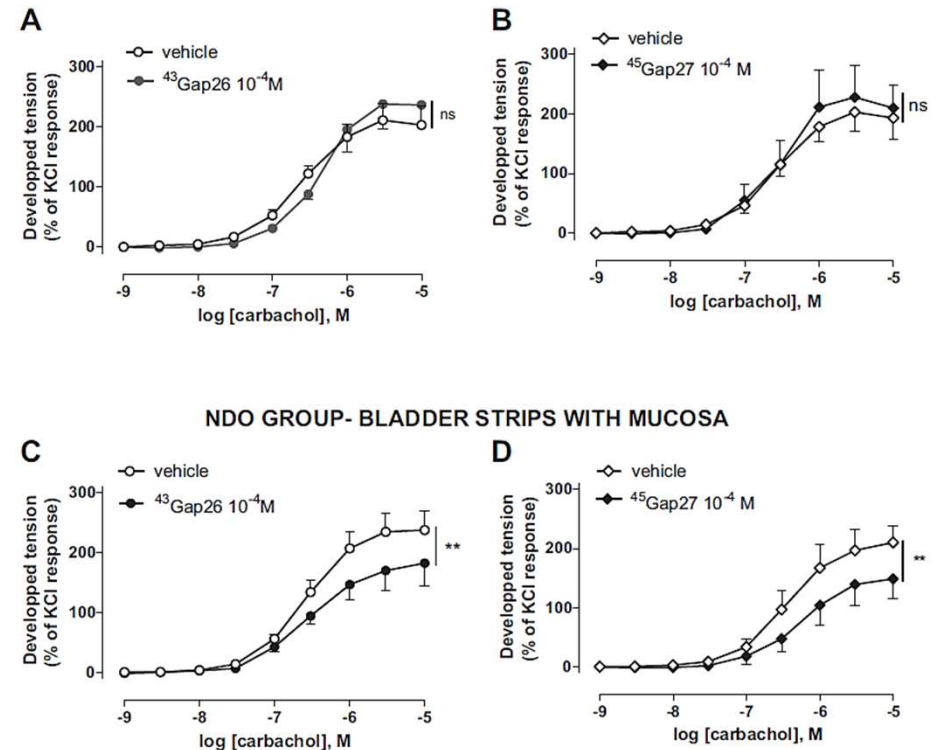
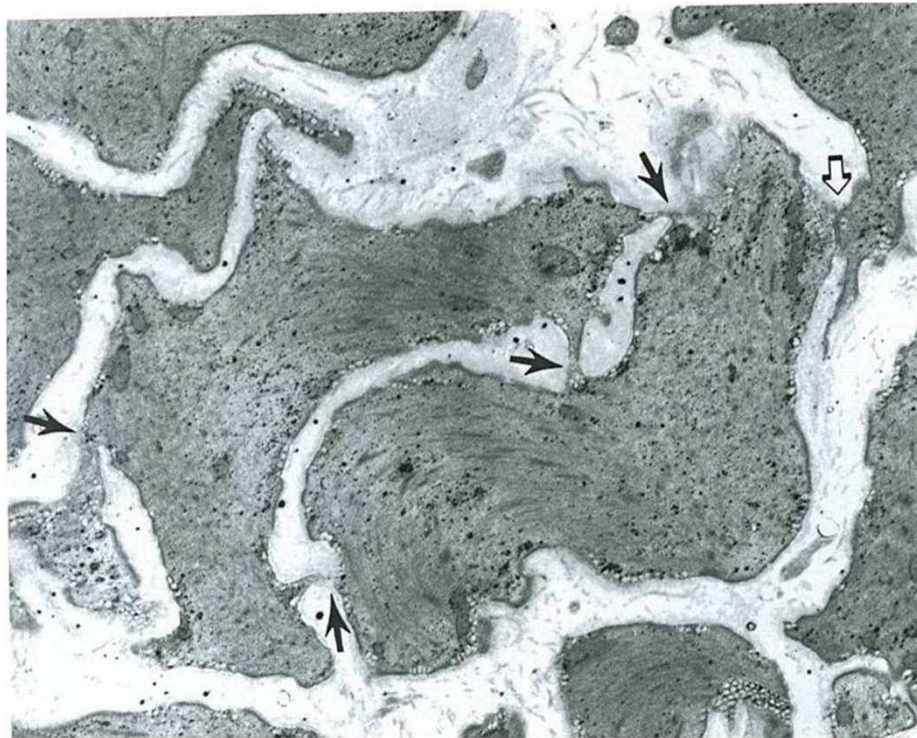
Neurotrophin sequestration in a rat model of cystitis

