Recent advances in the management of female OAB

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MIPS, Nîmes, november 29th 2014

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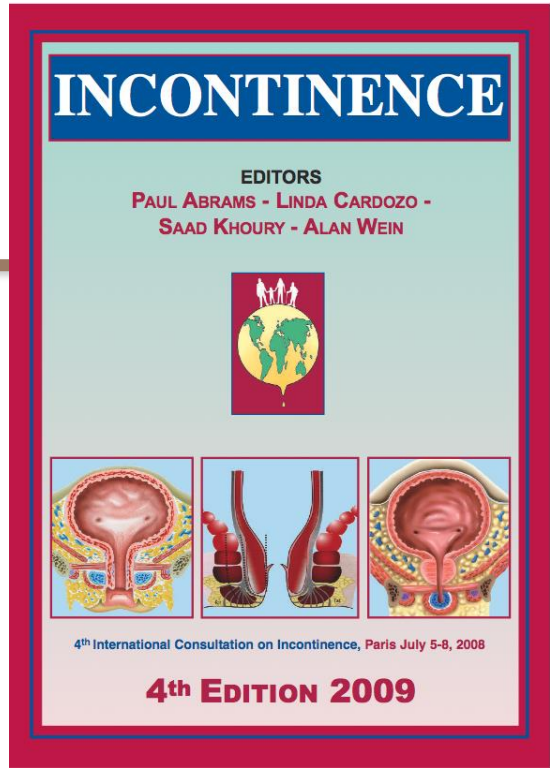
- Key definitions
- Prevalence
- Basic assessment and treatment
- Treatment failure
- Managing refractory OAB
- 4th International Consultation on Incontinence algorithms

What is OAB?



International Continence Society

Standardised terminology report, Abrams et al., Neurourol Urodyn 2002

Neurourology and Urodynamics 21:167–178 (2002)
DOI 10.1002/nau.10052

The Standardisation of Terminology of Lower Urinary Tract Function: Report from the Standardisation Sub-committee of the International Continence Society

Paul Abrams, Linda Cardozo, Magnus Fall, Derek Griffiths, Peter Rosier, Ulf Ulmsten, Philip van Kerrebroeck, Arne Victor, and Alan Wein

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Definition of OAB

- Urgency, with or without urgency incontinence, usually with frequency and nocturia.

> Urgency: a sudden compelling desire to pass urine which is difficult to defer

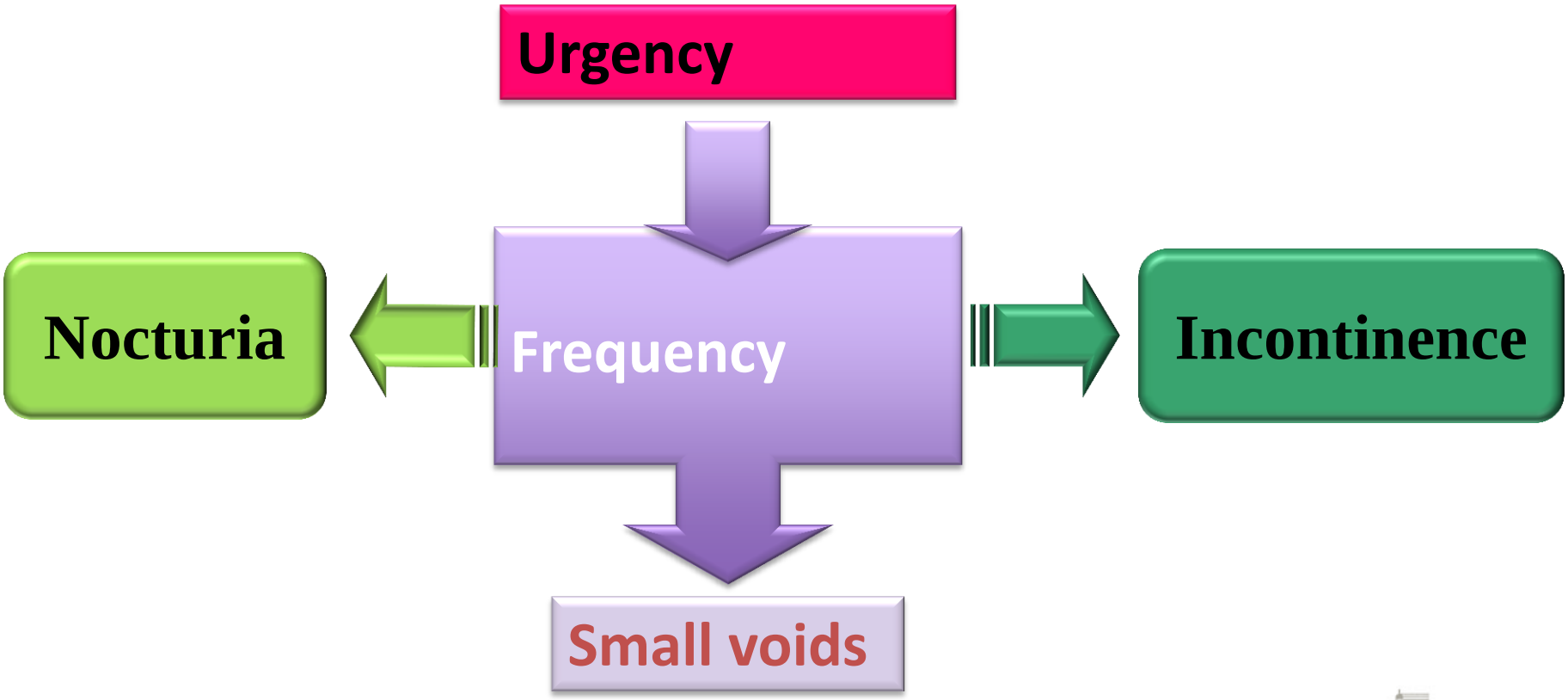
> Frequency: the complaint by a patient who considers that he/she voids too often by day

> Nocturia: the complaint that the individual has to wake at night 1 or more times to void

