W1: Botulinum Toxin-A for refractory Overactive Bladder: Efficacy, Mechanism of action and Practical Tips and Tricks.

Workshop Chair: Arun Sahai, United Kingdom

26 August 2013 14:00 - 17:00

Start	End	Topic	Speakers
14:00	14:10	Introduction, Formulations and Terminology	• Arun Sahai
14:10	14:35	Mechanism of action of botulinum toxin-A in the bladder	• Christopher Fry
14:35	14:40	Questions	All
14:40	15:05	Botulinum toxin-A in the management of neurogenic detrusor overactivity	• Jalesh Panicker
15:05	15:10	Questions	All
15:10	15:30	Cases / Discussion	All
15:30	16:00	Break	None
16:00	16:25	Botulinum toxin-A in the management of refractory overactive bladder and other forms of lower urinary tract dysfunction	• Arun Sahai
16:25	16:30	Questions	All
16:30	16:50	Patient assessment, technique of administration, tips and tricks in the use of bladder botulinum toxin-A	• Thomas Kessler
16:50	16:55	Questions	All
16:55	17:00	Discussion	All

Aims of course/workshop

Botulinum toxin-A is an effective treatment option for treating refractory overactive bladder and detrusor overactivity. This workshop will provide an overview of the published literature on the subject but will focus on level I evidence. Its use in neurogenic bladder, bladder oversensitivity and painful bladder syndrome will also be discussed. Current knowledge on mechanism of action will be presented. The workshop will deliver practical points, technical aspects of drug delivery, tips and tricks which will be helpful to both new and established users.

Botulinum Toxin-A for refractory Overactive Bladder: Efficacy, Mechanism of action and Practical Tips and Tricks

Formulations and terminology – Arun Sahai

FDA approved products and updated terminology (from FDA website)

Summary of FDA-Approved Botulinum Toxin Products			
Trade Name*	**NEW Drug Name**	**OLD Drug Name**	**Indication**
Botox	OnabotulinumtoxinA	Botulinum toxin type A	Cervical dystonia, Severe primary axillary hyperhidrosis, Strabismus, Blepharospasm
Botox Cosmetic	OnabotulinumtoxinA	Botulinum toxin type A	Temporary improvement in the appearance of moderate to severe glabellar lines
Dysport	AbobotulinumtoxinA	Botulinum toxin type A	Cervical dystonia, Temporary improvement in the appearance to moderate to severe glabellar lines
Myobloc	RimabotulinumtoxinB	Botulinum toxin type B	Cervical dystonia
* The marketed trade names and the product formulations have not changed.			

Botulinum Toxin – Mechanism of Action CH FRY

Botulinum toxin (BoNT) is produced mainly by the gram-postive anaerobic bacterium *Clostridium botulinum*. There are at least seven serologically distinct forms (BoNT-A to BoNT-G) with similar effects. BoNT is expressed as single polypeptide (≈150 kDa), with several functional sections (Fig 1-1). BoNT binds to a receptor on the surface membrane (e.g. SV2) or the target cell where it is internalised and cleaved to generate an active light chain that prevents fusion of neurotransmitter vesicles to the surface membrane. This it achieves through cleavage of proteins of the SNARE complex that facilitate vesicle fusion (Fig 1-2). The precise steps will be discussed in the workshop. Although most discussion concerns the action of BoNT at cholinergic neuromuscular junctions, there is in principle no reason why a similar action should not occur at other cells capable of vesicular exocytosis.

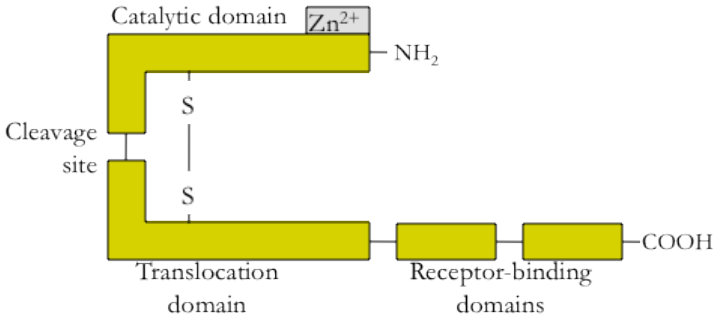


Fig 1-1 The structure of botulinum toxin

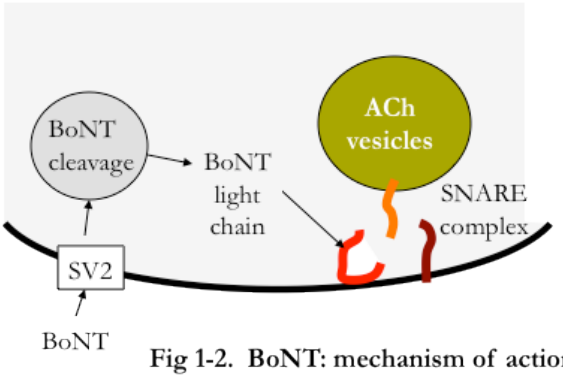


Fig 1-2. BoNT: mechanism of action

BoNT receptors have been identified on the surface membranes of several cell types – such as neurons and epithelia. Their differences will be discussed as a means to develop tissue specific toxins that may be of clinical use.

In the context of management of bladder dysfunction with BoNT a number of questions arise that will be addressed in turn during the workshop:

i) What is the extent of the distribution of BoNT after injection
ii) Does BoNT act on parasymapthetic cholinergic nerves to reduce efferent activation of detrusor smooth muscle
iii) Does BoNT act on the sensory arm of the micturition reflex to reduce afferent function.
iv) If there is evidence for BoNT acting on the sensory arm does it act on afferent nerves.
v) If there is evidence for BoNT acting on the sensory arm does it act on urothelium.