NGF (TrKA Ig2)

BDNF (TrKB Ig2)



Gap-junctions and inhibitors of Connexins 43 and 45 in Functional Mechanism of Human Detrusor Overactivity



Experiments with Cx inhibitors carried in NDO bladders
 Cx mimetic peptides 43Gap26 and 45Gap27 (Proteogenix,
 Oberhausbergen, France)

Elbadawi, Textbook of Female Urology
 Phe V. et al, Urology 2013

What pharmacotherapy remains to the patients who took all drugs:

Check compliance and diagnosis

Check if the drug is appropriate to the aetiology of the case

Consider drug combination

BoNT/A should work (if properly administered) in 75% of the patients

TRP antagonists, PDE5 inhibitors, cannabinoid receptor agonists, purinergic receptor antagonists, connexin inhibitors, manipulation of endogenous agonists (ATP, endocannabinoids) may be used in a near future

The patient doesn't want anything "invasive": What can we offer?

Case driven workshop on intractable overactive bladder Workshop 11

Dr Beth Shelly PT, DPT, WCS, BCB PMD

International Continence Society Annual Meeting

October 20, 2014 Rio de Janeiro, Brazil

Mrs R is a 67 year old female with a 3 year history of gradually increasing mixed UI. She has undergone urethral dilation twice and is now taking Flomax to increase flow. Urodynamics shows small bladder capacity (Vmax 200 ml), incomplete urethral relaxation. Fluoroscope shows mildly trabeculated bladder wall. Negative PVR. Medications have been reviewed by the physician and found to be uninvolved in her UI.

PMH - RA, osteoporosis, GERD, COPD, IBS, fibromyalgia with chronic wide spread pain, restless leg syndrome, constipation. Childhood sexual abuse. Patient also reports she had "urinary trouble" as a child.

Social history - Patient is retired but active, drives, and does her own housework. She participates in water exercise once per week.

Symptoms - patient reports UI several times per day of a small amount. Usually with urgency but occasionally with sneezing, bending, and lifting. Nocturia once per night. Patient notes UI upon standing from the toilet (post void UI) and has hesitancy and intermittency. She reports lower abdominal pain and a feeling of falling out at the perineum.

Tests and measures

ICIQ - 7/21

PFDI - 216.6/300

PFIQ - 123.6/300

Measured bladder diary - F24 - 11, Vmax 250 ml, Vage - 100 ml, nocturia - 1 to 2, average voiding interval 1 to 3 hrs with urgency 4 to 5 times per day, fluid intake 1200 to 2800 ml mostly water.

Manual examination - external no evidence of PFM elevation, left adductor very tender to palpation, Strength of PFM 2/5, with 3 second hold and poor relaxation. Moderate tenderness with palpation of PFM on the left and mild anterior wall laxity.

Problem list

- Urinary dysfunction - MUI and obstructive symptoms possibly related to poor PFM function with weakness and poor relaxation
- Chronic pain syndrome with pain on palpation in the pelvis
- Constipation and poor bladder habits.

Patient was started on bowel emptying routine, 1 1/2 hr voiding interval, 1500 ml water per day, and 3 second PFM exercises with equal focus on contraction and relaxation. Bladder training and PFM exercises were advanced with education and EMG training. Massage of the vaginal PFM, left adductor and left piriformis with home stretches was added.

One month re-evaluation - voiding with only 2 stops and feels empty after void. No post void dribbling, and 3 hr day voiding schedule. Urgency 2 times per week and no UI. Vaginal PFM strength 3/5 with 10 second hold and fairly good relaxation on EMG. Minimal tenderness on palpation of PFM.

Two month follow up - some mild POP symptoms, no UI, occasional urgency, encouragement given to continue self management.

