Fundació Puigvert

Treatment of female OAB: technique, results and follow up:

Botulinum Toxin A

Dr. Carlos Errando-Smet
Fundació Puigvert
Barcelona

Eligibility for BoNT injection

- Confirm a diagnosis of OAB (Voiding Diary)
- Inadequately controlled on anticholinergic therapy
- Confirm patient not in urinary retention (overflow incontinence)
- No recent (within 12-weeks) botulinum toxin injections for any indication
- Assess willingness and ability to catheterize (of permanent foley cath.)
- No urinary tract or injection site infections at the time of treatment
- Not allergic to botulinum toxin A or any of its excipients
- Rule out Pregnancy

Patient assessment

Bladder/sphincter function

- Voiding Diary
- Post-void residual
- Urinalysis
- Urodynamics

*Upper tract imaging (e.g. ultrasound).
NDO, neurogenic detrusor overactivity. Haylen B, et al. *Neurourol Urodyn* 2010;29:4–20.

Patient Assessment

- Urinalysis

  (-): Standard chemoprofilaxis:

  Cephalosporin 2nd IV, 60 min before procedure*

  (+): specific treatment: 3-day course treatment

- Antiplatelet/Anticoagulant

  Suspend, evaluating every case

- Aminoglycosides, tetracycline, lincosamide, polymyxine: avoid **

* Ann Pharmacother. 2014 Jan 6. [Epub ahead of print] Approach to Antimicrobial Prophylaxis for Urology Procedures in the Era of Increasing Fluoroquinolone Resistance. Marino Sabo E, Stern JJ.University of Pennsylvania Health System, Pennsylvania Hospital, Philadelphia,PA, USA

* * Dressler D, Benecke R. Pharmacology of therapeutic botulinum toxin preparations. *Disabil Rehabil.* 2007;29(23):1761-8

Anesthesia

- Local:

♀ 40mL lidocaine 2% in 40mL saline (30 min before)

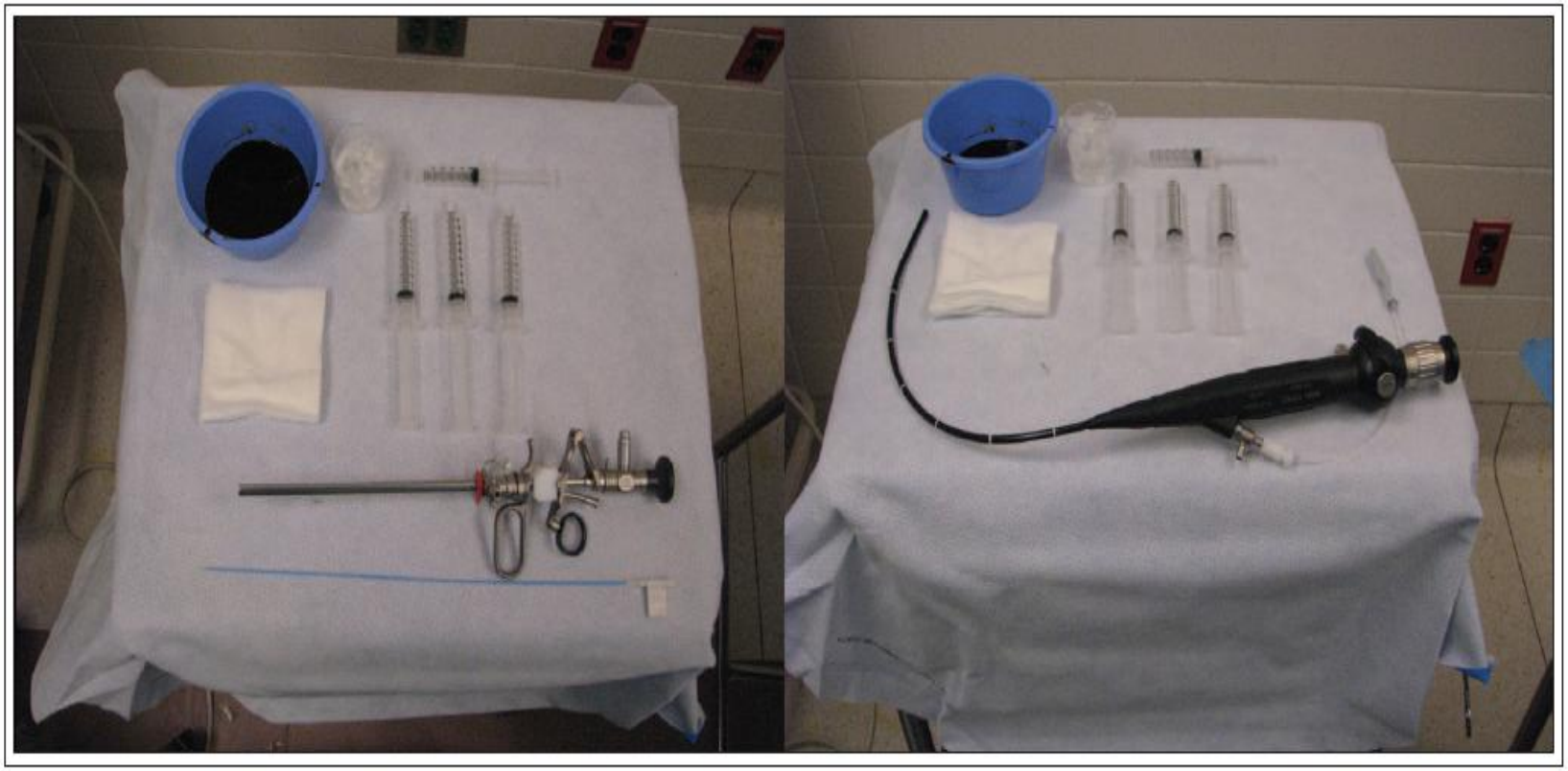
Diazepam 5mg + Pethidine 50mg SC (30 min before)

♂ + lidocaine gel (urethra)

