Aims of course/workshop
Botulinum toxin is an effective 2nd line treatment option for treating refractory overactive bladder syndrome and detrusor overactivity. This workshop will provide an overview of the published literature on the subject but will focus on level I evidence from randomized placebo controlled trials. Its use in 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.

Educational Objectives
Botulinum toxin is now recognised treatment for refractory OAB and is included in many incontinence guidelines such as EAU and NICE. It has recently obtained FDA approval for treating neurogenic bladder and its use amongst clinicians involved in overactive bladder management is increasing worldwide.

This workshop will concentrate on synthesizing the vast volumes of published literature on the subject and presenting it to the participant in a succinct, meaningful way, specifically focusing on level I evidence.

Furthermore patient assessment, technique of administration, tips, tricks and practical points will be discussed which will aid both clinicians starting up a service or with an established practice to ensure safe and effective treatment of their patients.

The workshop will allow plenty of time for discussion with the faculty, all of whom have an extensive experience with the use of botulinum toxin and a good track record in the published literature in this area.
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

Licensed indications (UK)

- Paediatric cerebral palsy
- Focal spasticity associated with stroke
- Hemifacial spasm
- Blepharospasm
- Cervical dystonia
- Hyperhidrosis
- Cosmesis

Case

- 48, female
- Multiple sclerosis- 10 years; secondary progressive
- Optic neuritis, paraparesis
- Uses one stick support for walking
- Urgency, frequency, incontinence
- Hesitancy, straining, double voiding
- Previously: PVR 70 mL, started oxybutinin 15 mg/day- urgency worsened

MS- a demyelinating disorder
- **Bladder scan**: 120 mL PVR
- **Dipstick negative**
Results: Urgency Incontinence

* \( p < 0.05 \) for differences between BoNT group and placebo
† \( p < 0.05 \) for difference within group changes from baseline

Reduction in number of UI episodes compared to baseline (%)

Schurch. J Urol, 2005

Results: Urodynamics – MCC

* \( p < 0.05 \) for within-group changes from baseline
† \( p < 0.05 \) for pairwise contrasts between BoNT groups versus placebo

Schurch. J Urol, 2005

Results: Quality of Life

* \( p < 0.05 \) for pairwise contrasts between BoNT groups and placebo
† \( p < 0.002 \) for within-group differences from baseline

Schurch. J Urol, 2005

Success of Repeat Detrusor Injections of Botulinum A Toxin in Patients with Severe Neurogenic Detrusor Overactivity and Incontinence

Joachim Geisse1, Guan Kastner, Manfred Holterm

Department of Urology, Endourology, and Male Urology, University Hospital Muenster, Muenster, Germany

Accepted 15 December 2004

% injected patients with 300 U BoNT: 1, 3, 5, 7

Injections 1-2 3-4

Geisse et al., 2005
Improvement in urgency, frequency, incontinence, QOL in MS (n=43)

Kalsi et al., 2007

Urogenital symptoms in MS (n=112)

UDI6 Scores

Khan et al. Poster BAUS, 2009

Incontinence

IIQ7 Scores

Khan et al. Poster BAUS, 2009

Botulinum toxin for NDO (n=112)

ADVERSE EVENTS (for 252 sessions)

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTION</td>
<td>12.1%</td>
</tr>
<tr>
<td>HAEMATURIA</td>
<td>0.39%</td>
</tr>
<tr>
<td>LIMB WEAKNESS</td>
<td>1.2%</td>
</tr>
<tr>
<td>MS RELAPSE</td>
<td>1.5%</td>
</tr>
<tr>
<td>ASTHENIA</td>
<td>7.9%</td>
</tr>
<tr>
<td>FLU LIKE SYMPTOMS</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Khan et al. Poster BAUS, 2009

Median inter injection interval (NDO/MS)

(n=112, MS)

Khan et al. Poster BAUS, 2009

Annual increase in workload

Khan et al. Poster BAUS, 2009
Duration of action of Botox® in 13 patients who had 4 injections

Open label study of 137 MS patients

Efficacy and Safety of Oxybutynin ER in Patients With Urinary Incontinence Due to Neurogenic Detrusor Overactivity

Figure 4. Kaplan-Meier Curve for Time to Request for Retreatment (ITT Population)

Bladder emptying before & 4 weeks after Botox® A

NB. CISC taught with PVR 100 mls
Patient Perception - Before

Before Botox my bladder was emptying intermittently immediately before I could reach a toilet. I was having 3-4 times daily due to accidents. I had advice on fabric floor exercises I had tried numerous and medication to help my nocturnal bladder. Nothing worked. I was having incontinence pads and I had been chronic for 14 years. I was getting up several times during the night. Restricting my liquid intake didn't help my incontinence. I was going out due to this embarrassing problem.