ICIQ - 0 = 100% better

PFDI - 58.3/300 = 73% better

PFIQ - 37.9/300 = 69.2% better

Ideal Candidates for behavioral management of OAB

- Self-toileting with good balance and finger dexterity
- Mentally active without cognitive limitation
- Motivated to participate in treatments
- Intact neurological system
- No urinary tract infection
- Absence of sudden onset urgency

Lifestyle changes

- Weight loss
 - First line treatment for morbidly and moderately obese women (ICI 2013 grade A)
 - Surgical weight loss (Bump 1992) and conservative weight loss (Subak 2005) decrease UUI
- Fluid modifications – type, amount, timing
 - Decrease fluid intake by 25% (not lower than one liter per day) (ICI 2013 grade B, Cardozo 2011, AUA 2012 - grade B)
 - Decrease caffeine and diet soft drinks, has been associated with decreased OAB symptoms (ICI 2013 grade B, Cardozo 2011, AUA 2012 - grade B)

Bladder Training and PFM training

- Bladder training - overall cure from 12% to 73%, overall improvement rates 57% to 87%
- Bladder training and PFM training - effectively resolved UI in women, statically significant for better QOL (Wallace 2009 - Cochrane, Shamliyan 2008 - 4 RCTs, ICI 2013 grade B AUA 2012 - grade B)
- Bladder training and PFM training - more effective together than either treatment alone (Dougherty 2002, Elser 1999, Kafri 2013, ICI 2013 grade B)
- Bladder training and anticholinergics are better than either alone, (Alhasso 2009 - Cochrane, Burgio 2000, Berghmans 2000, AUA 2012 - grade C)

Other treatments for resistant OAB

- Constipation - resolution of constipation significantly improves urgency and frequency in older patients (Charach 2001)
- Electrical stimulation - vaginal or rectal electrical stimulation (10 to 12 Hz). Might be better than no treatment (ICI 2013 grade B, Berghmans 2007) theory neuromodulation
- Relaxation training and meditation
 - Theory - Relaxation training decreases sympathetic nervous system activation and thus decreases irritation of bladder leading to less OAB (level 5)
 - Anxiety scores higher in patient with dry OAB (Knight 2012)
 - Deep breathing and guided imagery 15 min audio tape 2x/day for 2 weeks, > 50% UI (Abbasy 2009)
- Acidic foods and fluids
 - Theory - resistant OAB may have a component of neural hypersensitivity which may be aggravated by acidic foods and fluids. (level 5)
 - Consider decreasing acidic food intake and baking soda water
- Overactive and painful PFM (also called hypertonus PFM, PFM spasm, high-tone PFM)
 - Muscle is unable to relax and may contract during functions such as defecation or micturition resulting in obstructive voiding or defecation, dyspareunia, pelvic pain
 - Overactive PFM occurs in patients with OAB and contributes to dysfunction (Messelink 1999)
 - Overactive PFM can be related to (Lukban 2002)
 - Voiding dysfunction
 - Urgency
 - Frequency
 - Pelvic pain
 - Viscero-muscular reflex - irritated bladder signals increase irritation of the PFM and vice versa
 - Treated with - manual stretching, EMG relaxation of PFM
- Cognitive therapy
 - "Overactivity is due to a loss of balance between the lower urinary tract and the nervous system" (Mattiasson 2007)
 - Treatment of the nervous system can affect bladder sensations and OAB (level 5)
 - Education on normal bladder pattern helps restore normal pattern (Wyman 2009)
 - Bladder training reestablishes CNS control of micturition reflex through improved cortical suppression of sensory stimuli from an uninhibited bladder and improved cortical inhibition of an overactive detrussor muscle (Paraiso 2006)
 - The urgency challenge
 - Make a list of urgency triggers, in order of difficulty and provide graded exposure to desensitize
 - Sit in front of running water and suppress urge with gradually increasing volumes of urine
 - Do not void upon returning home or leaving the house with gradually increasing volumes of urine

If OAB is still resistant

- Recheck the accuracy of the records – cognitive, emotional, stress / time limitations
- Track adherence to bladder schedule and PFM exercises – keep continual diary
- Insensible UI - wetness can be sweat or vaginal discharge, consider the colored urine test.
- Shorten interval even more – if the patient does not have decrease UI with voiding intervals of 30 to 60 minutes then potential for success is low.
- Consider need for further testing and more invasive interventions

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May 28, 2014

ICS 2014 Workshop:

A Case-driven workshop on intractable overactive bladder.