- Spinal Anesthesia: ♂

Dysrreflexia, Painful Bladder Syndrome, Patient preference…

Procedure



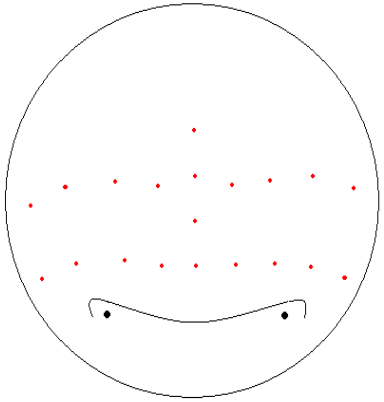
Procedure

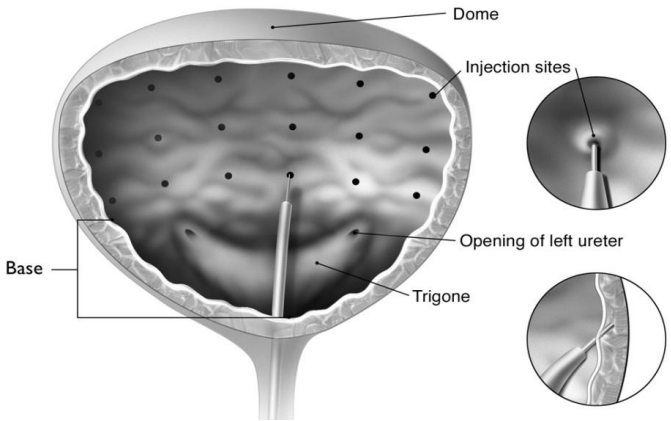
100 UI en 10mL de saline

20 injections 5U / 0,5mL

Intradetrusor

No trigone*

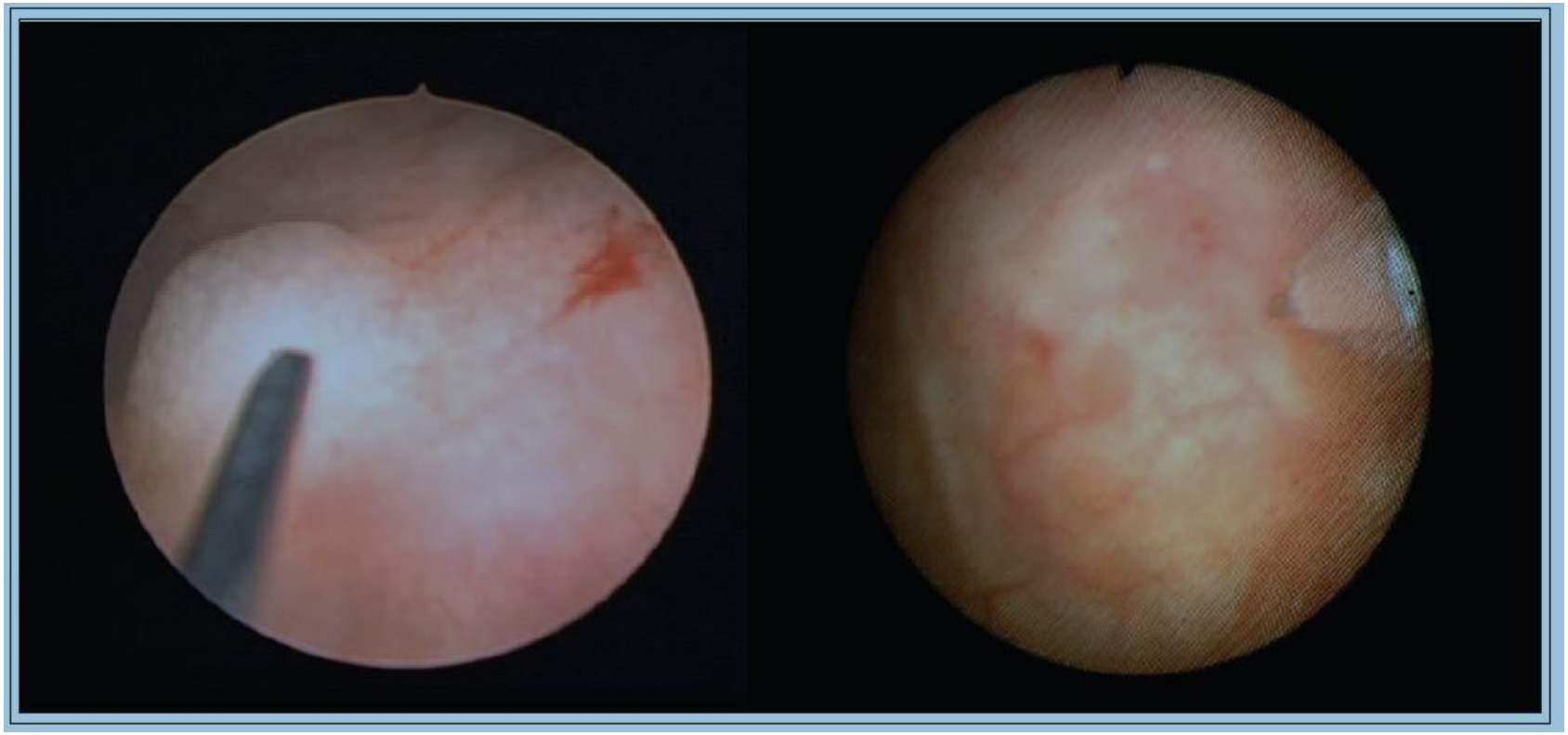




Kuo HC. Comparison of effectiveness of detrusor, suburothelial and bladder base injections of botulinum toxin a for idiopathic detrusor overactivity. J Urol 2007;178:1359-63.

Procedure

Sub-urotelial / Intra-Detrusor



*Spinal Cord. 2012 Dec;50(12):904-7. doi: 10.1038/sc.2012.76. Epub 2012 Jul 17. Intradetrusor versus suburothelial onabotulinumtoxinA injections for neurogenic detrusor overactivity: a pilot study. Krhut J, Samal V, Nemec D, Zvara P.

Evidence In OAB

Vol. 176, 177-185, July 2006

Experience With 100 Cases Treated With Botulinum-A Toxin Injections in the Detrusor Muscle for Idiopathic Overactive Bladder Syndrome Refractory to Anticholinergics

D. M. Schmid,* P. Sauermann, M. Werner, B. Schuessler, N. Blick, M. Muentener, R. T. Strebel, D. Perucchini, D. Scheiner, G. Schaer, H. John, A. Reitz, D. Hauri and B. Schurch

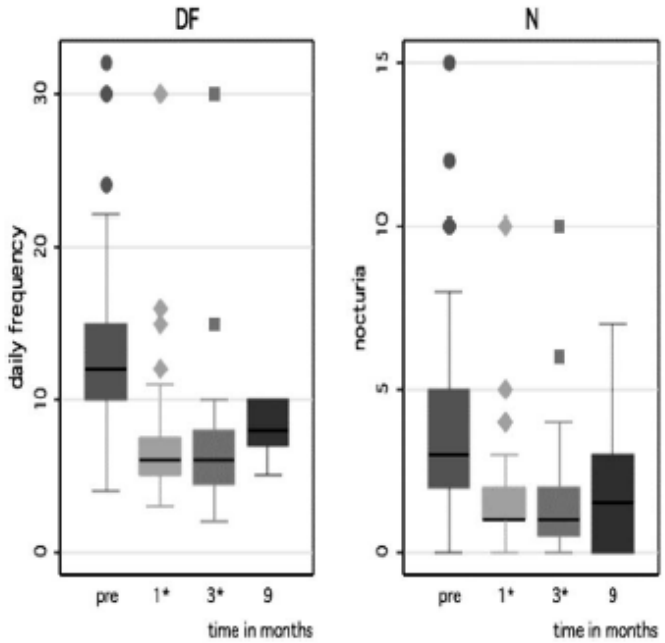


FIG. 5. Median DF and N (25th and 75th percentiles) before (*pre*), and 1, 3 and 9 months after intradetrusor BTX-A injections in 100, 100, 80 and 20 patients, respectively.

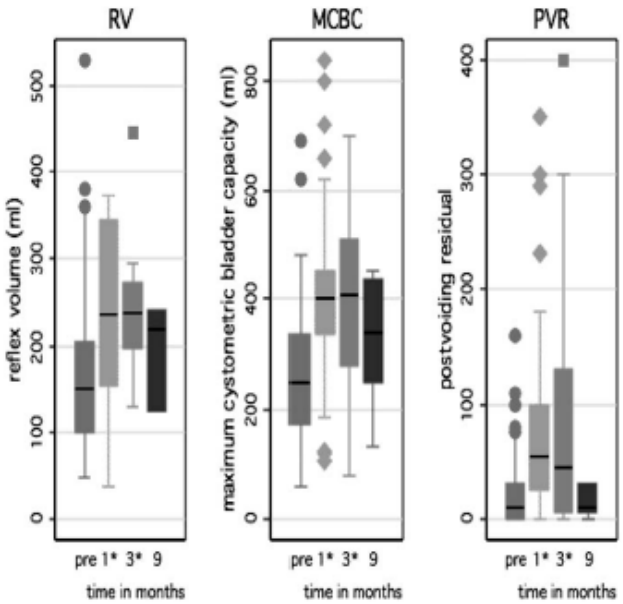


FIG. 1. Median RV, MCBC and PVR (25th and 75th percentiles) before (*pre*), and 1, 3 and 9 months after intradetrusor BTX-A injections in 100, 100, 80 and 20 patients, respectively.

BoNT in OAB: RCT Evidence

1. Sahai. Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial. J Urol.2007;177:2231

2. Brubaker. Refractory idiopathic urge urinary incontinence and botulinum A injection. J Urol. 2008;180:217

3. Flynn. Outcome of a randomized, double-blind, placebo controlled trial of botulinum A toxin for refractory overactive bladder. J Urol. 2009;181:2608

4. Dmochowski. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial.J Urol. 2010; 184: 2416

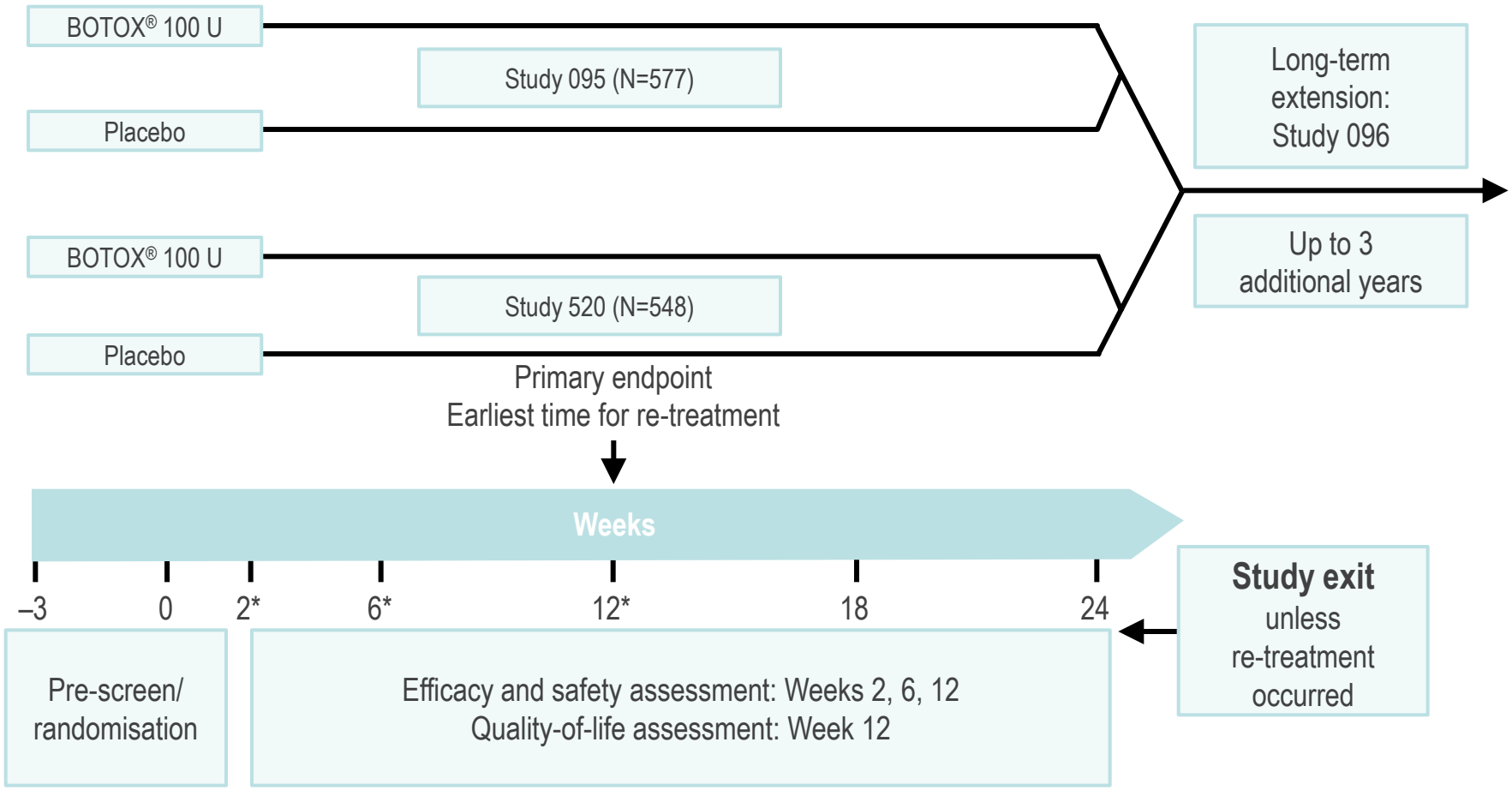
5. Denys P. Efficacy and Safety of Low Doses of Botulinum Toxin Type A for the Treatment of Refractory Idiopathic Overactive Bladder: A Multicentre, Double-Blind, Randomised, Placebo-Controlled Dose-Ranging Study. Eur Urol 2011; 25

6.Tincello DG Botulinum toxin a versus placebo for refractory detrusor overactivity in women: a randomised blinded placebo-controlled trial of 240 women (the RELAX study). Eur Urol. 2012;62:507

7.Nitti. EMBARK Study Group. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol. 2013;189:2186

8.Chapple. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2013;64:249

Two phase III pivotal trials (Embark Allergan® Trials)



EMBARK inclusion criteria of phase III pivotal studies

Population of patients with iOAB

- ≥3 urinary urgency incontinence episodes (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

Study 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)

I-QOL, Incontinence quality-of-life questionnaire; KHQ, King's Health Questionnaire.