Patient Perception - After

After Botox, injections which were a little bit uncomfortable but painful, I noticed a difference after a couple of days. By day 4 it was gone without medication, pads. I had no side effects from the Botox. It has reduced the urgency to empty the bladder and also no longer have to get up to empty the bladder during the night. At the time of writing also, my mobility after Botox, I am feeling better, have better bladder control and I am walking much better. I am also sleeping much better. My life is improved - Botox given me back my dignity, many many thanks.

- "botulinum toxin A is the 21st centenary penicillin for the bladder"
Questions

- What about other neurological conditions?
- Which toxin is the best?
- What is the optimal dose?
- How many sites to inject?
- Should the trigone be avoided?
- Which dilution to use?
- Needle diameter?

Conclusion

- Botulinum toxin is safe and effective in the management of NDO - level 1 evidence
- Attributes for the neurological patient - minimally invasive, low side effects, duration of effect
- Potential need for catheterisation
OnabotulinumtoxinA to treat refractory OAB and other forms of bladder dysfunction

Arun Sahai, Academic Clinical Lecturer in Urology ICS Workshop 2012, Beijing

Objectives
- Formulations and terminology
- Literature Review OAB - Level 1 evidence - Key papers
- Repeated Injections
- Other types of bladder dysfunction
- Questions?

Formulations
- Toxicity measured in mouse units (mU) "amount fatal to 50% batch of swiss webster mice"
- Unlicensed currently for OAB / IDO
- Old Formulations
  - Botulinum toxin-A: BOTOX®, Allergan Ltd; DYSPORT®, Ipsen Ltd
    - 1 U BOTOX equivalent to 3-4 U of DYSPORT
  - Botulinum Toxin-B: MYOBLOC™/NEUROBLOC™, Solstice Neurosciences Inc.

New Terminology
Summary of FDA-Approved Botulinum Toxin Products

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>New Drug Name</th>
<th>Old Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botox</td>
<td>OnabotulinumtoxinA</td>
<td>Botulinum toxin type A</td>
</tr>
<tr>
<td>Botox Cosmetic</td>
<td>OnabotulinumtoxinA</td>
<td>Botulinum toxin type A</td>
</tr>
<tr>
<td>Dysport</td>
<td>AbobotulinumtoxinA</td>
<td>Botulinum toxin type A</td>
</tr>
<tr>
<td>Myobloc</td>
<td>RimabotulinumtoxinA</td>
<td>Botulinum toxin type B</td>
</tr>
</tbody>
</table>

Urological applications of Botulinum Toxin

- IDO
  - 2003 – IDO Harper et al
  - 2007 – RCT IDO – Sahai et al
  - 2007 – RCT NDO – Ehren et al
  - 2008 – RCT IDO – Brubaker et al
  - 2009 – RCT IDO – Flynn et al
  - 2010 Allergan Phase II multi-centre trial RCT IDO
  - Awaited Allergan phase III multi-centre trial RCT IDO
- PBS / IC
  - 2004 – IC Smith et al
  - 2009 – RCT Kuo et al
- BO / Sensory urgency
  - 2010 Allergan Phase II multi-centre trial RCT
  - 2011 RCT BO – Dowson et al

Efficacy of Botulinum ToxinA for Treating Idiopathic Detrusor Overactivity: Results From a Single Center, Randomized, Double-Blind, Placebo Controlled Trial
Arun Sahai, Mohammad Shams Khan and Prokar Dasgupta* for the GRT Botulinum Study Group
From Guy’s, Kings and St. Thomas’ Hospitals, London, United Kingdom
RCT IDO

- 200 U
- 16 BTX; 18 Placebo
- Flexible cystoscopy technique

Results

Results: QoL

<table>
<thead>
<tr>
<th>Mean Value</th>
<th>BTX-A</th>
<th>Placebo</th>
<th>Difference between means (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIQ-7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>16.3</td>
<td>14.75</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>4 weeks</td>
<td>6.00 (12.31)</td>
<td>10.67 (4.11)</td>
<td>-4.67 (10.09 to -0.37)</td>
<td>0.023</td>
</tr>
<tr>
<td>12 weeks</td>
<td>7.94 (10.58)</td>
<td>12.59 (6.61)</td>
<td>-4.65 (13.92 to -2.90)</td>
<td>0.0065</td>
</tr>
<tr>
<td>UDI-6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.75</td>
<td>9.50</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>4 weeks</td>
<td>5.00 (5.55)</td>
<td>9.00 (9.50)</td>
<td>-4.00 (6.17 to -2.80)</td>
<td>0.0005</td>
</tr>
<tr>
<td>12 weeks</td>
<td>5.13 (6.65)</td>
<td>10.00 (4.90)</td>
<td>-4.87 (7.31 to -2.43)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