> UUI: involuntary leakage accompanied by or immediately preceded by urgency

OAB Syndrome: Idiopathic and neuropathic

Adapted from Chapple CR , et al. BJU Int. 2005; 95: 335–40



Components of nocturia

Polyuria

Urine output exceeds 40 ml / Kg / 24 hours

Nocturnal polyuria

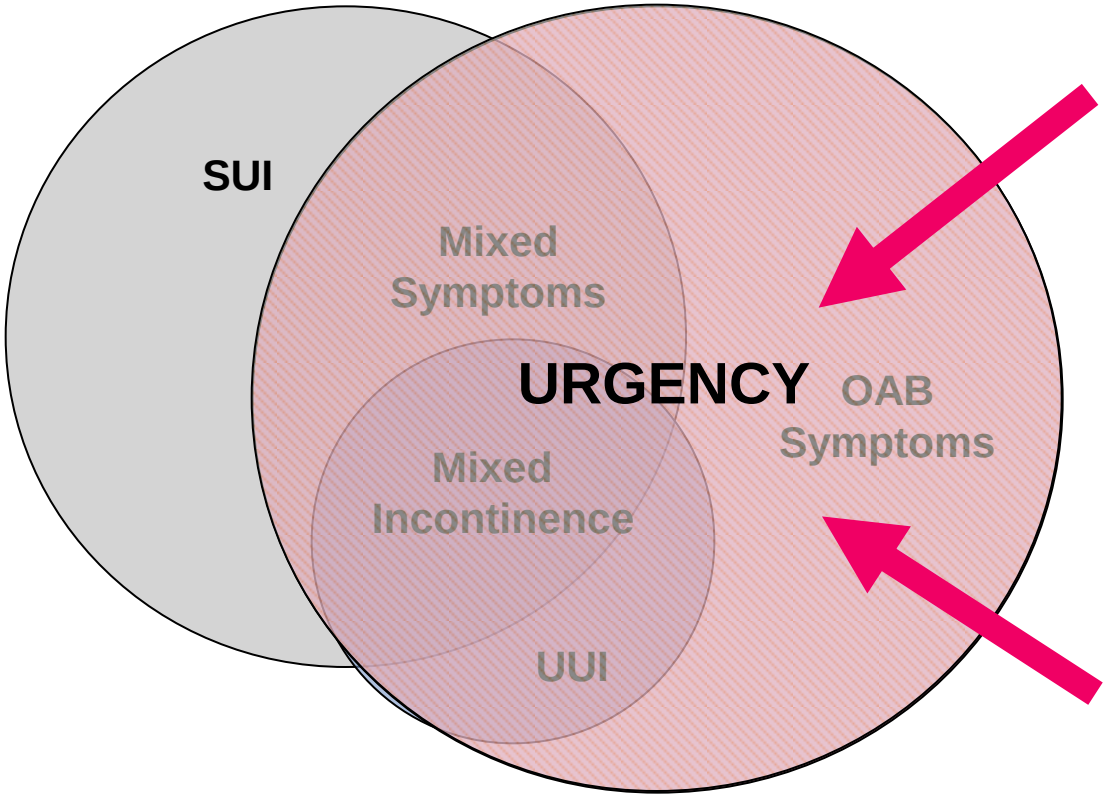
Urine output between 11pm and 7 am is
< 20% in young
and
< 33% in elderly

Low nocturnal bladder capacity

Van Kerrebroeck P, Abrams P, Neurourol Urodyn 2002;21:179-83; Marinkovic SP, BMJ 2004;328:1[illegible]

Spectrum of OAB

- OAB defined as “urgency, with or without urgency incontinence, usually with frequency and nocturia”



Urgency: **“a sudden compelling desire to pass urine, which is difficult to defer”**

Urgency: **“the only symptom a patient *must* have to be described as having OAB”**

Wein AJ. Rackley RR. J Urol 2006; 175:s5-10
Abrams P et al Neurourol Urodyn 2002;21:167-178
Abrams P BJU Int 2005; 96 (Suppl 1);1-3

OAB : idiopathic vs. neurogenic

- Neurogenic

  OAB where there is a relevant neurological condition

  – Sensation may be impaired, so urgency is unreliable

- Detrusor overactivity

  – bladder contractions during the storage phase which may be spontaneous and/or provoked