The best patient for Botox injection: “How, when and who to inject?”

10 minute interactive presentation

Lysanne Campeau, MDCM, PhD, FRCSC

Clinical scenario:

63 year old woman with urinary frequency every 30 minutes, urgency and occasional urgency urinary incontinence

Stage 2 anterior wall prolapse

Rare stress urinary incontinence

Post void residual of 120 ml

Failed oral medications

Key points:

Who?

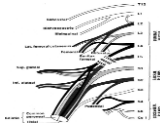
- Ideal candidate: gender, age, comorbidities, OAB wet or dry
- Prediction factors for success: clinical and urodynamic parameters
- Contraindications

When?

- Frequency of treatment
- Cessation of other pharmacotherapeutics?
- Follow-up after injection

How?

- Anesthesia
- Cessation of other pharmacotherapeutics?
- Location and depth of injection



The best patient for neuromodulation

Jacques Corcos MD
 McGill University
 Montreal, Canada

In fact there are 2 patients..

- 79 yo. Jenny, long standing idiopathic OAB
- Several co-morbidity : obesity, type 2 diabetes, sleep apnea. All being treated appropriately
- Tried “everything “ w/o success
- Lives at 3h from our hospital



Home program of tibial nerve stimulation

Second patient....



- 43 y.o Lydia, cashier in a supermarket, smoker++
- TAH / ovariectomy 7 y ago

Sacral nerve neuro modulation

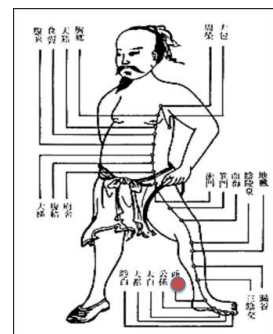
PTNS

Peripheral Tibial nerve stimulation



1683

Wilhelmus ten Rhyn
 first Western physician to describe the ancient Chinese
 technique of acupuncture



SP-6 acupuncture
 Similarity with TNS
 Used for PF dysfunctions

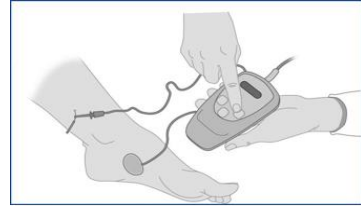


Modern history



- **McGuire** was the first to explore PTNS in 1983 on 15 patients with Neurogenic detrusor overactivity
- 1987: **Marshall Stoller** started research on PTNS as neuro modulative treatment in LUT dysfunction
- 2006 First publication on **tibial nerve implant** (Van der Pal)
- 2009 First randomized controlled trial by **K. Peters**

PTNS Technique



**A 34 gauge stainless steel needle
Approximately 3 to 4 cm (about 3
fingerbreadths) cephalad to the medial
malleolus, between the posterior margin of
the tibia and the soleus muscle**

Control of effective stimulation



- Nerve stimulation has a **effereent motor** effect and a **afferent sensory** effect
- PTN Stimulation results in
 1. Great toe flexion or fanning of the toes
 2. Sensory effect is a radiation tickling sensation of the foot sole.

Low voltage (9 volts) stimulator (Urgent PC®, Uroplasty)



- Low voltage (9 volts) stimulator (Urgent PC®, Uroplasty)
- Adjustable pulse intensity of 0 to 10 mA.,
- Fixed pulse width of 200 microseconds
- Frequency of 20 Hz .
- Amplitude slowly increased until the large toe starts to curl or toes start to fan.

Treatment duration

- 12 outpatient treatment sessions (30 min.) 1- 3/w
- If a good response occurs the patient is offered chronic treatment



Maintenance program

justification

- **6 week-pause** of therapy in successfully treated PTNS patients led to **> 50% worsening** of main symptoms in almost **all patients**
- Restarting PTNS improved complaints to the level present before the break in treatment
- Proposed maintenance: once/week

Van der Pal F BJU 2006

Results

- Most of studies used micturition diaries and general and/or disease specific quality of life questionnaires.
- **Subjective success: 59-64% of patients**
- **Objective success (> 50% decrease) in incontinence episodes and/or micturition frequency**
47-56% of patients

Vandoninck V, et al 2003
Klingler HC 2000
van Balken 2001

UD changes and prognosis factor

- When available UDS improvement rare
- Significant increments in BC and Vol at first cont.
- If no detrusor overactivity at baseline : 1.7 times more prone to respond to PTNS.
- The more the bladder overactivity was pronounced, the less respond to PTNS.