1. ClinicalTrials.gov. Identifier: NCT00910845. Available from www.clinicaltrials.gov. Last accessed January 2013.
2. ClinicalTrials.gov. Identifier: NCT00910520. Available from www.clinicaltrials.gov. Last accessed January 2013.

Demographics and baseline characteristics

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 (mean, kg/m^2)	29.9	30.9
Duration of iOAB (years)	6.04	6.14
Number of prior anticholinergics used (mean)	2.4	2.5
Urinary incontinence episodes (per 24 hours)	**5.49**	**5.39**
Urgency episodes (per 24 hours)	**8.82**	**8.31**
Micturition episodes (per 24 hours)	11.99	5.39
Nocturia episodes (per 24 hours)	2.17	2.04
Volume voided per micturition (mL)	150.37	156.89

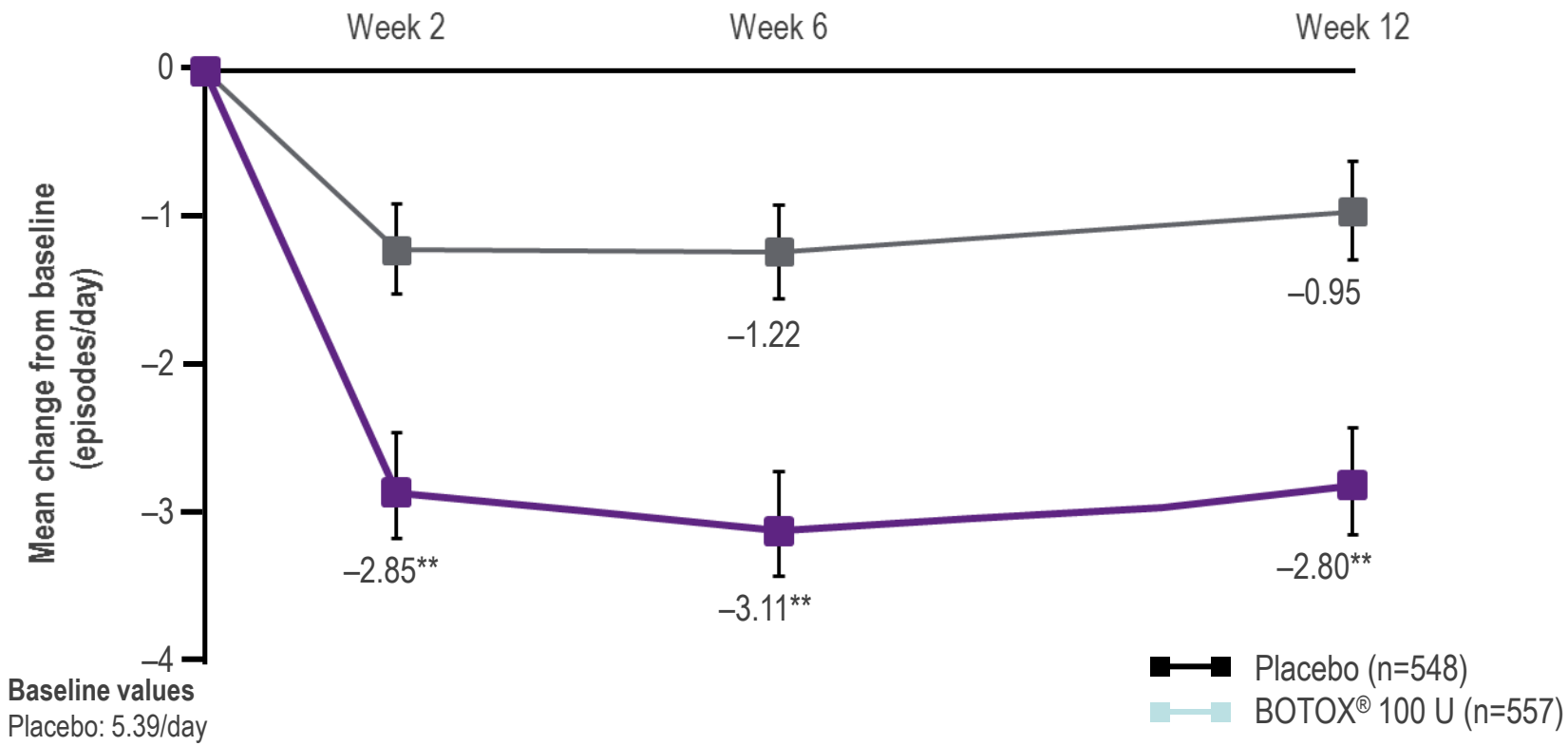
Groups were well balanced with no significant differences between treatment groups.

BMI, body mass index; iOAB, idiopathic overactive bladder; OAB, overactive bladder.

1. Allergan Data on File.

Primary Endpoint:

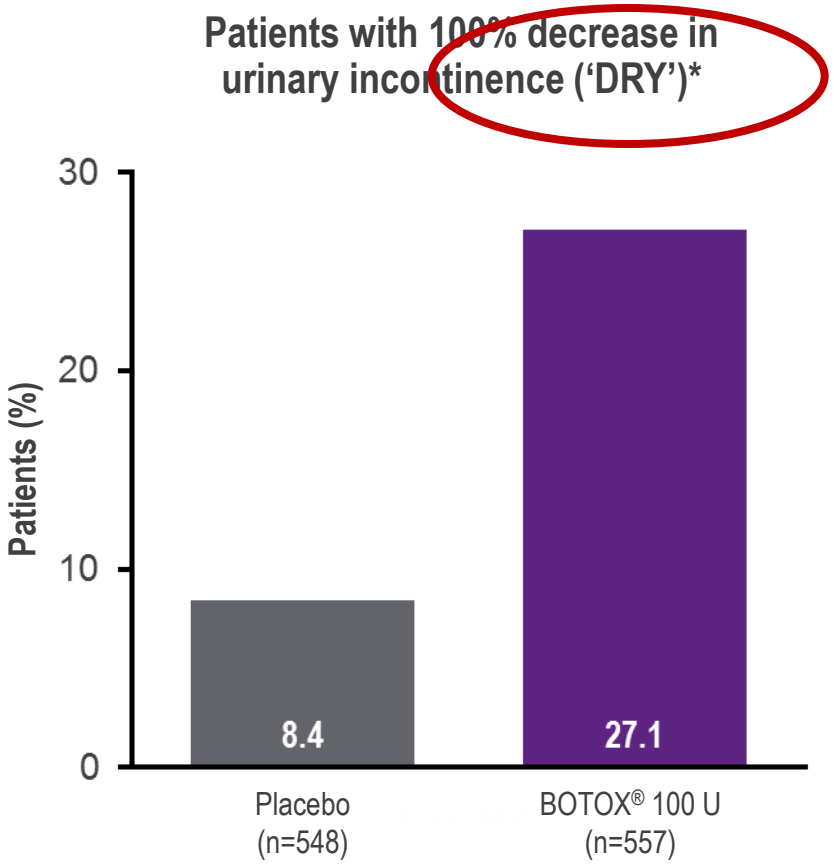
At Week 12: 51% reduction from baseline in UI episodes versus 18% with placebo (p<0.001)

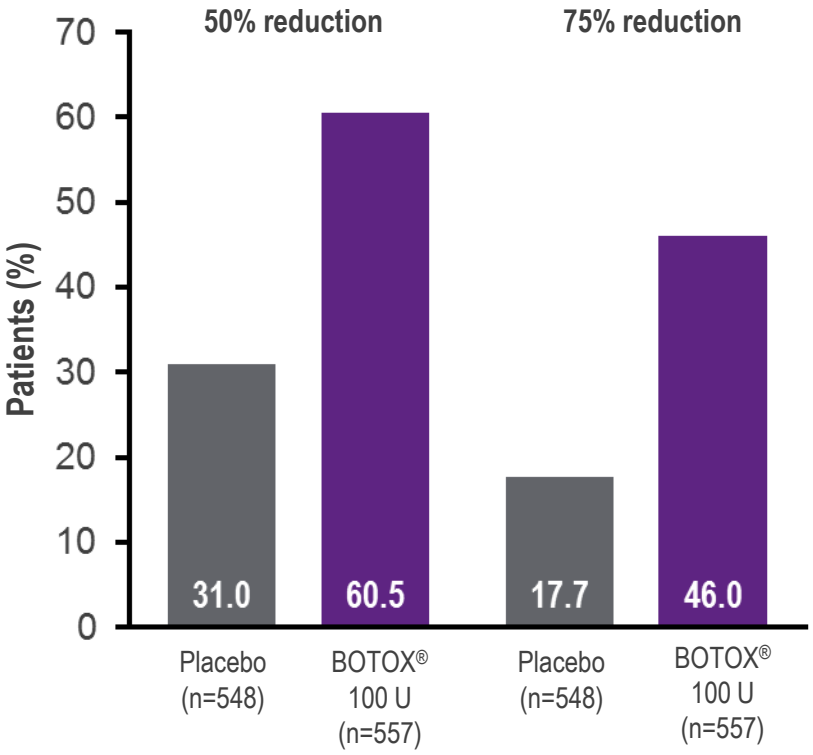


Baseline values
Placebo: 5.39/day
BOTOX® 100 U: 5.49/day

Chappel Eur Urol. 2013 Aug;64(2):249-56 Nitti J Urol. 2013 Jun;189(6):2186-93.