OAB may originate from…

Nervous system

7. Obstruction

6. Efferent function

1. Comorbidities

Non neurogenic OAB

4. Afferent urothelium function

2. Ageing

3. Myogenic origin

5. Bladder afferents

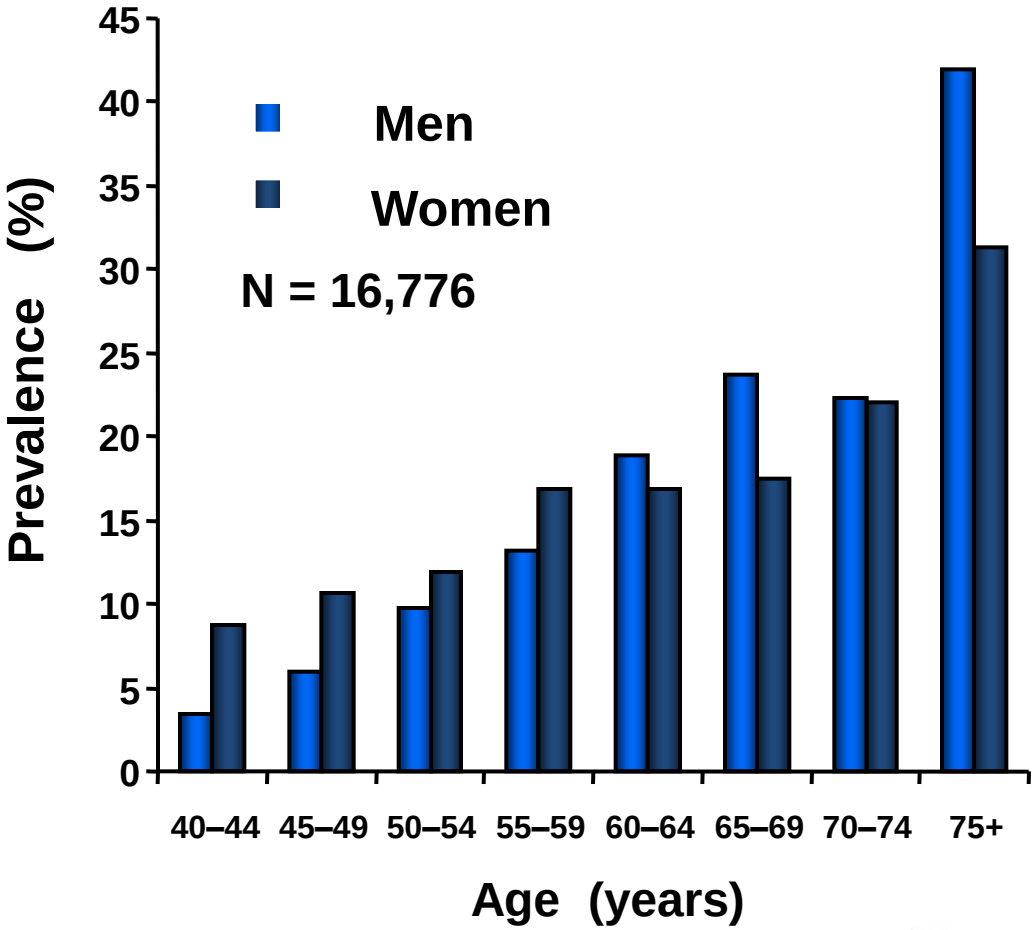
Bladder

Urothelium

Neurogenic OAB…

OAB in Europe

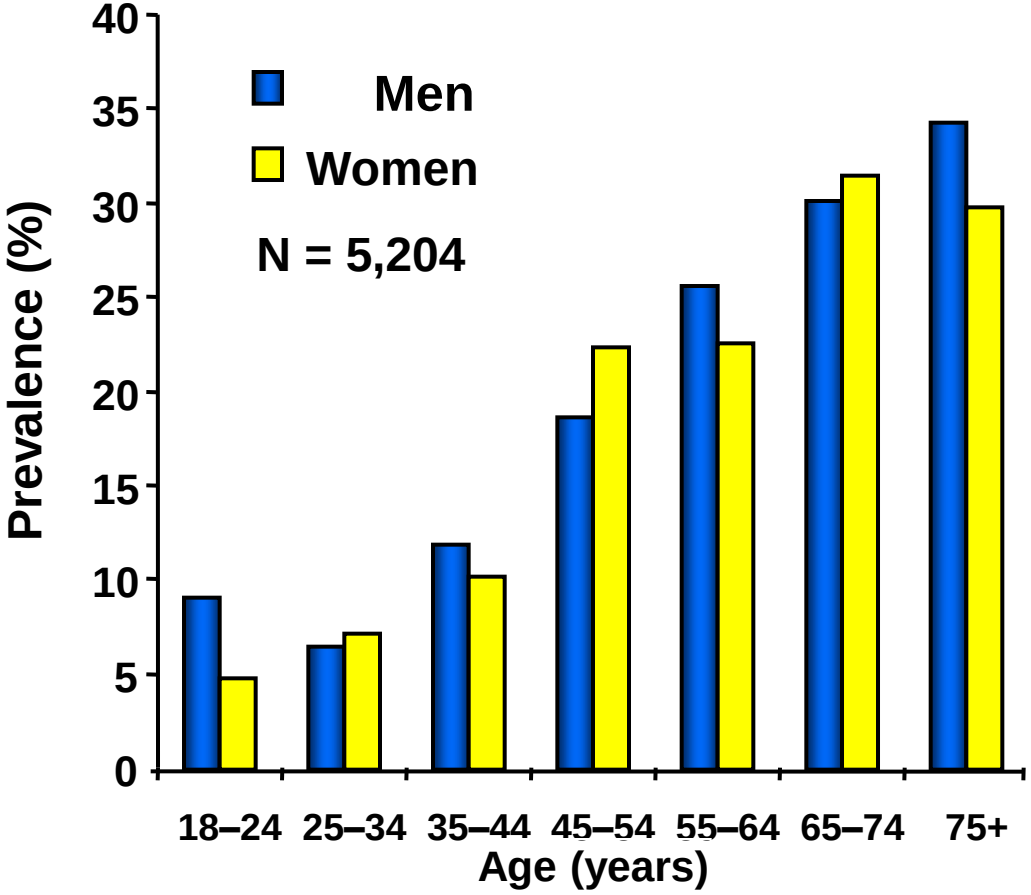
- 16.6% of the population over 40 years in 6 European countries have OAB symptoms
- OAB prevalence increases with age



Milsom I et al. *BJU Int.* 2001;87:760-766

OAB in US

- **16.5% of the population over 18 years (~33 million) have OAB symptoms**



Stewart W et al. *World J Urol.* 2002

OAB prevalence (standardised definition); EPIC

Table 1. Prevalence of OAB by Sex and Country

Country		Prevalence (%)*			Estimated Population With OAB (millions)		
		Men	Women	Total	Men	Women	Total
Germany	(n=4244)	11.6	13.7	12.7	3.8	4.8	8.6
Italy	(n=4893)	11.6	13.0	12.3	2.6	3.2	5.9
Sweden	(n=1921)	14.2	22.5	18.4	0.5	0.8	1.3
United Kingdom	(n=3608)	9.4	11.4	10.4	2.0	2.7	4.8
Total	(N=14,666)	11.1	13.2	12.2	8.9	11.5	20.4

*Weighted data for individuals ≥18 years.