There are data from urodynamic measurements as well as investigative laboratory studies. The latter include results from animal experiments to investigate the fundamental modes of action of BoNT as well as from huamn tissue obtained from bladders that have previously been treated with BoNT. The above questions will be addressed as follows.

i) BoNT distribution after injection has been assessed by measuring the appearance of SV2 and SNARE complex fragments, indicative of a biological action. The data suggest that there is a considerable area of distribution.
ii) BoNT can affect nerve-mediated bladder contractions. Points to be discussed in the workshop will be its efficacy of action in this context and if it affects equally the release of all excitatory neurotransmitters
iii) There is urodynamic evidence that BoNT affects the sensory arm of the micturition reflex and this will be discussed in the workshop
iv) Experimental evidence indicates that BoNT can alter afferent nerve firing during filling. Does BoNT have a primary effect on afferent nerves or is afferent function modulated due to the action of BoNT on sensory transducers that influence afferent firing.
v) During physical and chemical stresses to the bladder wall the urothelium releases several substances that may act as sensory mediators. The evidence that BoNT can influence the release of these modulators will be discussed.

The bladder wall also releases inflammatory mediators that may be measured in the urine, and thus are potential biomarkers of underlying conditions that cause bladder dysfunction. The release of such mediators may be altered by BoNT. The value of this observation to be discussed in the workshop is that we can understand more about the control of release of such mediators.

Overall, this section of the workshop will seek to improve our understanding of the mode of action of botulinum toxin in the bladder wall and how this knowledge may be used to control more effectively bladder dysfunction.

Slide 1

Botulinum toxin in NDO

Jalesh Panicker
Consultant Neurologist in Uro-Neurology
The National Hospital for Neurology and Neurosurgery,
Honorary Senior Lecturer,
UCL Institute of Neurology
Queen Square, London, UK

ICS Barcelona August 2013

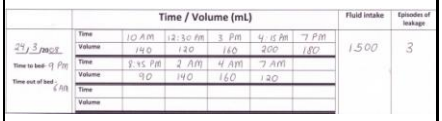
UCL

Slide 2

Case scenario

- 48, female
- Secondary Progressive multiple sclerosis- 10 years
- Optic neuritis, paraparesis
- Urgency, frequency, incontinence
- Hesitancy, straining, double voiding

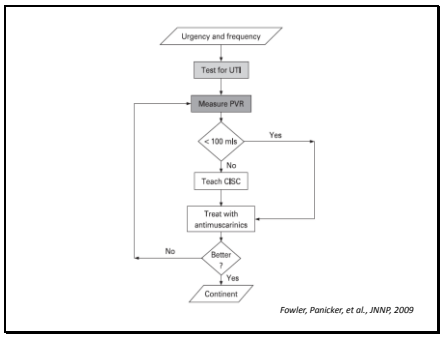
Slide 3



	Time / Volume (mL)					Fluid intake	Episodes of leakage
24/3 pm-8	Time	10 AM	12:30 PM	3 PM	4:15 PM	7 PM	1500	3
Time to bed- 9 PM	Volume	140	120	160	200	180		
Time out of bed- 6 AM	Time	8:15 PM	2 AM	4 AM	7 AM			
	Volume	90	140	160	120			
	Time							
	Volume							

- Bladder scan- PVR 180 mL
- Urine dipstick- normal
- Urodynamics- DO

Slide 4



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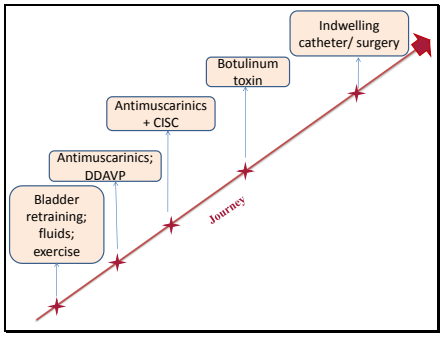


Slide 6

History

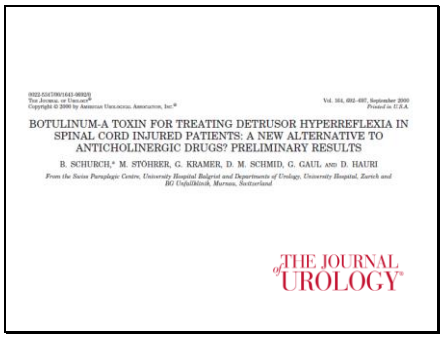
Botulinum toxin for the first time in the lower urinary tract

Dykstra DD et al. Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. J Urol 1988; 139: 919-22.

→ urethral pressure ↓

→ post void residual ↓

Slide 7



BOTULINUM-A TOXIN FOR TREATING DETRUSOR HYPERREFLEXIA IN SPINAL CORD INJURED PATIENTS: A NEW ALTERNATIVE TO ANTICHOLINERGIC DRUGS? PRELIMINARY RESULTS

B. SCHURCH,* M. STÖHRER, G. KRAMER, D. M. SCHMID, G. GAUL, AND D. HAURI

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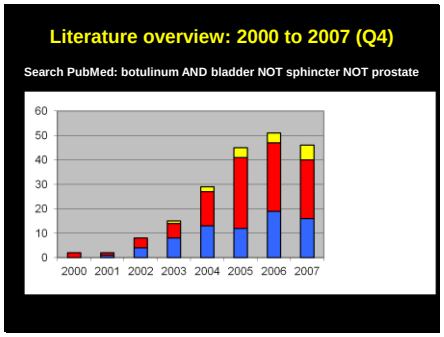