KHQ Domain scores

<table>
<thead>
<tr>
<th>Domain</th>
<th>45/2</th>
<th>12/52</th>
<th>24/52</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Health Perception</td>
<td>0.7289</td>
<td>0.6219</td>
<td>0.5696</td>
</tr>
<tr>
<td>Incontinence Impact*</td>
<td>&lt;0.0001*</td>
<td>0.0037*</td>
<td>0.0029*</td>
</tr>
<tr>
<td>Symptom Severity Score*</td>
<td>0.0044*</td>
<td>0.0013*</td>
<td>0.0066*</td>
</tr>
<tr>
<td>Role Limitations</td>
<td>0.0857</td>
<td>0.0035*</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Physical Limitations*</td>
<td>0.0026*</td>
<td>0.0006*</td>
<td>0.0004*</td>
</tr>
<tr>
<td>Social Limitations*</td>
<td>0.0172*</td>
<td>0.0005*</td>
<td>0.0009*</td>
</tr>
<tr>
<td>Personal Relationships</td>
<td>0.7281</td>
<td>0.0927</td>
<td>0.0220*</td>
</tr>
<tr>
<td>Emotions*</td>
<td>0.0102*</td>
<td>0.0101*</td>
<td>0.0011*</td>
</tr>
<tr>
<td>Sleep / Energy</td>
<td>0.0699</td>
<td>0.0344*</td>
<td>0.0096*</td>
</tr>
<tr>
<td>Severity Measures*</td>
<td>0.0317*</td>
<td>0.0031*</td>
<td>0.0056*</td>
</tr>
</tbody>
</table>

Extension study / safety

- 6 month extension study
- Average pain scores: 4.25 BTX; 4.0 Placebo (Non significant)

Adverse events:

- CISC – 6/16 (37.5%) in those who received BTX
- UTI – 7/34 (20.5%) but 6 performing CISC
RCT IDO 2
- Females with refractory IDO
- 200 U
- OAB Sx + UUI
- 60% clinical response
- Efficacy 1 year

Adverse Events
- CISC 43%
- UTI

| Table 3. Urinary retention requiring CISC greater than 30 days after injection |
|---|---|---|---|
| Pt No | Initial PRV (cc) | To CISC Start | To CISC End |
| 1 | 150 | 205 | 206 |
| 2 | 180 | 185 | 186 |
| 3 | 200 | 185 | 186 |
| 4 | 180 | 185 | 186 |
| 5 | 150 | 185 | 186 |
| 6 | 170 | 185 | 186 |
| 7 | 160 | 185 | 186 |
| 8 | 180 | 155 | 125 |
| 9 | 150 | 185 | 186 |
| 10 | 110 | 185 | 186 |
| 11 | 120 | 185 | 186 |
| 12 | 130 | 185 | 186 |

Outcome of a Randomized, Double-Blind, Placebo Controlled Trial of Botulinum A Toxin for Refractory Overactive Bladder

N=22

Allergan 077 Phase II study

Efficacy and Safety of OnabotulinumtoxinA for Idiopathic Overactive Bladder: A Double-Blind, Placebo Controlled, Randomized, Dose Ranging Trial
- N=313
- Randomised placebo controlled trial
- Dose escalation (50-300 IU)
- IDO and BO allowed
- Treatment consisted of 20 injections (0.5 ml per site)

Results

Weekly UUI

KIQ

Urodynamics

Conclusions

- 100 IU best balance between efficacy and AE
- Phase III data awaited
Guy’s Experience

- Not one dose will ‘fit all’
- Tailored approach per patient
- Dose escalation for efficacy? Reduction for AEs

Guy’s Experience

Female Urology

Urodynamic Assessment of Poor Responders After Botulinum Toxin A Treatment for Overactive Bladder

Arun Sahat, Mohammad S. Khan, Nishant In G, and Prakar Dangoura

Assessment of urodynamic and detrusor contractility variables in patients with overactive bladder syndrome treated with botulinum toxin A: is incomplete bladder emptying predictable?