Figure 2. Prevalence* of OAB by Sex and Age Group

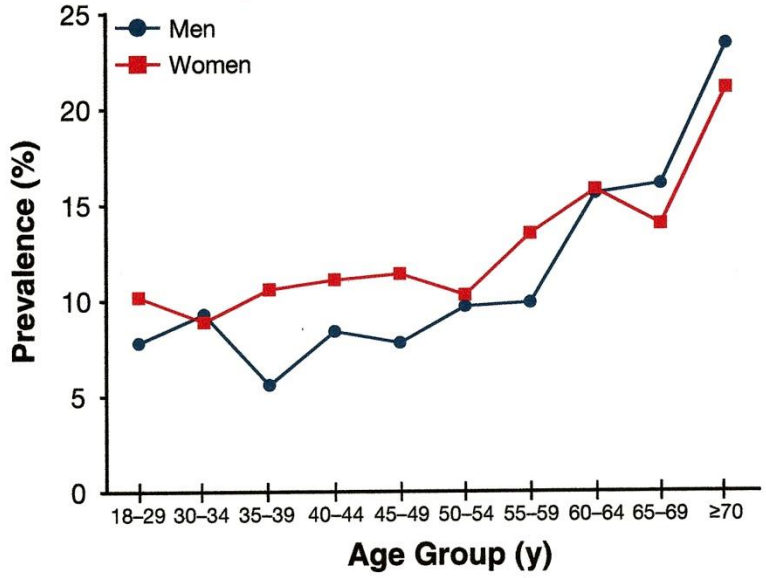
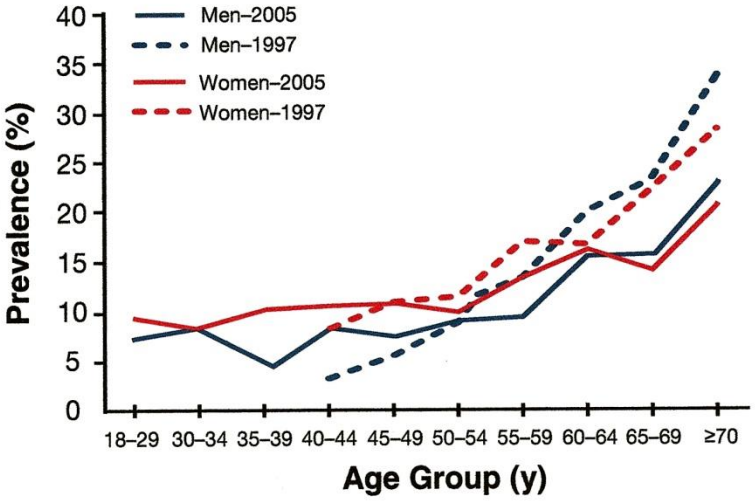


Figure 3. OAB Prevalence* Comparison Between Milsom 1997 Weighted Estimates and EPIC 2005 Weighted Estimates



Assessment : LUTS

- LUTS, severity and bother
  - Exclude malignancy, neurological and UTI
  - Fluid intake
  - Use a symptom assessment tool e.g ICIQ
- Frequency volume chart
- Dipstick urinalysis/ MSU
- Flow rate and residual
- Uncomplicated OAB can be treated without further investigation

LUTS = Lower urinary Tract Symptoms

DAY	Time / Volume (mls.) Day-Time	Night -Time	Number of pads used in 24 hour period
1	8.20 am, 11.30, 12.30, 1.30 pm, 2.40, 4, 4.50, 5.45, 7, 7.20, 8.15, 10 150, 100 W, 100, 100 W, 100, 75 W, 125, 140 W, 140 W, 125, 100 W, 140	2.40 am, 3, 5, 5.15, 6.45, 9.20 a.m 250 W, 125, 50, 50, 300, 200	
2	10.30 am, 12 noon, 3.30 p.m, 6 p.m, 9.15 p.m, 11 p.m. •, •, •, •, 100, 125	1 a.m, 2.50 a.m, 4.30 a.m, 6.30 am, 7.30 am, 9 am 150, 200, 50, 150, 200, 200	taking
3	9 am, 10.30, 1.00 pm, 5, 7, 7.45, 9.20, 11.00 pm 150, 100, 100 W, 150, 100, 150, 200, 100	1.20 am, 2.35, 4.15, 6.00 am, 6.50, 8.30 am 200, 200, 200, 100 W, 200 W, 250	while
4	9.30 am, 10.30, 11, 1.15 pm, 2.20 pm, 3, 4.30, 5.45, 7, 7.45 pm, 8.15, 9, 9.30, 10.45, 11.30 150, Wet Wet, 150, 200 W, •, 130, 150, 100, 100 W, 100, 200, 100, 200, •	2.10 am, 400 am, 5.00, 6, 630 am, 8.00 am 250 W, 250 W, 50, 200 W, 190, 250	running pants
5	9 am, 1030, 11, 1.15 pm, 2.20 pm, 3, 4.30, 5.45, 7, 7.45, 8.15 pm, 9, 9.30, 10.45, 11.30 Wet Wet W, 150, 200 W, •, 130, 150, 100, 100 W, 150, 200, 100, 200, •	1 am, 2.25 am, 4, 8 200, 250, 200, 200	Drops off pads
6	9 am, 11, 11.30, 12 noon, 12.40, 2 pm, 3, 4.20 pm, 9.30, 10.30 100, 200, 100, 125, 200, 200, 180, 150, 100, 100	2 am, 430 am, 8.00 2.20, 150, 100	3 ‖ No
7	9 am, 10.30, 12 noon, 1.15 pm, 3, 4 pm, 5, 5.45, 7.15 pm, 8.05, 8.40, 10 pm 100, 50, 100, 100, 200, 200, •, 150, 130 W, 150, 140, 150	1 am, 3, 4.30 am, 7 am 250 W, 150, 200, 200	a) b) N.B

* instructions on other side *

AVERAGE DAILY FLUID INTAKE (in cups) = 14

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ICIQ-UI short form

Symptoms & QoL-

baseline severity

gauging treatment outcome

www.iciq.net

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Primary management

- Only if patient wants treatment
  - Bother, QoL, …
- Reassurance
- Bladder training
- Suitable fluid intake

PFMT: Pelvic Floor Muscle Training and OAB

- Has to be prescribed
- 10 sessions:
  - To reinforce bladder sensation control
  - To prevent any malfunction of abdominoperineal reflexes
- Caregiver has to be trained
  - Physiotherapist

- To discuss: Tibial nerve stimulation

5th International Consultation in Incontinence Antimuscarinics/ Mixed Action Drugs

Fourth International Consultation On Incontinence (ICI) Paris 2012 - Drug Treatment Committee Highlights,

Drug	Level of evidence	Grade of recommendation
Darifenacin	1	A
Fesoterodine	1	A
Solifenacin	1	A
Tolterodine	1	A
Trospium	1	A
Oxybutynin	1	A
Propiverine	1	A

Comparative studies between Antimuscarinics

- Very limited
  - STAR; solifenacin vs tolterodine
  - ACET; oxybutynin vs tolterodine
  - Fesoterodine vs tolterodine
- Reviews and “meta-analysis”
- No clear winner
- Oxybutynin probably is a clear looser