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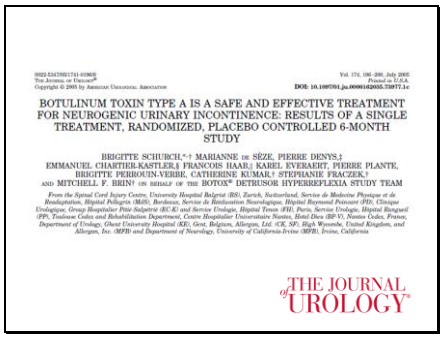

BOTULINUM TOXIN TYPE A IS A SAFE AND EFFECTIVE TREATMENT FOR NEUROGENIC URINARY INCONTINENCE: RESULTS OF A SINGLE TREATMENT, RANDOMIZED, PLACEBO CONTROLLED 6-MONTH STUDY

BRIGITTE SCHURCH,*,† MARIANNE DE SÈZE, PIERRE DENYS,‡ EMMANUEL CHARTIER-KASTLER,§ FRANCOIS HAAB,‖ KAREL EVERAERT, PIERRE PLANTE, BRIGITTE PERROUIN-VERBE, CATHERINE KUMAR,† STEPHANIE FRACZEK,† AND MITCHELL F. BRIN¶ ON BEHALF OF THE BOTOX® DETRUSOR HYPERREFLEXIA STUDY TEAM

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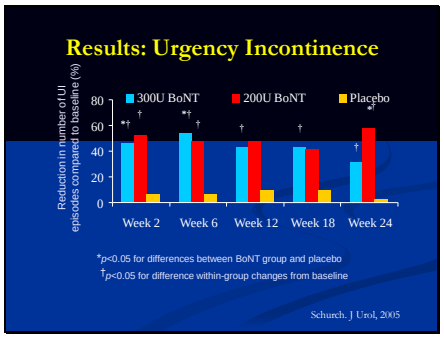

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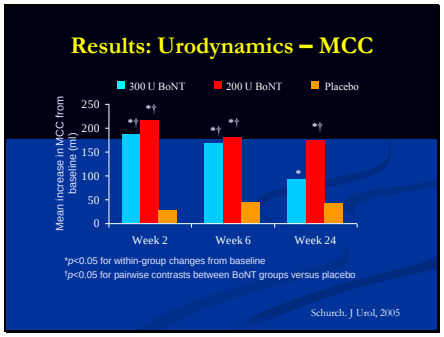

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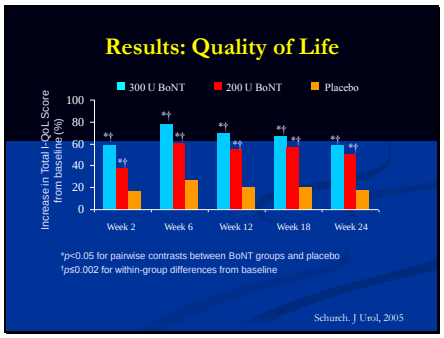

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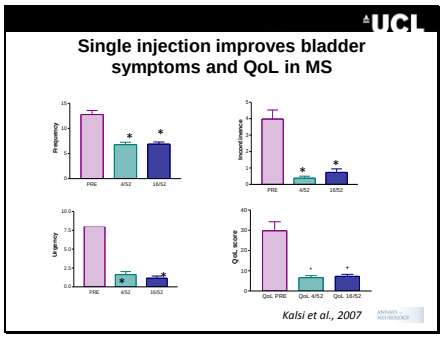

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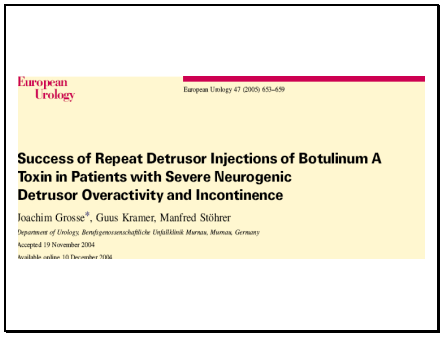

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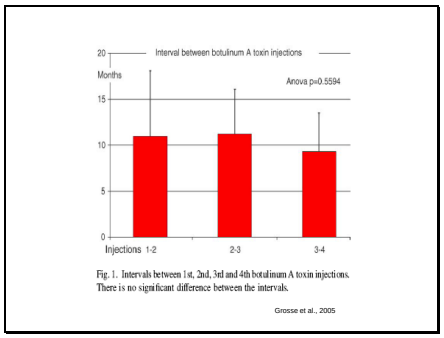

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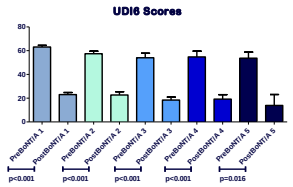
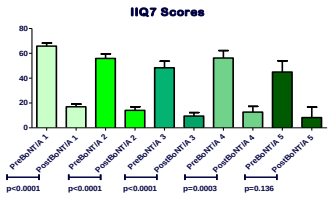
Urogenital symptoms in MS (n=112)



Khan et al. Poster BAUS, 2009

Slide 17

Incontinence



Khan et al. Poster BAUS, 2009

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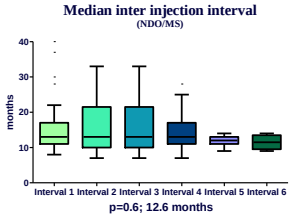

(n=112, MS)

Khan et al. Poster BAUS, 2009

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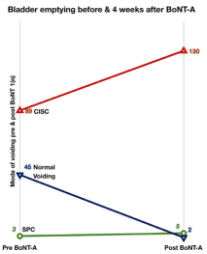
Botulinum toxin for NDO (n=112)

ADVERSE EVENTS (for 252 sessions)	
INFECTION	12.1%
HAEMATURIA	0.39%
LIMB WEAKNESS	1.2%
MS RELAPSE	1.5%
ASTHENIA	7.9%
FLU LIKE SYMPTOMS	2.3%

Khan et al. Poster BAUS, 2009

Slide 20

Open label study of 137 MS patients



Khan S, et al. J Urol. 2011 Apr;185(4):1344-9.