Urinary incontinence



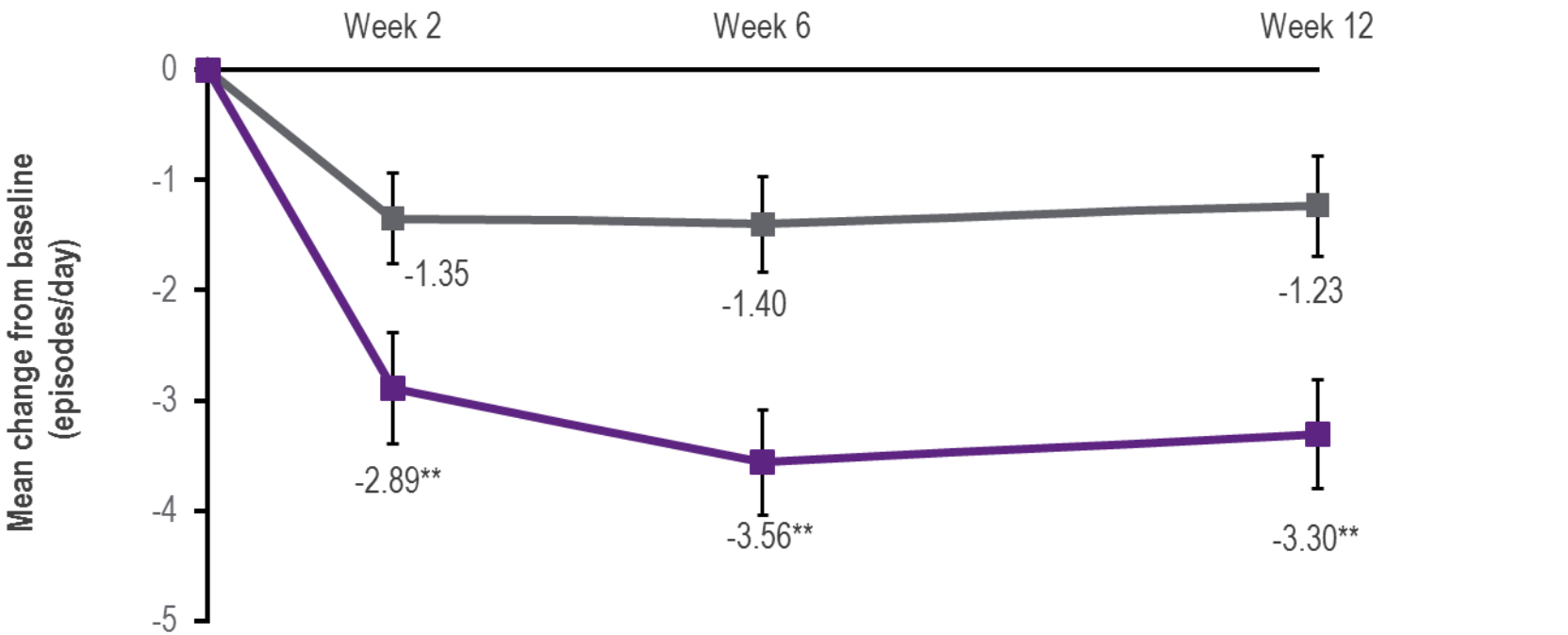


*Patients must have had no incontinence episodes in the 3 days preceding the 12-week time point.

Chappel Eur Urol. 2013 Aug;64(2):249-56 Nitti. J Urol. 2013 Jun;189(6):2186-93.

Daily urgency episodes

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



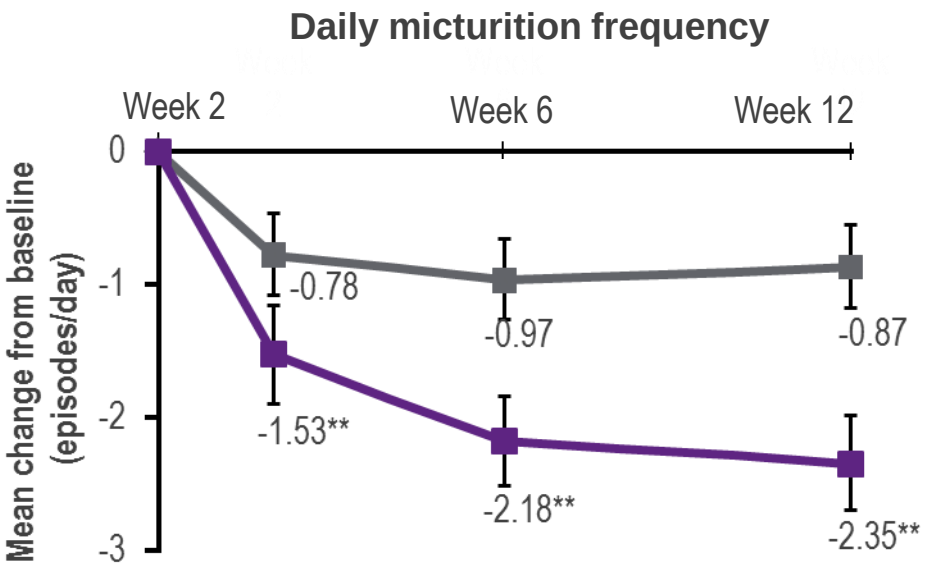
Baseline values
Placebo: 8.31/day
BOTOX® 100 U: 8.82/day

**p<0.001.

**p<0.001 vs. placebo.

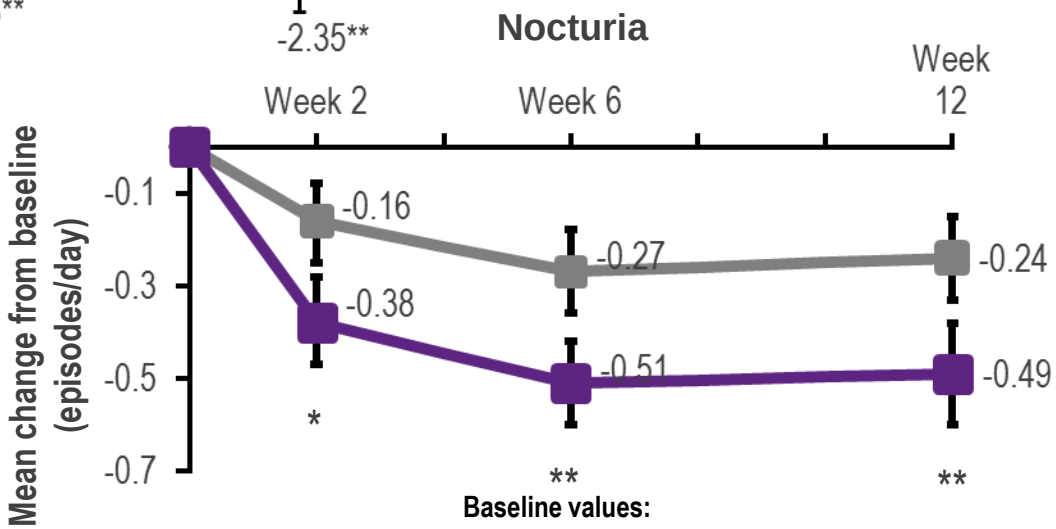
Chappel Eur Urol. 2013 Aug;64(2):249-56 Nitti. J Urol. 2013 Jun;189(6):2186-93.

Daily micturition frequency and nocturia



Baseline values:
Placebo: 11.48/day
BOTOX® 100 U: 11.99/day

At Week 12,
a 20% reduction from baseline in daily micturition frequency versus 8% with placebo (p<0.001)
and a
21% reduction from baseline in nocturia versus 12% with placebo (p<0.05)



Placebo (n=548)
BOTOX® 100 U (n=557)

*p≤0.05; **p<0.001 vs. Placebo.

Baseline values:
Placebo: 2.04/day
BOTOX® 100 U: 2.17/day

Chappel Eur Urol. 2013 Aug;64(2):249-56 Nitti. J Urol. 2013 Jun;189(6):2186-93.

The median duration of response following botulinum toxin A treatment, based on patient request for re-treatment,
was 166 days (~5.5 months)

Chappel Eur Urol. 2013 Aug;64(2):249-56 Nitti. J Urol. 2013 Jun;189(6):2186-93.