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

The anti-muscarinics were found to be safe AND efficacious
There were significant differences between the anti-muscarinics in terms of withdrawal and rates and range of adverse events and efficacy outcomes

Efficacy of antimuscarinics compared to placebo: results from meta-analyses

Outcome	Intervention and Daily Dose (mg/day)														
	Dar 7.5	Dar 15	Dar (t 7.5)	Oxy IR 5-7.5	Oxy IR 8.8-15	Oxy TDS 3.9	Pro IR 30	Pro IR 45	Pro ER 30	Sol 5	Sol 10	Tol IR 2	Tol IR 4	Tol ER 4	Tro 40
CUE*										n=512 -1.44 (-2.08, -0.80)##	n=509 -1.66 (-2.32, -1.00)##		n=498 -0.64 (-1.28, 0.00)#	n=854 -1.10 (-1.50, -0.70)##	
CIE*					n=327 -0.72 (-1.09, -0.34)	n=495 -0.55 (-1.05, -0.04)				n=294 -0.66 (-1.13, -0.19)##	n=311 -0.69 (-1.19, -0.19)##	n=455 -0.23 (-0.91, 0.45)	n=2025 -0.50 (-0.70, -0.30)	n=2108 -0.73 (-0.93, -0.53)	
CM*					n=250 -0.80 (-1.62, 0.03)	n=491 -0.55 (-1.03, -0.07)				n=519 -0.99 (-1.52, -0.46)##	n=517 -1.41 (-1.97, -0.85)##	n=478 -0.68 (-1.15, -0.22)	n=2294 -0.67 (-0.92, -0.42)	n=2108 -0.73 (-0.96, -0.49)	
RC**				n=110 3.53 (1.94, 6.41)#	n=127 1.79 (0.82, 3.92)#	n=238 1.75 (1.16, 2.62)##		n=76 1.80 (0.96, 3.38)#						n=240 1.72 (1.14, 2.58)##	n=821 2.00 (1.40, 2.86)
AMNP**			n=395 1.70 (1.19, 2.42)#												
CVV*					n=249 39.8 (28.0, 51.6	n=238 23.0 (8.0, 38.1)##		n=98 27.9 (-8.18, 64.0)#		n=519 25.5 (18.2, 37.8)##	n=517 31.8 (24.2, 39.4)##	n=478 13.0 (5.11, 20.8)	n=2150 17.5 (12.7, 22.3)	n=2414 17.4 (13.2, 21.5)	

Efficacy of antimuscarinics compared to active control: results from meta-analyses

Outcome	Interventions and Daily Dose (mg/day)																		
	Oxy IR 10 vs Tro 40	Oxy IR 10 vs Pro IR 45	Oxy IR 10 vs Oxy ER 10	Oxy IR (t 15) vs Oxy ER (t 15)	Oxy IR (t 5) vs Oxy ER (t 5)	Oxy IR (t) vs Oxy TDS (t)	Pro IR 30 vs Pro ER 30	Tol IR 4 vs Tol ER 4	Tol IR 4 vs Oxy IR 10	Tol IR 4 vs Oxy IR 15	Tol IR 4 vs Oxy ER 10	Tol IR 2 vs Oxy ER 5	Tol IR 4 vs Pro IR 30	Tol IR 4 vs Sol 5	Tol IR 4 vs Sol 10	Tol IR 4 vs Tro 40	Tol ER 4 vs Oxy IR 9	Tol ER 4 vs Oxy ER 10	Tol ER 4 vs Oxy TDS 3.9
CUE*														n=514 0.80 (0.17, 1.43)#	n=511 1.02 (0.37, 1.67)#				
CIE*								n=1021 0.18 (-0.12, 0.48)#	n=88 -0.80 (-1.66, 0.06)#	n=279 0.16 (-0.42, 0.73)		n=57 -0.60 (-1.65, 0.45)#		n=298 0.28 (-0.17, 0.73)#	n=315 0.31 (-0.17, 0.79)#			n=775 0.29 (0.01, 0.57)#	n=244 -0.30 (-1.03, 0.43)#
CM*								n=1021 0.10 (-0.31, 0.51)#	n=128 -0.80 (-1.73, 0.13)#	n=346 -0.22 (-0.84, 0.40)		n=206 0.06 (-0.75, 0.87)#		n=516 0.31 (-0.20, 0.82)#	n=514 0.73 (0.19, 1.27)#			n=775 0.33 (-0.04, 0.70)#	n=244 -0.30# (-0.97, 0.37)#
RC**			n=128 1.08 (0.79, 1.48)##		n=93 0.98 (0.60, 1.60)#	n=74 1.25 (0.56, 2.81)#												n=775 0.72 (0.55, 0.96)#	n=244 0.98 (0.72, 1.35)#
AMNP**																			
CVV*					n=63 -9.10 (-70.0, 51.8)#			n=1021 -5.00 (-11.0, 1.02)#		n=345 -12.1 (-22.8, -1.3)		n=206 4.33 (-12.9, 21.5)#	n=155 -1.70 (-22.2, 14.8)#	n=516-8.50 (-16.9, -0.13)#	n=514 -14.8 (-23.4, -6.18)#				n=244 -3.00 (-17.1, 11.1)#

Chapple C, Khullar V, Gabriel Z, Dooley JA. Eur Urol. 2005; 48: 5-26

Antimuscarinic failure

- A second antimuscarinic can achieve success if the first does not
  - Crucial to engage the patient
- Options;
  - Increase dose (maybe exceed licensed dose)
  - Combine drugs (e.g transdermal + low dose oral)
  - Manage adverse effects e.g. artificial saliva (salivart)
- Glaucoma, GORD

Reasons for failure

- Drug did not work (persistent urgency)

- Adverse effects
- Unrealistic expectations
- Failure to perceive benefit
- Compliance
- Other LUTS
- Other symptoms:
  - Fecal incontinence, pelvic pain, psychological disorders
- Wrong diagnosis

Wrong diagnosis

- UTI
- Post void residual
- Pelvic inflammation attributed to the bladder
- Spinal