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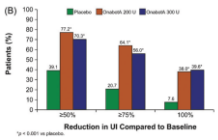

Efficacy and Safety of OnabotulinumtoxinA in Patients with Urinary Incontinence Due to Neurogenic Detrusor Overactivity: A Randomised, Double-Blind, Placebo-Controlled Trial

Francisco Cruz, Sender Herschorn, Philip Aliotta, Mitchell Brin, Catherine Thompson, Wayne Lam, Grace Daniell, John Heesakkers, Cornelia Haag-Molkenteller

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2011

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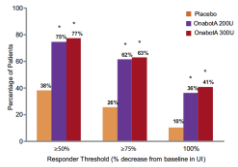

•Time to retreatment: 254 vs. 256 vs. 92 days
•Initiating ISC: 42% vs. 35% vs. 10%
•Commonest adverse effects: UTI, retention

Phase 3 Efficacy and Tolerability Study of OnabotulinumtoxinA for Urinary Incontinence From Neurogenic Detrusor Overactivity

David Ginsberg,*,† Angelo Gousse,‡ Veronique Keppenne, Karl-Dietrich Sievert,§ Catherine Thompson,§ Wayne Lam,§ Mitchell F. Brin, Brenda Jenkins§ and Cornelia Haag-Molkenteller§

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2012

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Inferences

- Onabotulinum toxin A significantly improves symptoms
- Likelihood of ISC: dose dependent
- No clinically relevant benefit in efficacy or duration for 300 U over 200U

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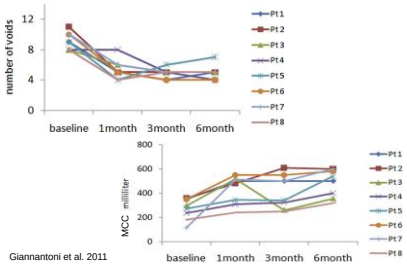
Botulinum toxin in Parkinson's disease?



Giannantoni et al. 2011

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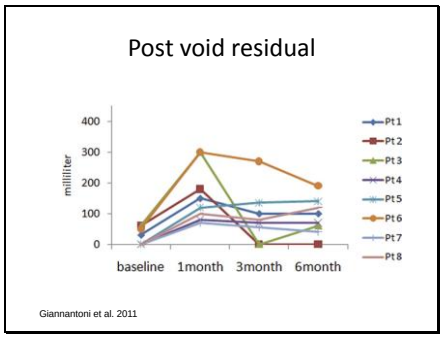

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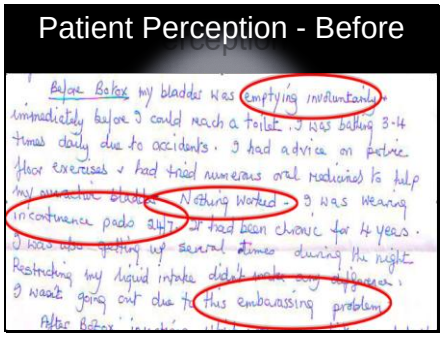

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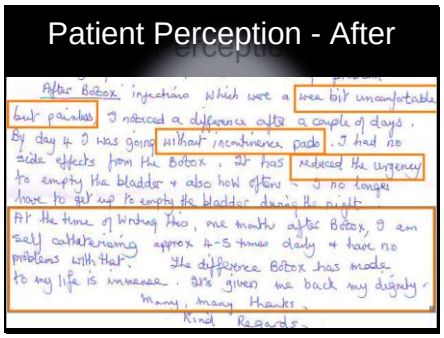

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Slide 29

"botulinum toxin A is the 21st century penicillin for the bladder"

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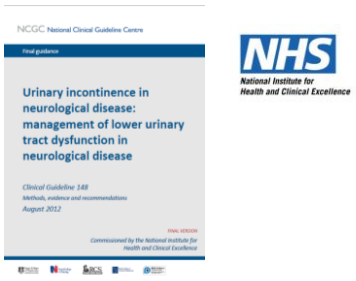

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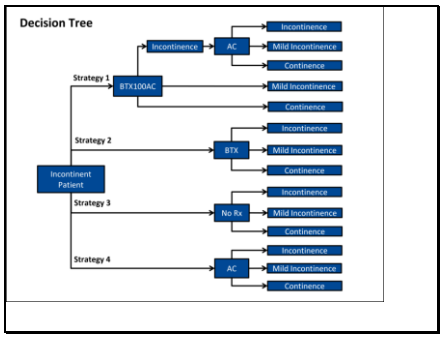

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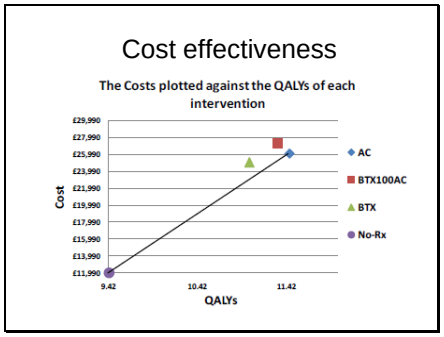