Definitions for adverse events

	EMBARK study
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)

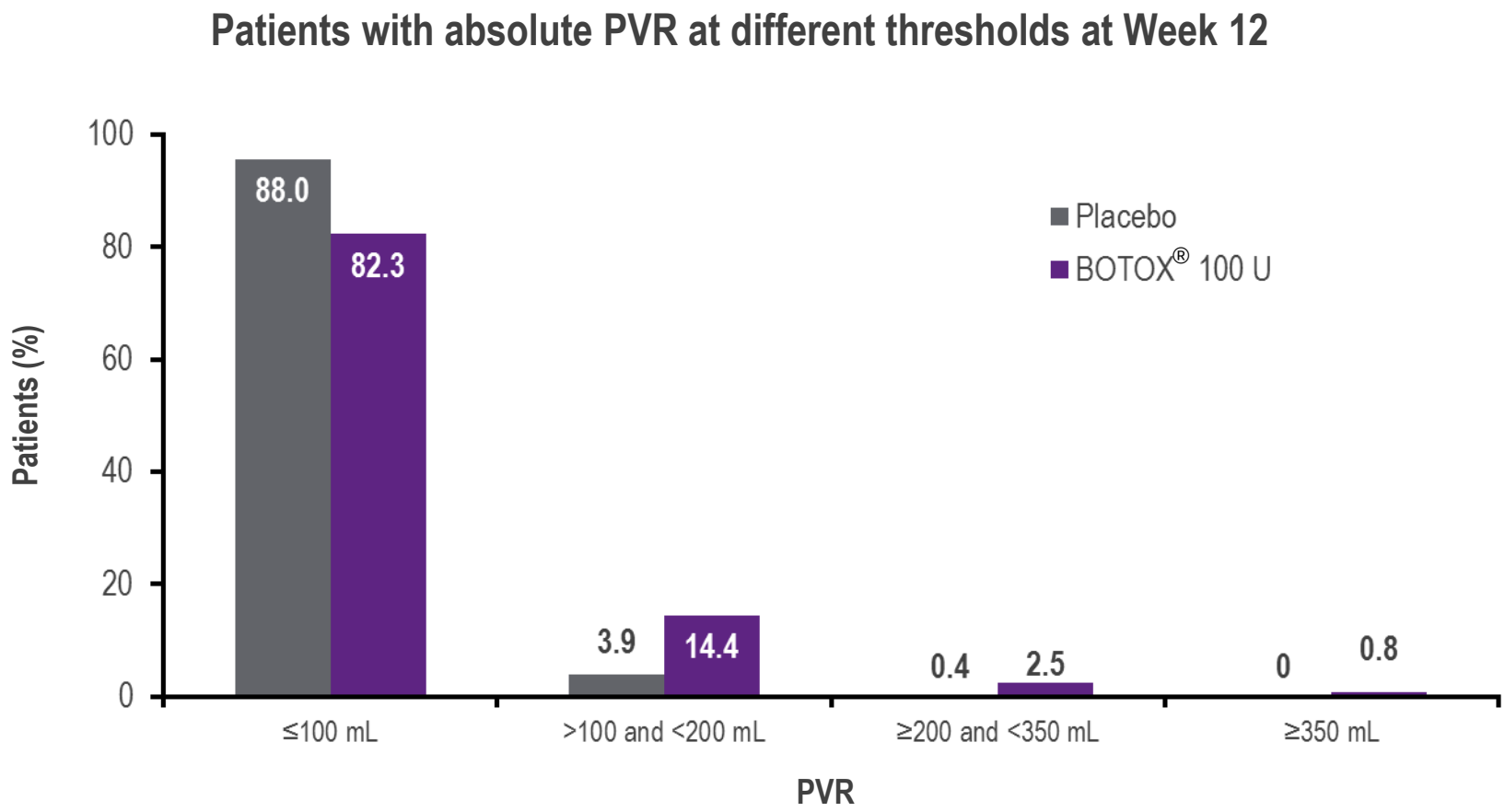
CFU, colony-forming units; CIC, clean intermittent catheterisation;
HPF, high-power field; PVR, post-void residual; UTI, urinary tract infection.

Chappel Eur Urol. 2013 Aug;64(2):249-56 Nitti. J Urol. 2013 Jun;189(6):2186-93.

Urinary tract infection and dysuria

Adverse event ≥3%, n (%)	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)

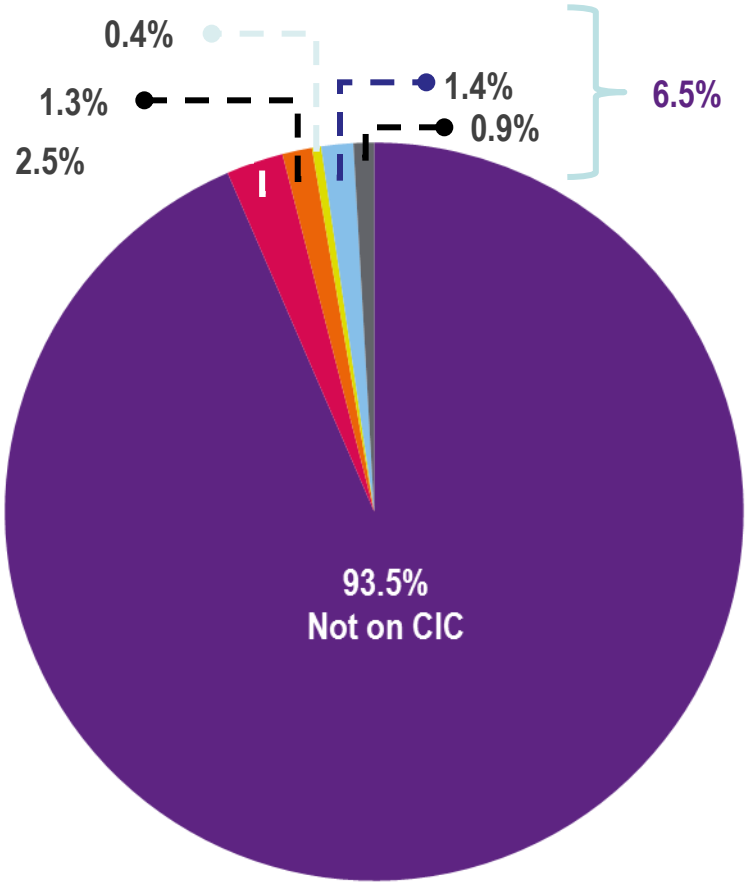
PVR ≤100 mL



PVR, post-void residual.

Chappel Eur Urol. 2013 Aug;64(2):249-56 Nitti. J Urol. 2013 Jun;189(6):2186-93.

CIC requirement



CIC = 6.5% (36/552 patients)*

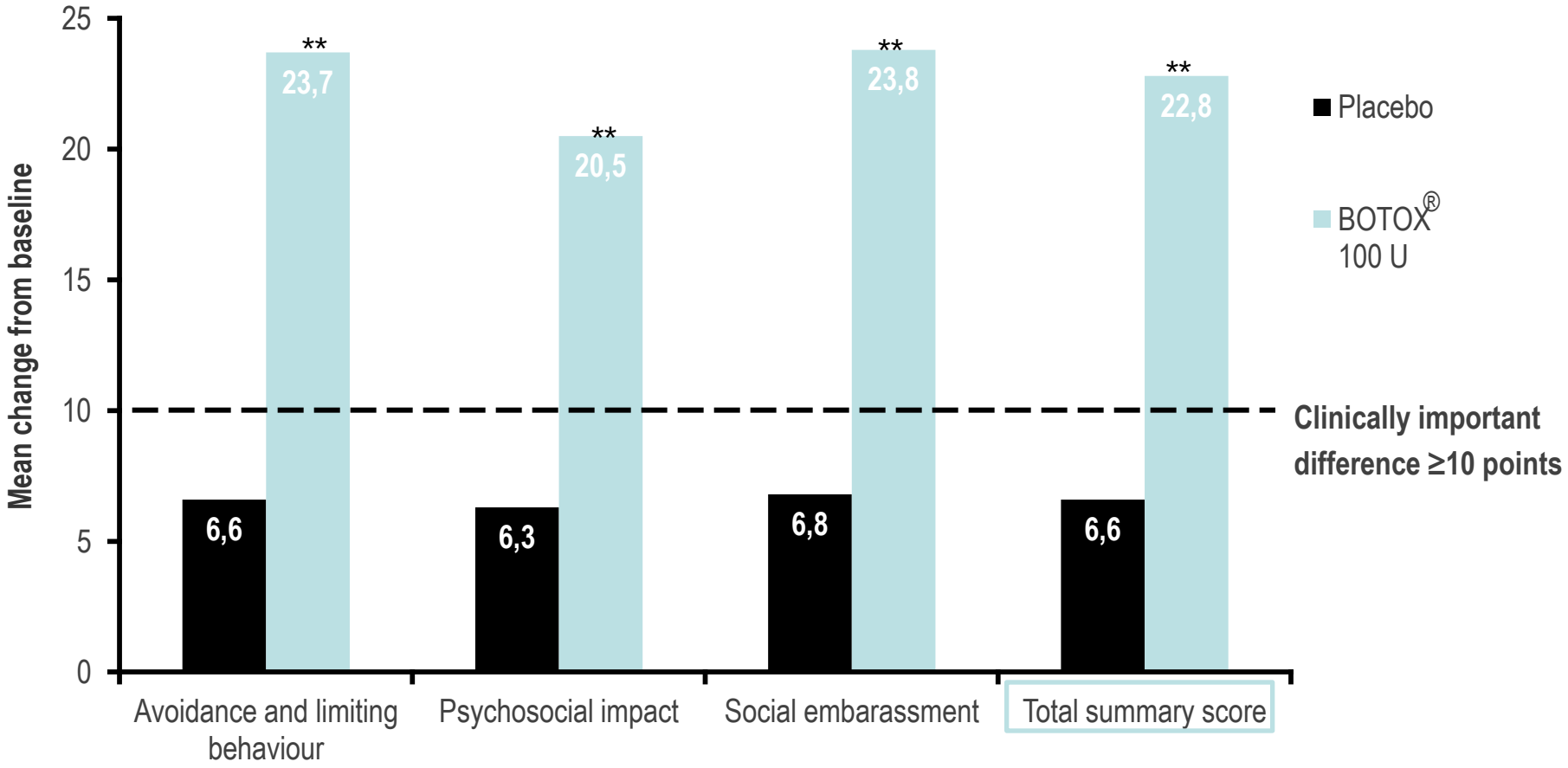
% of Patients

- Did not initiate CIC
- Used CIC ≤6 weeks
- Used CIC >6 and ≤12 weeks
- Used CIC >12 and ≤18 weeks
- Used CIC >18 and ≤24 weeks
- Used CIC >24 weeks

*Patients requiring CIC at any point during treatment cycle 1.
CIC, clean intermittent catheterisation.