Which basic evaluation

- Voiding diary
- Bacterial analysis of urine

- Ultrasound:
  - Kidneys: bladder (post void residal urine)
- Urine cytology
- Cystoscopy (optionnal as a first line management of OAB except unusual symptoms and smokers)

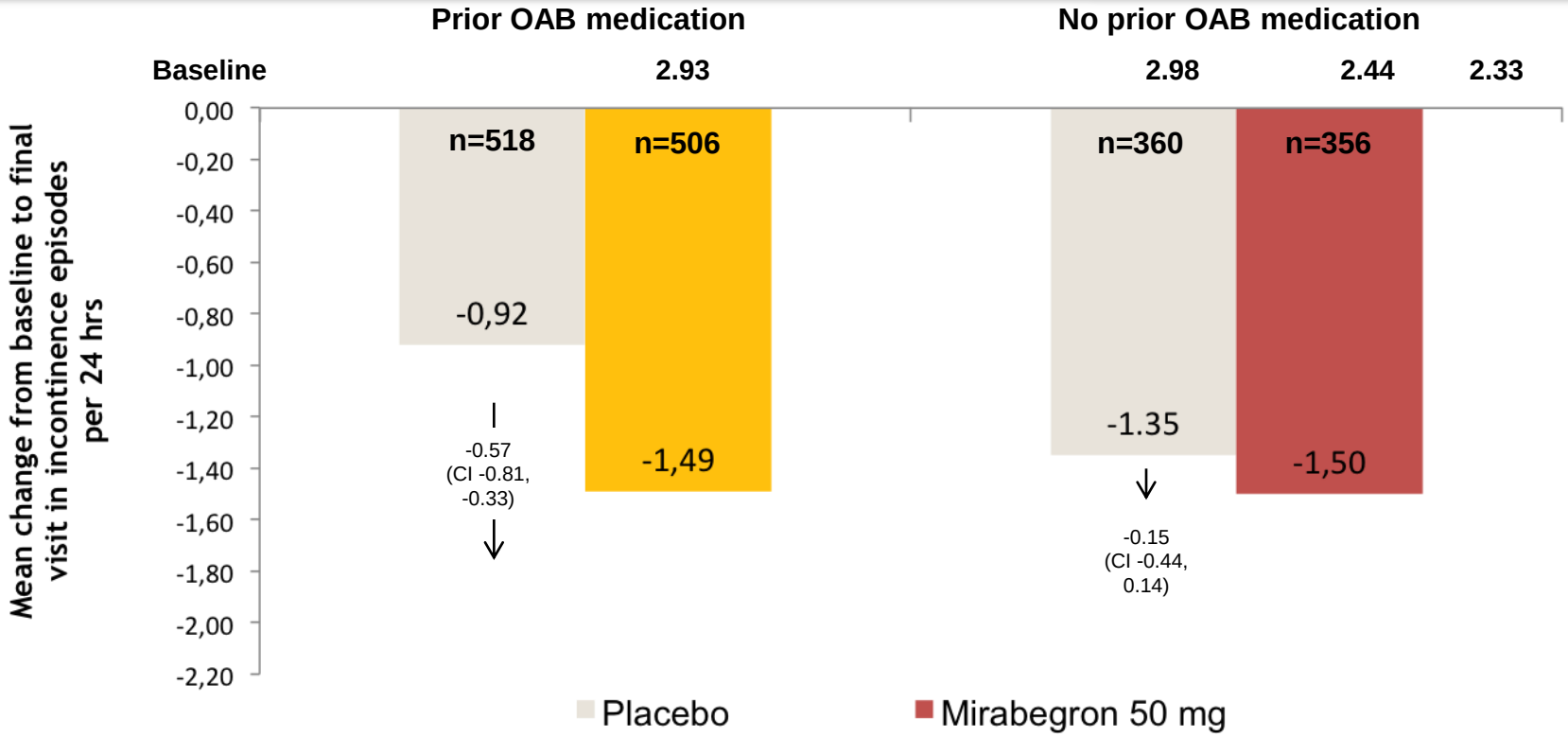
Which antimuscarinic?

- All of them work
- Extended release preferred to immediate
- For the immediate release agents, dose escalation can yield benefits
- No clear first line agent

- Transdermal agents
- Beta-3 agonist

Novara G et al. Eur Urol 2008; 54: 740

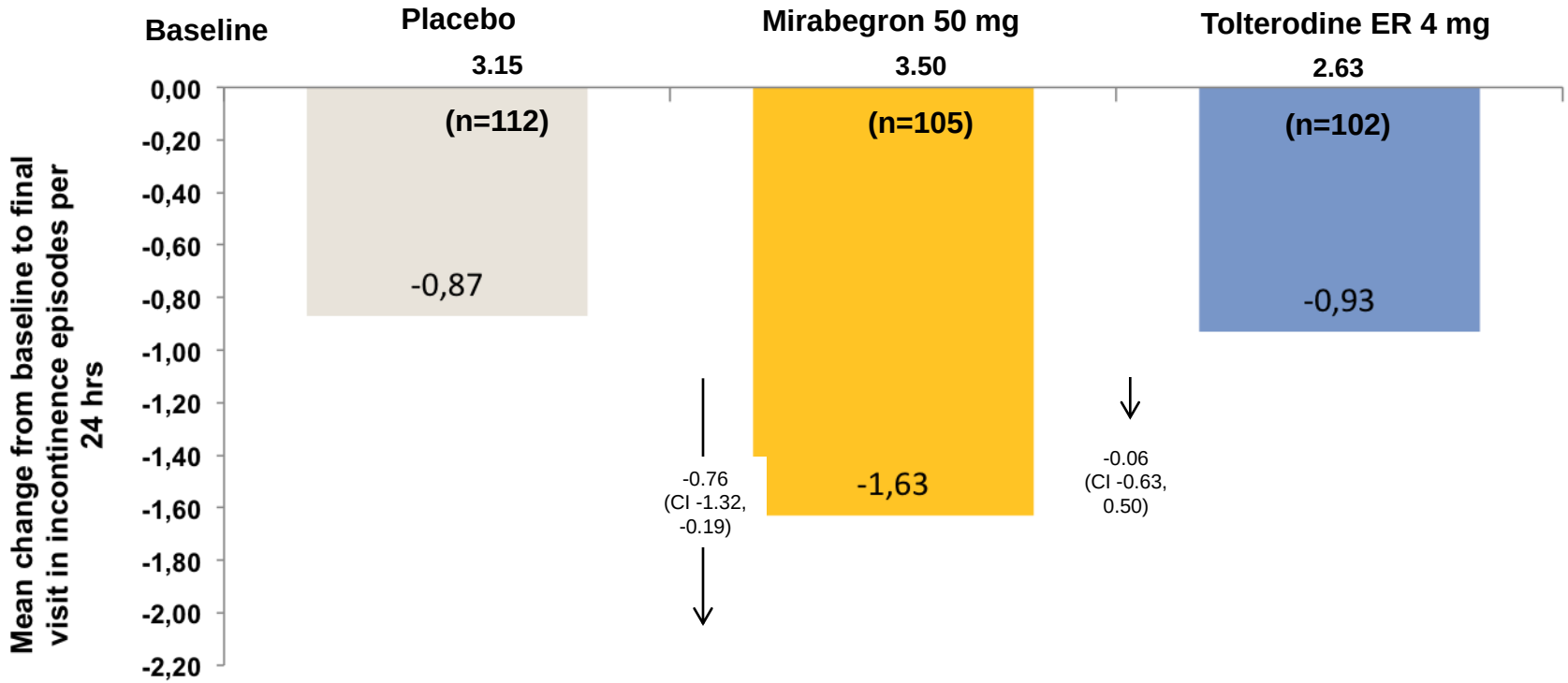
Prior OAB therapy and Mirabegron
Pooled data ISE (046/047/074): incontinence episodes