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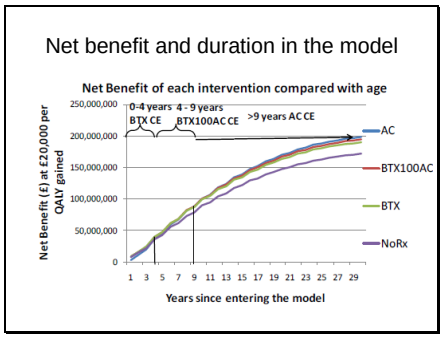

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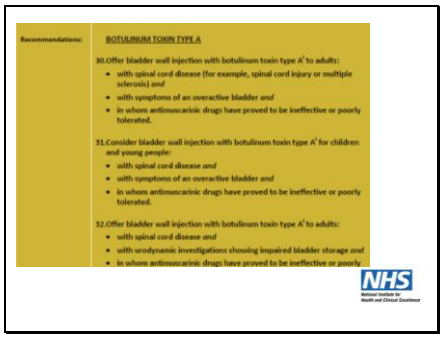

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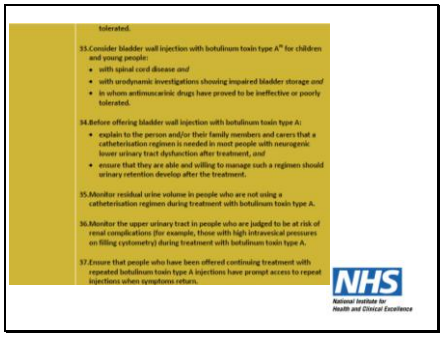

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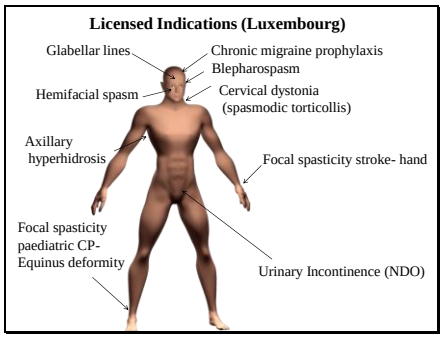

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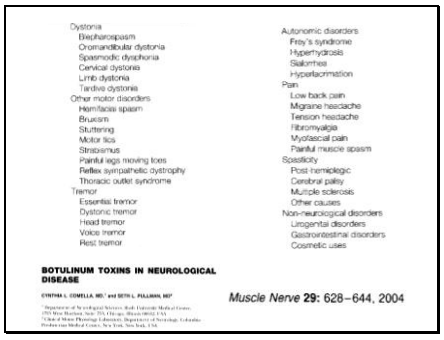
Dystonia
- Blepharospasm
- Oromandibular dystonia
- Spasmodic dysphonia
- Cervical dystonia
- Limb dystonia
- Tardive dystonia

Other motor disorders
- Hemifacial spasm
- Bruxism
- Stuttering
- Motor tics
- Strabismus
- Painful legs moving toes
- Reflex sympathetic dystrophy
- Thoracic outlet syndrome

Tremor
- Essential tremor
- Dystonic tremor
- Head tremor
- Voice tremor
- Rest tremor

Autonomic disorders
- Frey's syndrome
- Hyperhydrosis
- Sialorrhea
- Hyperlacrimation

Pain
- Low back pain
- Migraine headache
- Tension headache
- Fibromyalgia
- Myofascial pain
- Painful muscle spasm

Spasticity
- Post-hemiplegic
- Cerebral palsy
- Multiple sclerosis
- Other causes

Non-neurological disorders
- Urogenital disorders
- Gastrointestinal disorders
- Cosmetic uses

BOTULINUM TOXINS IN NEUROLOGICAL DISEASE

Muscle Nerve **29:** 628–644, 2004

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Multiple indications

Ensuring patient safety when botulinum toxin is used for different indications

- Multidisciplinary teams
- Communication between teams
- Timing & dosing per indication
- Timing & total dosing per patient case

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Conclusion

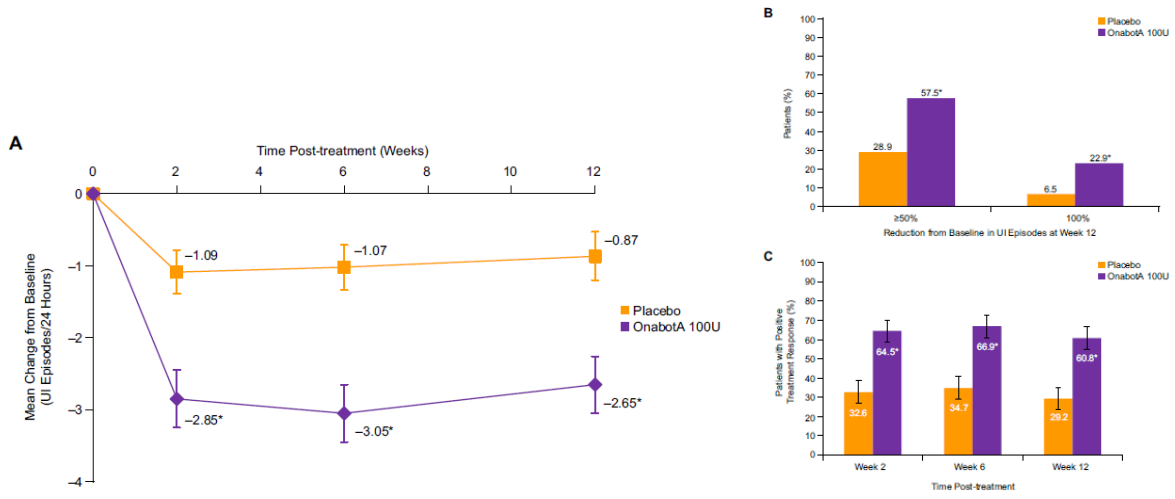
- Botulinum toxin is safe and effective in the management of NDO- level 1 evidence
- Attributes for the neurological patient- minimally invasive, minimal side effects, duration of effect
- Potential need for catheterisation