Vandoninck V NUU 2003

Study of UrgentPC versus Sham Effectiveness in Treatment of OAB (SUMIT)

Peters et al. 2009

- RCT comparing efficacy of PTNS to sham through 12 weeks of Tt
- 2 groups of 110 patients
- At 12 w. PTNS improved all parameters vs sham
- GRA improved in 55% compared to 21% in the sham group
- Another sham controlled study performed by Finazzi et al. (2010) showed similar results

Chronic treatment for responders

Peters et al followed 50 participants from the SUMIT Trial

- Fixed-schedule 14-week tapering protocol + personal Tt plan
- The tapering studies show that one treat. / 2 or 3 weeks is sufficient
- 29 patients completed the 36-month and received 1.1 Tt/m
- At 3y. 77% maintained moderate or marked improvement (voids per day ↓12.0 to 8.7 and UE/d ↓3.3 to 0.3)
- All QoL parameters remained markedly improved
- No prognostic factor found

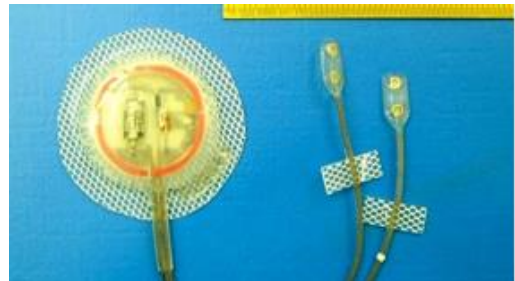
NeuroUrol Urodyn. 2011 Mar.

Transcutaneous posterior tibial nerve stimulation for treatment of OAB in multiple sclerosis.

de Sèze M et al.



Implanted PTNS





Van der Pal et al 2006

- The pioneering work
- 8 patients
- At 3, 6 and 12 months, respectively 5, 6 and 4 patients met the primary objective.
- No local infection, erosion, or dislocation
- **Jansen et al 2012** : 6/7 patients still had sensory and motor responses on stimulation at 9-year FU

Cost : PTNS vs. SNM

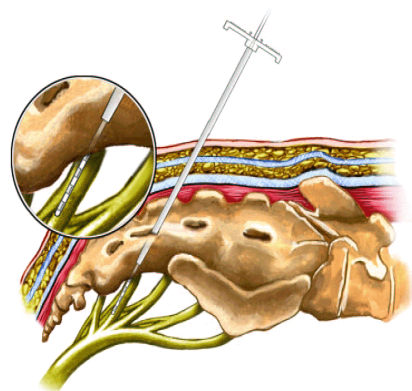
- Leong et al 2011: cost of SNS Netherlands is \$15.743 over a 2 year time period.(20)
- D'Ausilio et al 2012 calculated the 10 years cost for SNS in Italy at €33.897
- Staskin et al (2012) PTNS \$7.565 vs. SNS: \$24.681 for 3 y. in USA
- Chen et al (2012) calculated that one year treatment for PTNS costs \$4.375 per patient.(23)

Sacral neuro modulation (SNM)