FAS-I, FAS Incontinence
ISE, Integrated Summary of Effectiveness

1. Adapted from Nitti V, et al. Poster presented at the 37th Annual Meeting of IUGA, September 2012, Brisbane, Australia. Poster 34.
2. Astellas Pharma Europe Ltd. Data on file (MIR/12/00010/EU).

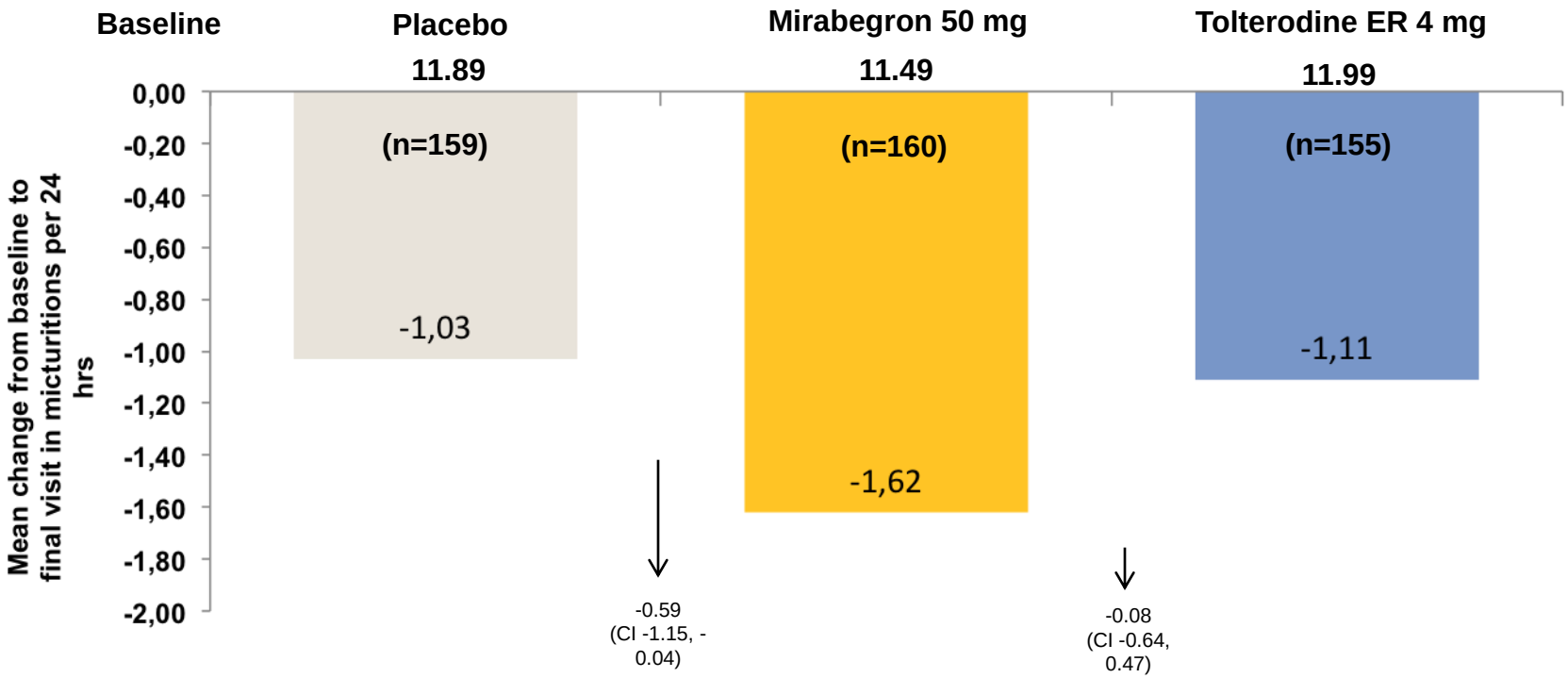
Post-hoc subgroup analysis (046): Previous OAB therapy discontinued due to insufficient efficacy: incontinence (FAS-I)



FAS-I, FAS Incontinence

1. Adapted from Nitti V, et al. Poster presented at the 37th Annual Meeting of IUGA, September 2012, Brisbane, Australia. Poster 351.
2. Betmiga™ Summary of Product Characteristics. Available at: http://www.ema.europa.eu/ema/ Last accessed February 2013.

Post-hoc subgroup analysis (046): Previous OAB therapy discontinued due to insufficient efficacy: micturitions (FAS)



FAS, Full Analysis Set

1. Adapted from Nitti V, et al. Poster presented at the 37th Annual Meeting of IUGA, September 2012, Brisbane, Australia. Poster 351.
2. Betmiga™ Summary of Product Characteristics. Available at: http://www.ema.europa.eu/ema/ Last accessed February 2013.