Arun Sahai

Botulinum Toxin A for Refractory Overactive bladder / Idiopathic detrusor overactivity

Ref: Botulinum Toxin-What Urologic Uses Does the Data Support? Seth J, Khan MS, Dasgupta P, Sahai A. Curr Urol Rep. 2013 Apr 27. Epub ahead of print

A large phase III, placebo controlled study was carried out involving 557 patients with OAB and urge urinary incontinence (UUI) who were refractory to antimuscarinic therapy and were treated with 100 U OnabotulinumtoxinA (1). Patients did not have to have IDO to be included. Outcome measures included measurement of daily UUI episodes, scoring on the treatment benefit response scale, and health related QoL scores. At 12 weeks post treatment, significant improvements were seen for these measures in those that received BTX-A, with 22.9% of BTX-A patients achieving continence versus 6.5% in placebo. Some of the results are summarised below. De novo CIC rates in this population have traditionally been a concern but in this study was only required in 6.1% .



BTX-A treatment has also been directly compared in a head to head study with antimuscarinic therapy (2). In this double blind, placebo controlled randomised trial, 247

patients with UUI were randomised into either a daily antimuscarinic tablet (solifenacin / trospium chloride) and an intradetrusor injection of saline, or an intradetrusor injection of OnabotulinumtoxinA (100 U) and a daily oral placebo tablet. In both arms significant improvements were seen at 6 months follow up. Both groups had a reduction of incontinence episodes from 5.0 per day to 3.4 and 3.3 for antimuscarinics and BTX-A, respectively. The BTX-A arm had significantly higher rates of complete resolution of UUI than the antimuscarinic arm (27% vs 13%). QoL also improved in both groups, without significant differences between the two arms. The antimuscarinic group had a significantly higher rate of dry mouth, but had significantly lower CIC rates and UTI episodes (2).

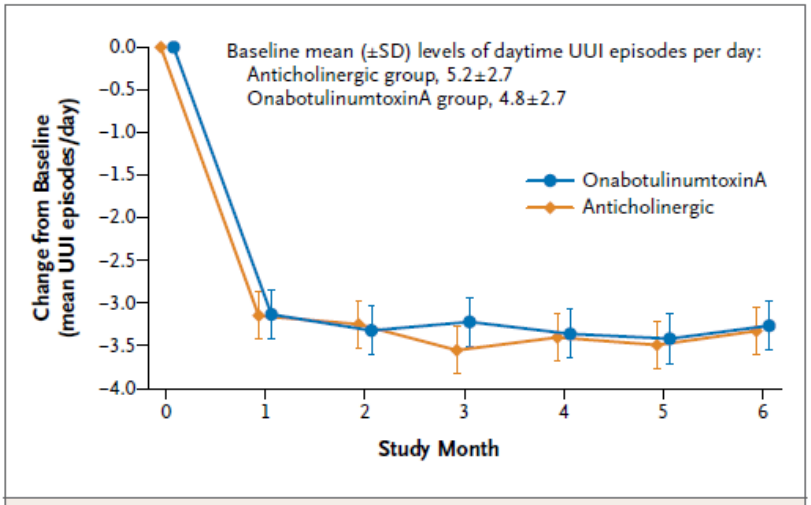


Figure 2. Reduction from Baseline in Number of Episodes of Urgency Urinary Incontinence (UUI) per Day.

The primary outcome of the study (the adjusted mean reduction from baseline in the number of episodes of urgency urinary incontinence per day) is shown in the modified intention-to-treat population, according to treatment group. I bars indicate 95% confidence intervals.

Long term effects of the toxin are largely unknown with regards to continuing efficacy, antibody formation and its effects on bladder function. However, medium term efficacy and discontinuation rates have recently been reported in a prospective study of 100 patients who had repeated injections of OnabotulinumtoxinA to treat refractory IDO (6). For those who

had up to five injections, there was statistically significant improvement in OAB symptoms and QoL compared to baseline, with a mean inter-injection interval of 322 days. The main reasons for those who dropped out of treatment were poor efficacy in 13%, and CIC related issues in 11% (6). Dropout rates were highest in the first 2 years following treatment and then very rare. Other studies have confirmed the efficacy of repeated injections in this patient population (7, 8).