Chappel Eur Urol. 2013 Aug;64(2):249-56 Nitti. J Urol. 2013 Jun;189(6):2186-93.

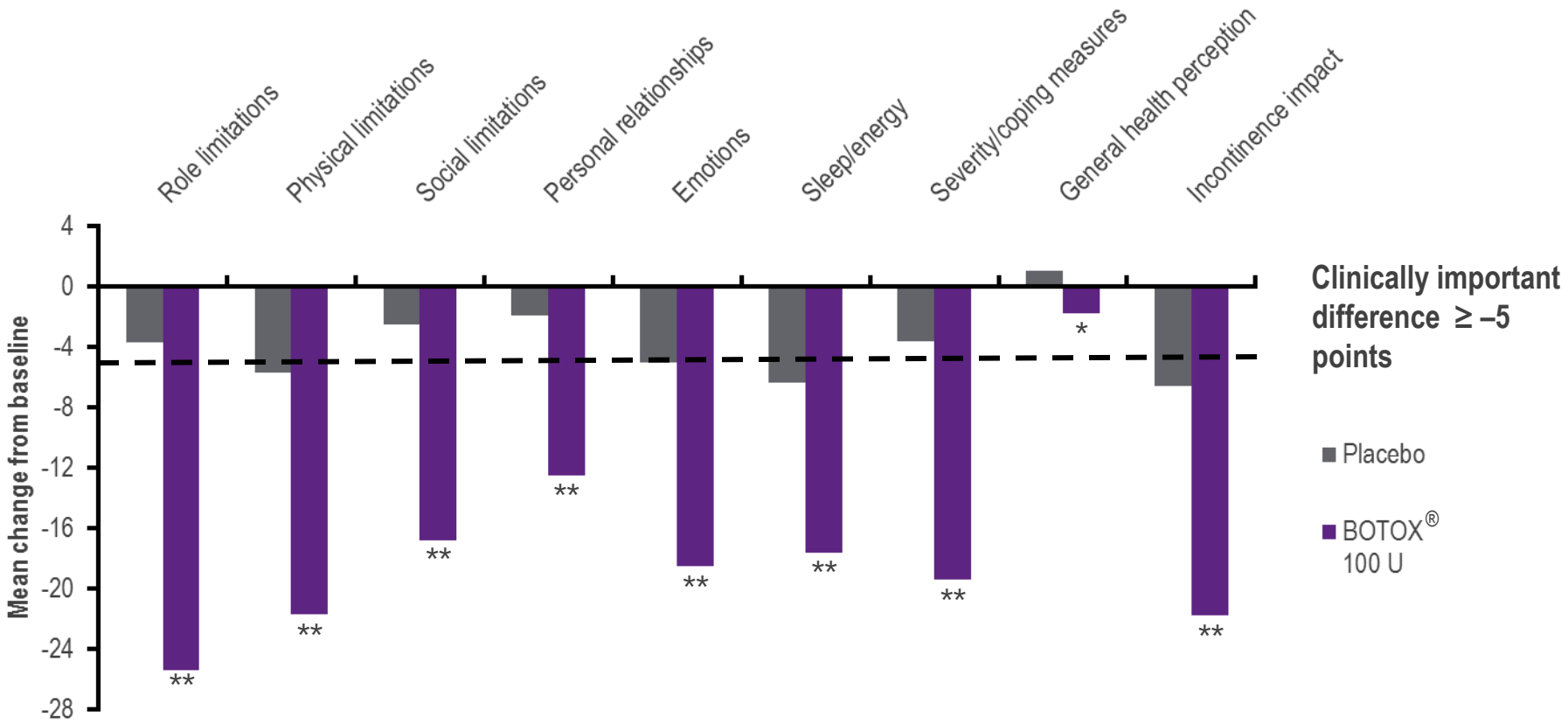
Change from baseline in I-QOL domain scores at Week 12



**p<0.0001 vs. placebo.
I-QOL, Incontinence quality-of-life questionnaire.

Adapted from Allergan Data on File - 002.
ISE Tables 3–54 to 3–54.3.

Change from baseline in KHQ domain scores at Week 12



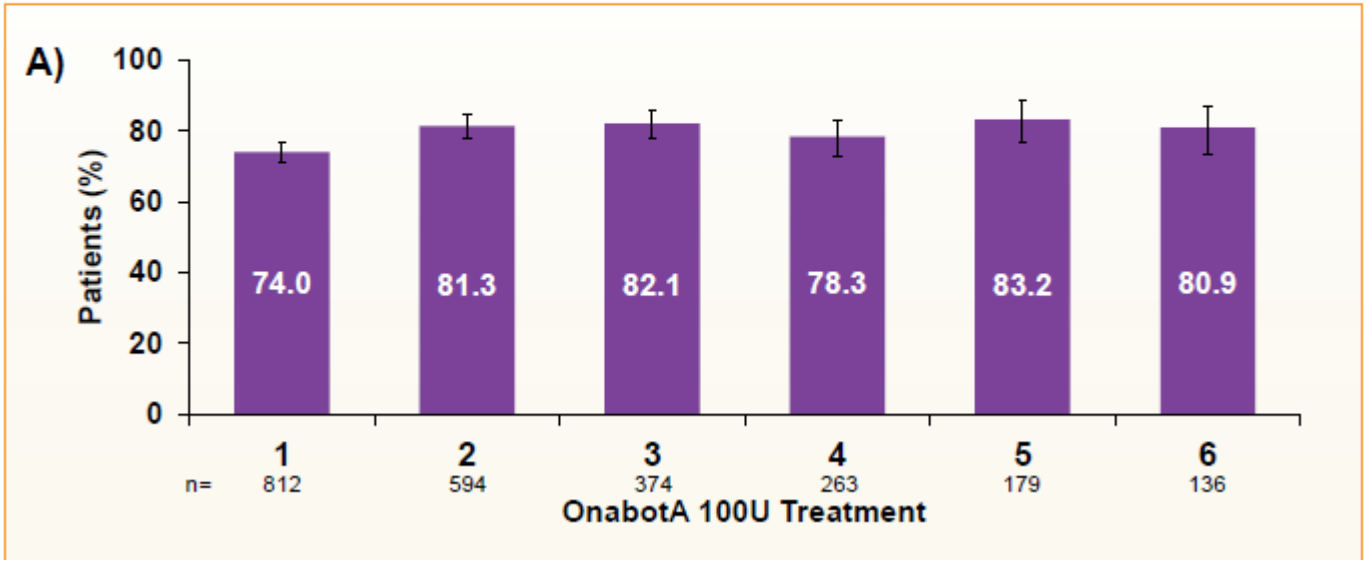
*p≤0.005; **p≤0.001 vs. placebo.
KHQ, King's Health Questionnaire; iOAB, idiopathic overactive bladder.
Adapted from Allergan Data on File - 002.
ISE Tables 3–59.1 to 3–59.7.

Durable Duration of Effect and Positive Treatment Response With Long-term OnabotulinumtoxinA Treatment in Patients With Overactive Bladder Syndrome: Final Results of 3.5 Years' Study

Dirk De Ridder[1], Victor Nitti[2], David Sussman[3], Peter Sand[4], Karl-Dietrich Sievert[5], Sidney Radomski[6], Brenda Jenkins[7], Yan Zheng[8], Christopher Chapple[9]

Presented at the 30th Annual Congress of the European Association of Urology, 20–24 March 2015, Madrid, Spain

Figure 1. Proportion of Patients Reporting Improvement in Their Urinary Condition at Week 12 in the (A) Overall 100U Population and (B) Discrete Subgroups of Patients



Improvement was defined as patients reporting their urinary condition as 'improved' or 'greatly improved' on the Treatment Benefit Scale at week 12.

OnabotulinumtoxinA Demonstrates Similar Improvements in Urinary Incontinence and Quality of Life Regardless of the Use of Clean Intermittent Catheterization or the Presence of Urinary Tract Infection in Patients With Overactive Bladder

Karel Everaert[1], Jennifer Gruenenfelder[2], Heinrich Schulte-Baukloh[3], Steven Guard[4], Yan Zheng[5], David Sussman[6]

Presented at the 44th Annual Meeting of the International Continence Society (ICS), October 20–24, 2014, Rio de Janeiro, Brazil

35 of 557 patients (6.3%) used CIC for >1 day

Figure 1. Proportion of Patients Reporting a Positive Response (Condition "Greatly Improved" or "Improved") on the TBS at Week 12

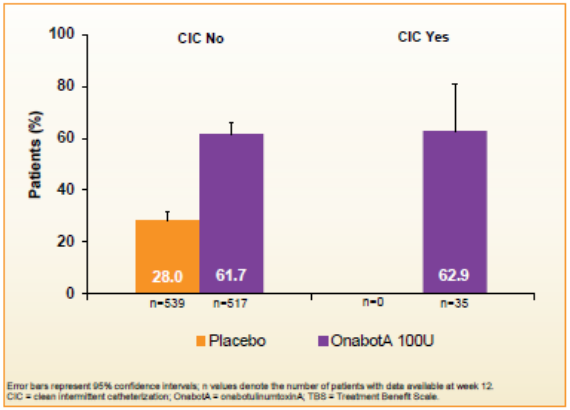
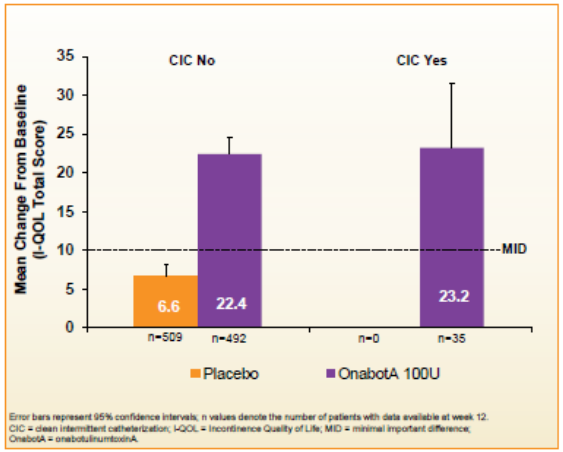