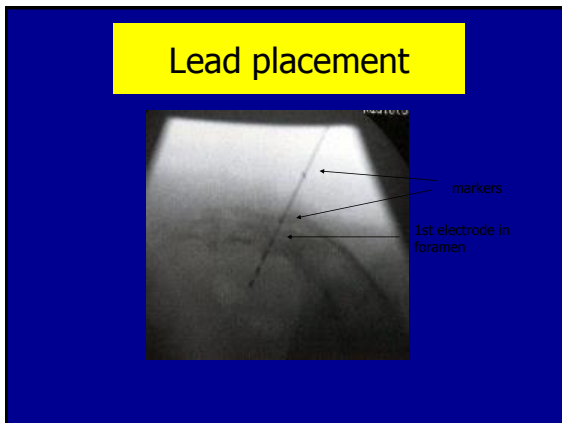
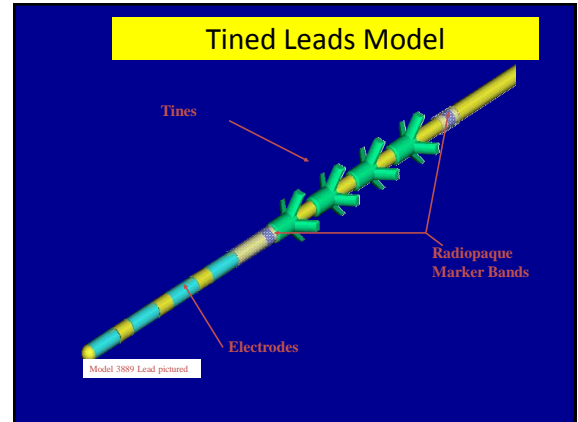
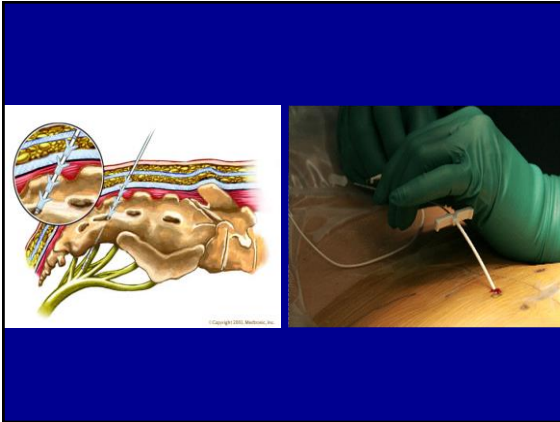


Sacral Neuro Modulation (SNM)

- Approved by the FDA in 1997 for the treatment of **urgency, frequency, urge incontinence, and non obstructive urinary retention**
- Marketed as **InterStim** (Medtronic, Inc., Minneapolis, USA)
- SNM involves the use of an **implantable electrode** in the **S3 foramen** to continuously stimulate S3 root.



©Copyright 2003, Medtronic, Inc.



Results

- A number of randomized controlled trials have previously been published showing the efficacy of SNM in patients with urge incontinence
- Success reported in 33–88% of patients at 6 months

Everaert et al Eur Urol 2004
Weil et al Eur. Urol 2000

Long Term results > 64 months

- “good results” 61 % van Voskuilen et al 2004
- “good results” ... 52 % Bosch & Groen 2002
- Satisfied patients.....54% at 12 y. Elhilali , Corcos

Patient's satisfaction

- Satisfaction studies have shown a significant improvement in QoL scores in patients with UI
- Capellano* et al. At 18-month FU, 90% of patients stated they would undergo this treatment again and 100% stated they would recommend it to a relative
- Foster ** et al. 84% of patients with UI to be satisfied with SNM

*J Urol 2001
** NUU 2007

Results of a Prospective, Randomized, Multicenter Study
Evaluating SNM Compared to Standard Medical Therapy (SMT) at
6-Months in subjects with Mild Symptoms of
Overactive Bladder
Siegel et al NUU 2014

- 147 subjects randomized (70 to SNM, 77 to SMT)
- 93% were female and mean age was 58.
- OAB Tt success: 76% SNM vs 49% for SMT ($P=0.002$).
- SNM :significant improvements in QoL vs SMT ($P<0.001$)
- 86% of SNM reported improved *urinary symptom interference score* at 6 months, compared to 44% for SMT subjects.
- Device-related AE rate was 30.5% vs. 27.3%. for med-related AE

SNM after Botox ?

Smits et al J urol 2013

- 20 patients who had previously failed BoNT/A.
- One year after implant,79% were satisfied with their implant
- Conclusion: patients who do not respond to BoNT/A are still candidates for SNM.

Complications of SNM

Long-term complications:

- Van Kerrebroeck et al *: 105 patients over 5-year
 - 39% experienced AE
 - Most common: device exchange or component repositioning
 - 10% of patients required explantation due to lack of efficacy or complications
-
- Peeters** et al : 41% required at least one reoperation
 - 26% were explanted
 - Mean time to failure of 24.6 months

*J Urol 2007
** BJU int 2013



Thank you



Notes