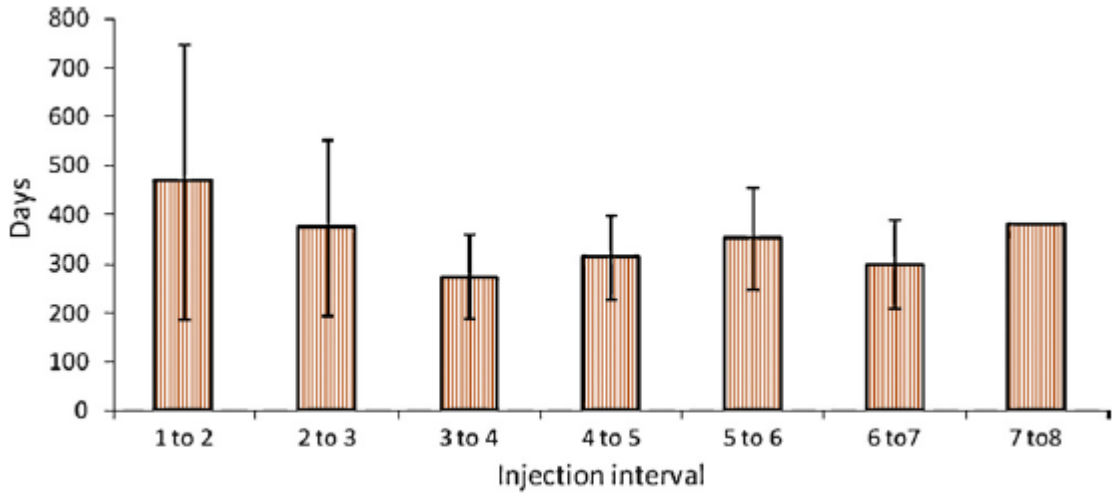


Fig. 1 – Interinjection interval for entire cohort (days).

However, Mohee et al., in their retrospective study noted different outcomes with BTX-A, in a predominatly OAB / IDO population (although some patients with NDO were included) (9). In 137 patients with at least 3 years of follow up approximately 60% had discontinued treatment mainly as a result of CIC related issues or UTI. Limitations include lack of antiobiotic use and outcomes were based on patient reported factors as opposed to specific instruments or diaries and the retrospective nature of the study. Interestingly many of the patients had reverted back to conservative treatments and antimuscarinic therapy to which they were initially refractory (9).

1. Nitti VW, Dmochowski R, Herschorn S, et al. OnabotulinumtoxinA for the Treatment of Patients with Overactive Bladder and Urinary Incontinence: Results of a Phase 3 Randomized Placebo-Controlled Trial. J Urol. 2012. Epub 2012/12/19.
2. Visco AG, Brubaker L, Richter HE, et al. Anticholinergic therapy vs. onabotulinumtoxina for urgency urinary incontinence. N Engl J Med. 2012;367(19):1803-13. Epub 2012/10/06.
3. Fowler CJ, Auerbach S, Ginsberg D, et al. OnabotulinumtoxinA improves health-related quality of life in patients with urinary incontinence due to idiopathic overactive bladder: a 36-week, double-blind, placebo-controlled, randomized, dose-ranging trial. European urology. 2012;62(1):148-57. Epub 2012/04/03.
4. Rovner E, Kennelly M, Schulte-Baukloh H, Zhou J, Haag-Molkenteller C, Dasgupta P. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. Neurourology and urodynamics. 2011;30(4):556-62. Epub 2011/02/26.
5. Tincello DG, Kenyon S, Abrams KR, et al. Botulinum toxin a versus placebo for refractory detrusor overactivity in women: a randomised blinded placebo-controlled trial of 240 women (the RELAX study). European urology. 2012;62(3):507-14. Epub 2012/01/13.
6. Dowson C, Watkins J, Khan MS, Dasgupta P, Sahai A. Repeated botulinum toxin type A injections for refractory overactive bladder: medium-term outcomes, safety profile, and discontinuation rates. European urology. 2012;61(4):834-9. Epub 2011/12/30.
7. Game X, Khan S, Panicker JN, et al. Comparison of the impact on health-related quality of life of repeated detrusor injections of botulinum toxin in patients with idiopathic or neurogenic detrusor overactivity. BJU international. 2011;107(11):1786-92. Epub 2010/11/03.
8. Granese R, Adile G, Gugliotta G, Cucinella G, Saitta S, Adile B. Botox((R)) for idiopathic overactive bladder: efficacy, duration and safety. Effectiveness of subsequent injection. Archives of gynecology and obstetrics. 2012;286(4):923-9. Epub 2012/05/25.
9. Mohee A, Khan A, Harris N, Eardley I. Long-term outcome of the use of intravesical botulinum toxin for the treatment of overactive bladder (OAB). BJU international. 2013;111(1):106-13.

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Botulinum toxin injections into the detrusor:

Technique and practical tips

Ass. Prof. Thomas M. Kessler, MD
Neuro-Urology, Spinal Cord Injury Center & Research
Balgrist University Hospital
University of Zürich

Universität Zürich

BJUI Surgery Illustrated – Surgical Atlas
Botulinum toxin injections into the detrusor

Jens Wöllner*† and Thomas M. Kessler*
*Neuro-Urology, Spinal Cord Injury Center and Research, University of Zürich, Balgrist University Hospital, Switzerland and †Department of Urology, University Medical Center, University of Mainz, Germany

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Workup

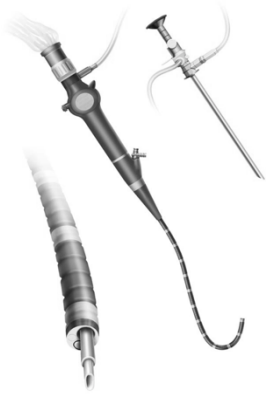
- Medical history & physical examination
- Bladder diary
- Urine analysis / urine culture
- Urinary tract ultrasonography
- Urethro-cystoscopy / bladder washing cytology
- Urodynamics