Figure 2. Mean Change From Baseline in I-QOL Total Score at Week 12



UTI occurred in 99 of 557 patients (17.8%)

Figure 3. Proportion of Patients Reporting a Positive Response (Condition "Greatly Improved" or "Improved") on the TBS at Week 12

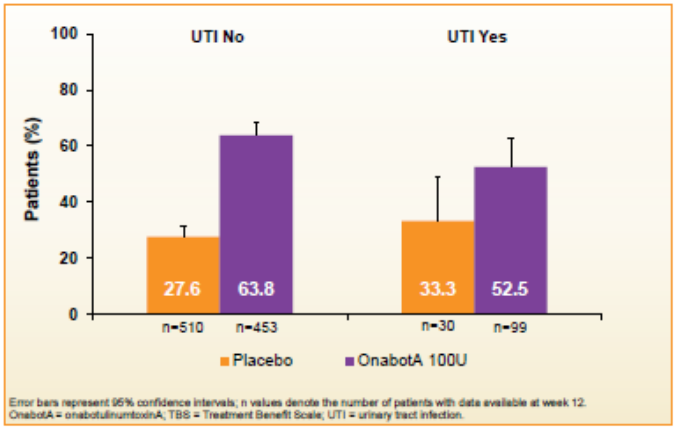
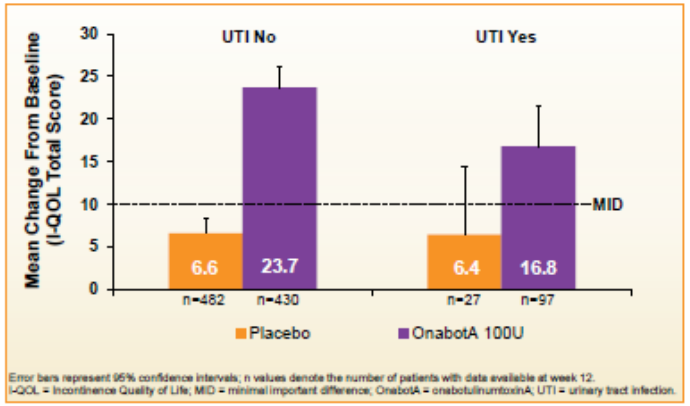
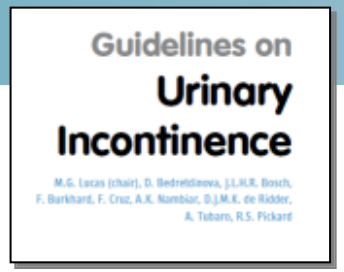
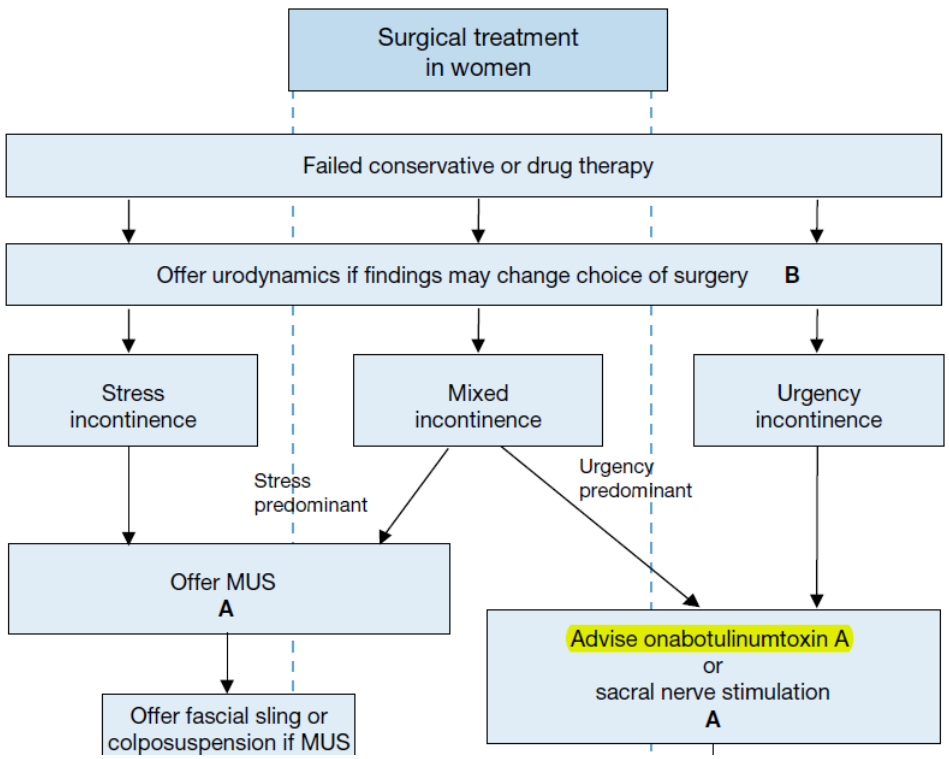


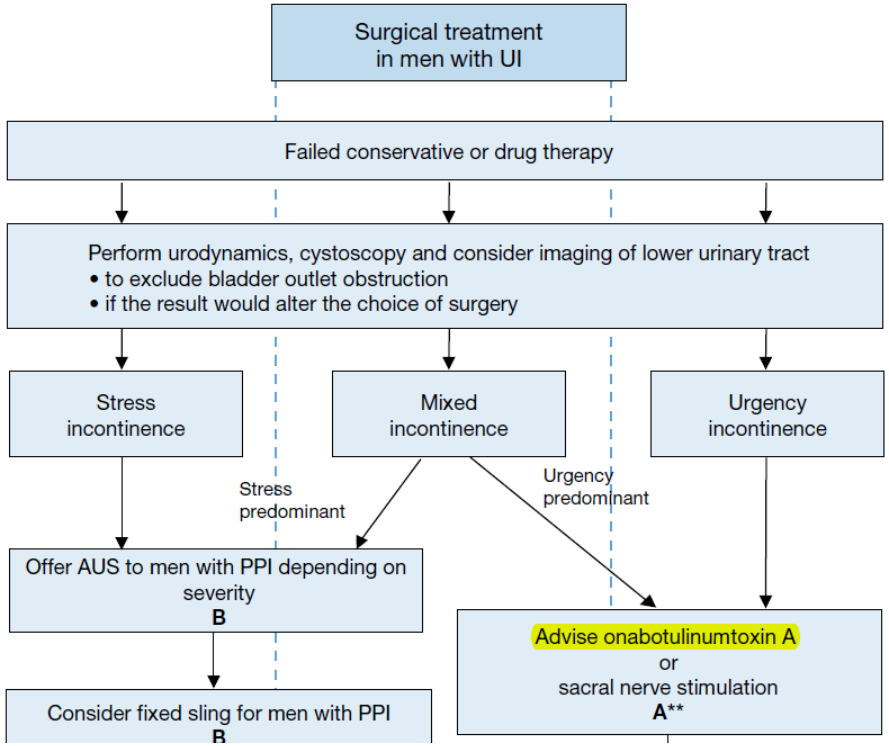
Figure 4. Mean Change From Baseline in I-QOL Total Score at Week 12