ICI assessments, 2012

Drug	Level	Grade
β_2-AR agonists (terbutaline, salbutamol, clenbuterol)	3	C
β_3-AR agonists (mirabegron*)	1	B

**Japanese warning: Avoid administration to patients of reproductive age (based on rat studies)*

Accordingly to KE Andersson

Refractory OAB…
no clear definition, no consensus

Conservative measures
Antimuscarinics

Refractory OAB symptoms

Unacceptable impact on quality of life

Realistic expectations
Medically fit
Willing to accept risk

Next step, filling cystometry...

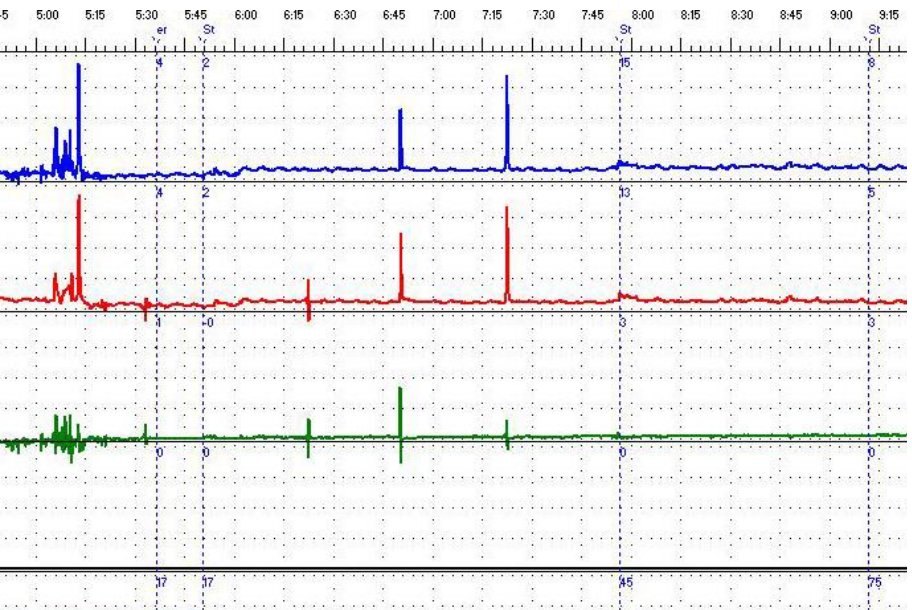
OAB; urodynamics

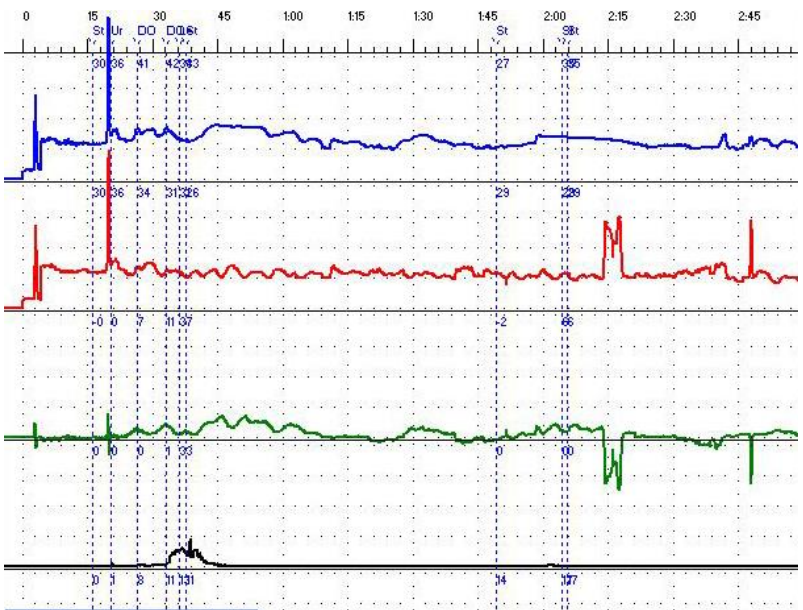
Increased filling sensation

- urgency in the absence of pressure change

Detrusor overactivity

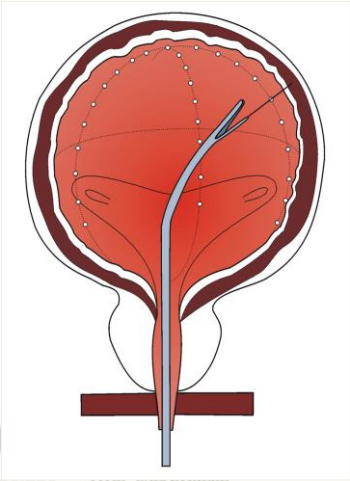
- changes in pressure when filling (with or without sensation)





Treatment options

- First “second line therapies”
  - Botulinum toxin A bladder injections (Botox 100 units/6-9 months)
  - Sacral nerve stimulation (S3, Interstim, Medtronic)
- Second “second line therapies”
  - Enterocystoplasty
  - Detrusor myectomy
  - Urinary diversion
  - “Other stuff”



Some of the key references

- [1] Abrams P, Andersson KE, Birder L, Brubaker L, Cardozo L, Chapple C, et al. Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. Neurourol Urodyn. 2010;29(1):213-40.
- [2] Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, 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(2):167-78.
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- [4] Novara G, Galfano A, Secco S, D'Elia C, Cavalleri S, Ficarra V, et al. A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. Eur Urol. 2008 Oct;54(4):740-63.
- [5] van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, Lycklama a Nijholt AA, Siegel S, Jonas U, et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. J Urol. 2007 Nov;178(5):2029-34.
- [6] Anger JT, Weinberg A, Suttorp MJ, Litwin MS, Shekelle PG. Outcomes of intravesical botulinum toxin for idiopathic overactive bladder symptoms: a systematic review of the literature. J Urol. 2010 Jun;183(6):2258-64.

IUGA's 40th Annual Meeting 2015 Nice, France

A joined congress with the 2nd world pelvic pain congress

Chairmen:
E Chartier-Kastler and B Fatton
www.iugameeting.org

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