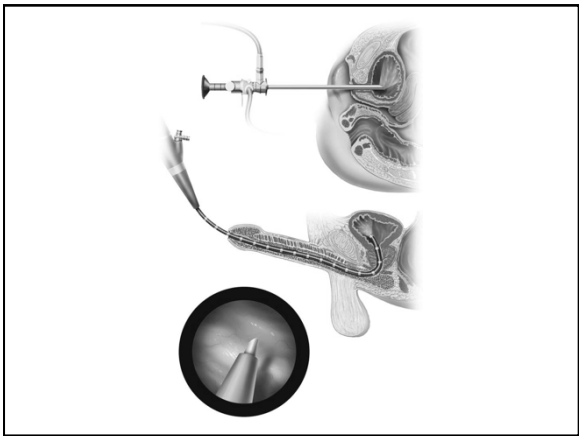
Patient selection / information

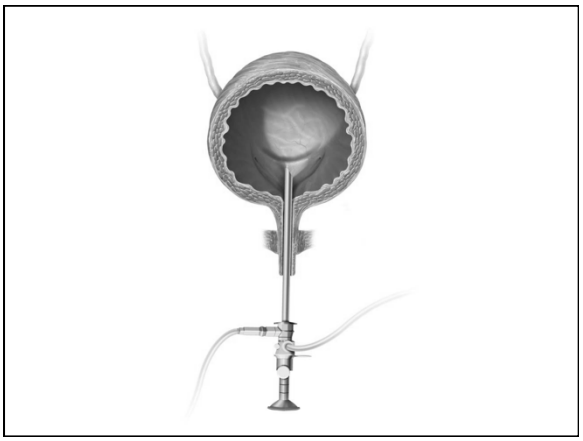
- Refractory overactive bladder syndrome
- Potential need for catheterization
- Temporally limited effect → repeat injections
- Legal issues

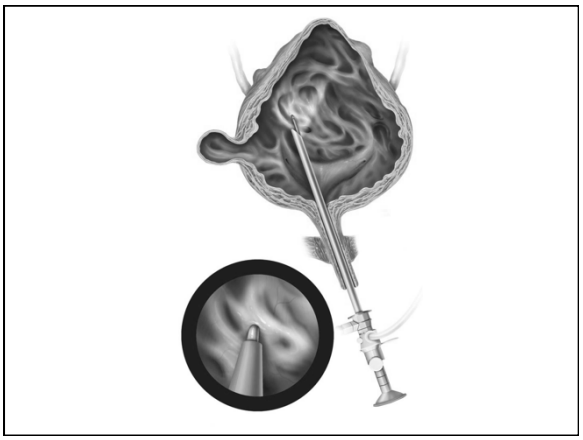
- Flu-like symptoms / muscle weakness
- Haematuria

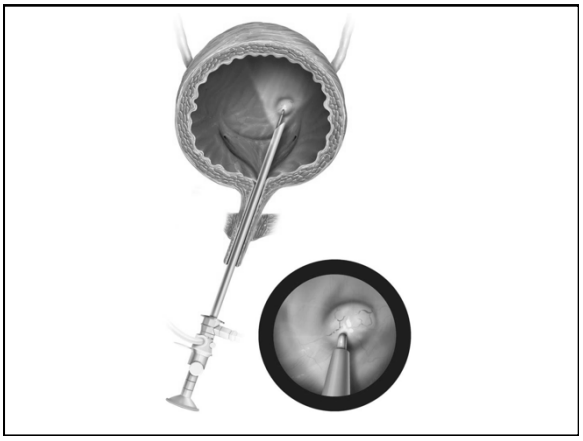
Equipement & technique

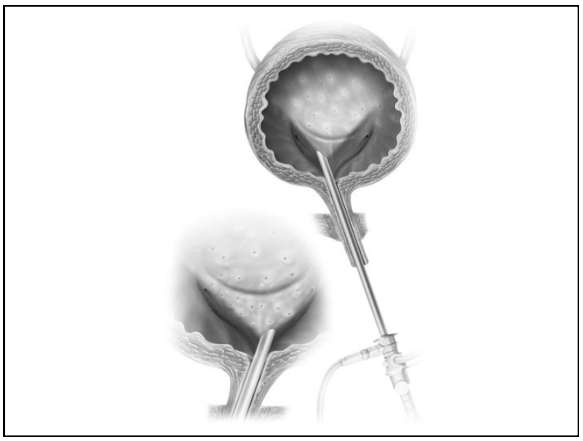


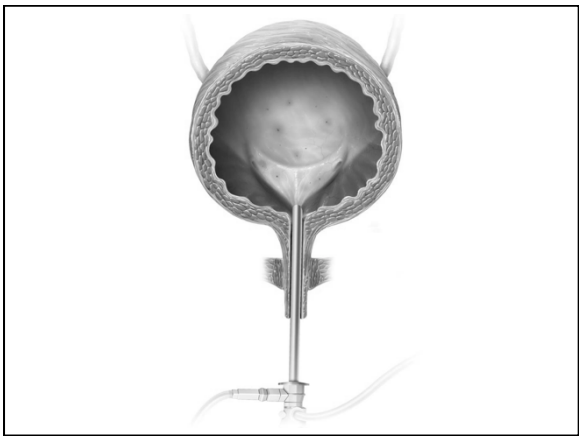












Postoperative care

- Outpatient setting
- Effect after 5-10 days (not immediately)
- Spontaneous voiders: PVR after 2 weeks
- Catheterization: PVR >150mL & LUTS
- Follow-up urodynamics
    - in selected patients (high-pressure, reflux)
    - before repeat injections

Tips & tricks

- Informed consent procedure (→ PVR)
- Ultrafine single-use needles → injections safe
    - under oral anticoagulation
    - under antiplatelet treatment

Tips & tricks

- Caution: potentiated effect in case of
    - aminoglycoside antibiotics
    - neuromuscular blockers
- Caution: spinal cord injury at / above T6
    - continuous cardiovascular monitoring
    - anaesthesiological stand-by

Notes