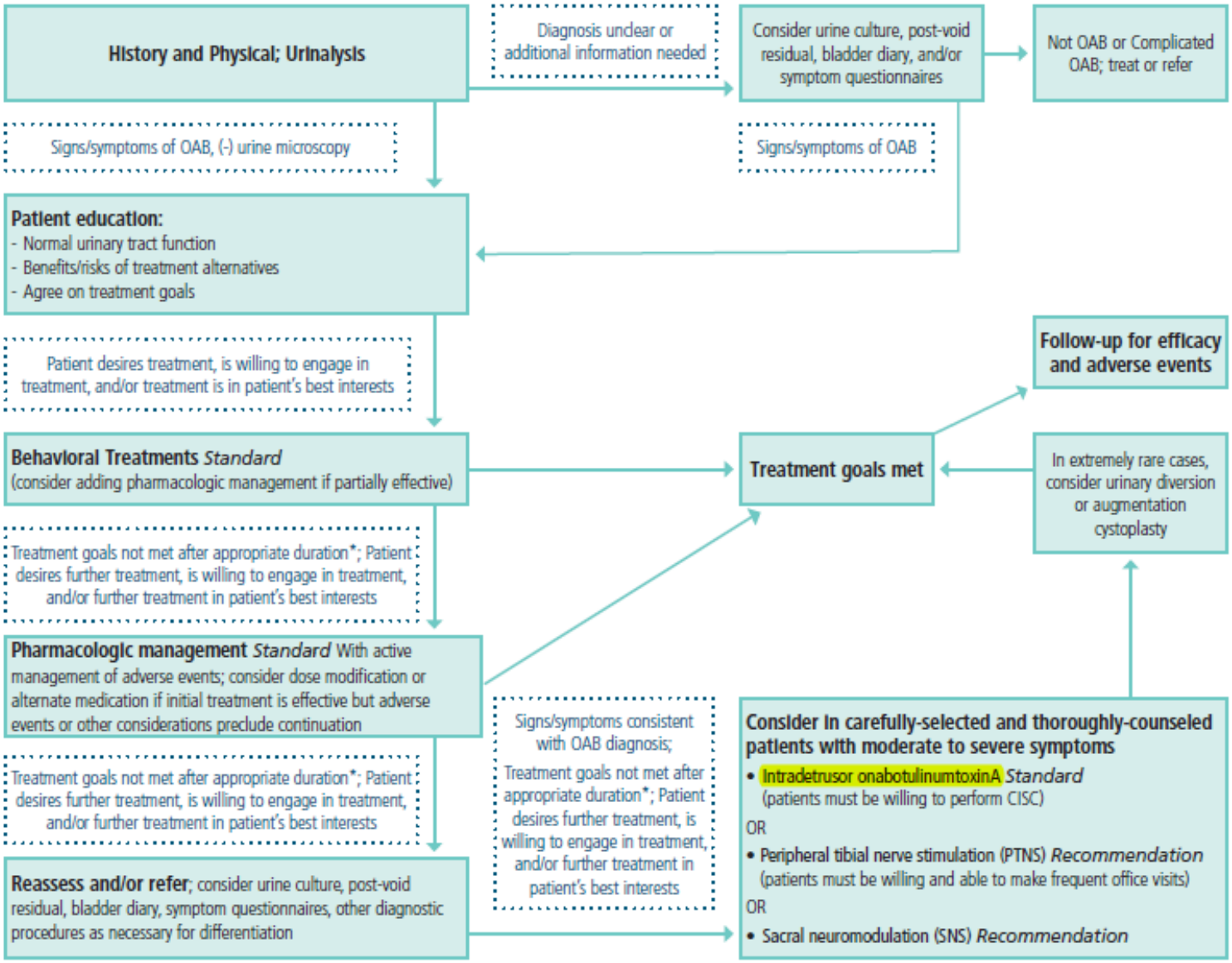
EAU guidelines 2015





Recommendations	GR
Offer bladder wall injections of onabotulinum toxin A (100 units) to patients with urgency urinary incontinence refractory to antimuscarinic therapy.	A
Warn patients of the limited duration of response, risk of UTI and the possible prolonged need to selfcatheterise (ensure that they are willing and able to do so) and risk of UTI.	A

Diagnosis & Treatment Algorithm: AUA/SUFU Guideline on Non-Neurogenic Overactive Bladder in Adults



Contemporary Management of Lower Urinary Tract Disease With Botulinum Toxin A: A Systematic Review of Botox (OnabotulinumtoxinA) and Dysport (AbobotulinumtoxinA)

Altaf Mangera [a,], Karl-Erik Andersson [b], Apostolos Apostolidis [c], Chris Chapple [a], Prokar Dasgupta [d], Antonella Giannantoni [e], Stavros Gravas [f], Stephan Madersbacher [g]*

Conclusions: We identified good-quality studies that evaluated onabotulinumtoxinA for all the indications described above in adults; such was not the case with abobotulinumtoxinA. Although this does not imply that onabotulinumtoxinA is more effective than abobotulinumtoxinA, it should be a consideration when counselling patients on the use of botulinum toxin in urologic applications. The two preparations should not be used interchangeably, either in terms of predicting outcome or in determining doses to be used.

BOTOX® in urology

- BOTOX® is licensed in most European countries for the management of urinary incontinence in adults with neurogenic detrusor overactivity due to stable sub-cervical **spinal cord injury or multiple sclerosis**

- Most recently, BOTOX® has been licensed in several countries for the treatment of **urge incontinence** due to idiopathic overactive bladder in adult patients who have an inadequate response to, or are intolerant of, anticholinergic medication

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anticholinergic Therapy vs. OnabotulinumtoxinA for Urgency Urinary Incontinence

Anthony G. Visco, M.D., Linda Brubaker, M.D., Holly E. Richter, Ph.D., M.D.,

RCT, n = 241

Table 2. Secondary Outcomes: Efficacy, Quality of Life, and Adverse Events.

Outcome	Anticholinergic Drug	OnabotulinumtoxinA	P Value*
Efficacy outcome†			
Complete resolution of urgency urinary incontinence — no./total no. (%)‡	16/119 (13)	30/112 (27)	0.003
Complete resolution of all incontinence — no./total no. (%)‡	13/119 (11)	26/112 (23)	0.003
>75% reduction in episodes of urgency urinary incontinence — no./total no.(%)‡	48/119 (40)	61/112 (54)	0.06
Change from baseline in score on OABq-SF§			
Symptom-severity scale	−44.55	−44.08	0.87
Quality-of-life scale	37.05	37.13	0.98
Change from baseline in PFDI-SF total score¶	−43.69	−48.20	0.47
Change from baseline in PFIQ-SF total score‖	−32.82	−33.85	0.88
PGI-I — no./total no. (%)**			
Month 3	59/116 (51)	61/111 (55)	0.37
Month 6	67/116 (58)	60/111 (54)	0.71

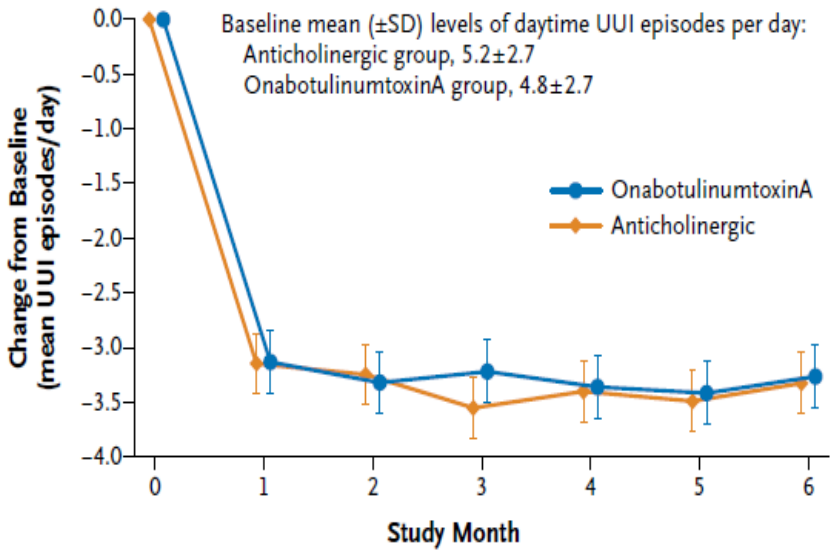


Figure 2. Reduction from Baseline in Number of Episodes of Urgency Urinary Incontinence (UUI) per Day.

N Engl J Med 2012;367:1803-13.
DOI: 10.1056/NEJMoa1208872

Botulinum toxin: yes, but…

- Cohort studies have shown the effectiveness of bladder wall injections of onabotA in the elderly and frail elderly, though the success rate might be lower and the PVR (> 150 mL) higher in this group.
- Small number of males included in the registration trials.
- Botox is licenced in Europe to treat OAB with persistent or refractory UUI in adults
- The continued efficacy of repeat injections is the rule but discontinuation rate may be high

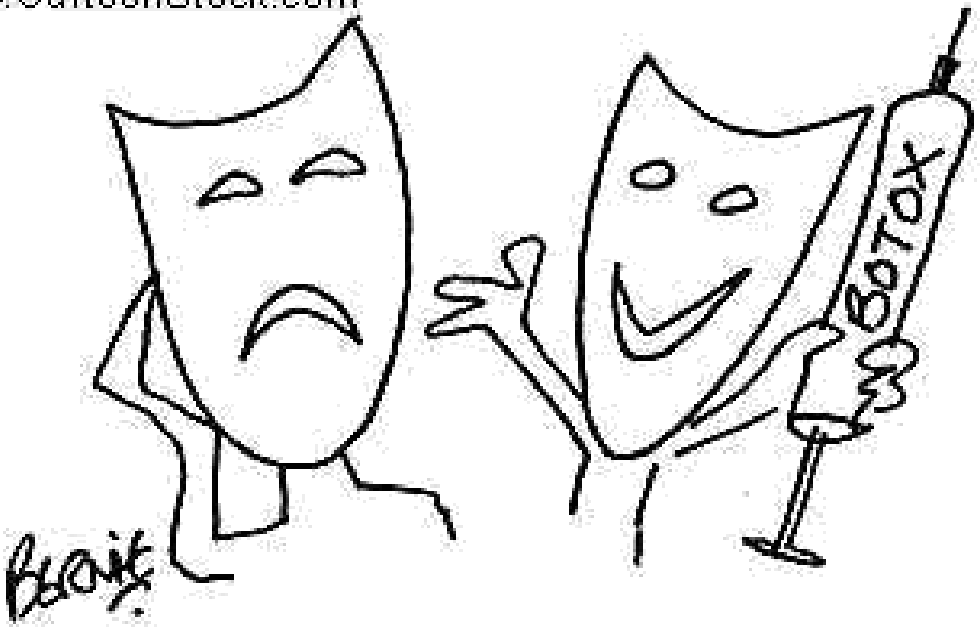
Table 1. Causes of OnabotulinumtoxinA treatment discontinuation (2007-2014)

	Hospital A		Hospital B		Total	
	N	%	N	%	N	%
Patients interviewed	73		93		166	
Discontinuation rates	29	39,7	43	46,2	72	43,4

Table 2. Reasons of the Discontinuation rates of treatment groups

	HOSPITAL A		HOSPITAL B		TOTAL	
	n	%	n	%	n	%
N	29		43		72	
Expectations	22	75,9	26	60,5	48	66,7
Hospital access difficulties	4	13,8	9	20,9	18	25
Complications	1	3,4	8	18,6	9	12,5
Unknown	2	6,9	0	0	2	2,8

Adherence BoNT



TRAGEDY & REMEDY