Arun Sahat, Philippa Sangster, Vinu Kaly, Mohammad S. Khan, Clare A. Foxlow, and Prakar Dangoura.

Arun Sahat (affiliation)

PBS / IC

- Few studies
- Small numbers
- Kuo et al., BJUI 2009
- BTX + HD
- N=67
- 70% success
Questions ??

"We need something for his verbal incontinence. He has a blother control problem."
Botulinum Toxin injections for Overactive Bladder: Mechanism of Action

Prokar Dasgupta
ICS 2012

Summary
- Efferent effect
  - NMJ
- Afferent effect
  - Non-neuronal neurotransmitters
  - Neurotrophins
- Inflammatory effect

Clostridium botulinum
- "The capacity of nerve conduction is interrupted by the toxin in the same way an electrical conductor is by rust."
  - Justinus Kerner 1817
- Clostridium botulinum, a gram (+) anaerobic rod bacterium produces the toxin:
  - C. botulinum is typically found in water and soil
  - Botulinum neurotoxin is the most potent toxin known


Normal Neurotransmitter Exocytosis

Neurotransmitter Exocytosis: Intracellular Inhibition with BoNT

Recording single unit afferent nerve firing
Animal bladders
Demonstrate a correlation between spontaneous contractions and afferent nerve firing in SCT mice
BTX-A seen to subsequently reduce afferent nerve recordings and hence firings
Suburothelial nerve fibres (PGP9.5) and BoNT/A


No change in suburothelial neuronal population post BoNT/A


Increased afferent suburothelial innervation in DO


Suburothelial P2X₃ after BoNT/A
Progressive decrease and ‘normalisation’


UroNeurology, NINN

Successful treatment of OAB with BTX-A is associated with a significant decrease of TRPV1 and/or P2X3 levels toward control values. BoNT/A may act directly on the afferent innervation of the bladder.

BTX-A injections do not appear to produce significant inflammatory changes, fibrosis, or dysplastic changes in human bladder urothelium/suburothelium after a single injection and in a limited number of repeat treatment biopsies.

Apostolidis et al., 2005; J Urol
Urine NGF levels decrease after successful treatment with BTX-A in IDO and NDO.

No decrease in levels in non-responders to BTX-A.

Kuo et al., Rev Urol 2010

Tissue NGF levels pre and post BTX-A in Interstitial Cystitis

Liu et al, Urology 2007

Botulinum A infusion significantly attenuates the response of the bladder to an acetic acid infusion (p=0.04).

Frequency of bladder contraction at fixed rate for 2 hours

Outcome measure: frequency of bladder contractions

Frequency of bladder contraction at increasing rates of bladder fill

Botulinum A infusion has no significant effect on the response of the bladder to an increasing filling rate of normal saline.
NGF Effect

Bladder contraction frequency post NGF infusion in botulinum toxin treated animals

Botulinum A significantly attenuates the response of the bladder to a 30 min infusion of NGF compared to placebo.

NGF and BDNF
Pinto et al, European Urology 2010

Trigonal injections of BTX-A for PBS

Chuang et al, European Urology 2009

Safety - inflammation
Apostolidis et al, European Urology 2008

Further research areas....
- Mechanisms of action
- IC / painful bladder / Sensory urgency
- Interstitial cells
- Biomarkers

Conclusions
- Efferent effect
  - NMJ
- Afferent effect
  - Non-neuronal neurotransmitters
  - Neurotrophins
- Hence effective for IDO/NDO
- Role in inflammatory conditions e.g. interstitial cystitis
What I Do…

Dr Muhammad Shamim Khan
Consultant Urologist

IDO
- Hx / Ex
- Assess for confounding issues:
  - previous surgery
  - mixed incontinence
  - prolpase
- Refractory OAB ie failed anti-cholinergics and conservative measures
- URODYNAMICS !!
- Dose 100-200 U- Not for everyone

NDO
- Tend to be better worked up
- Have had good assessment usually
- Typical scenario – UUI despite CISC / anti-cholinergics
- Dose 200 U

Patient Information 1
- Unlicensed for IDO and for NDO in UK
- Significant OAB ; failed anti-cholinergics
- Not life long ; One injection per year

Patient Information 2
- Incomplete bladder emptying
- UTIs
- Flu
- Haematuria
- Distal muscle weakness
- CISC – can they do it?

To be avoided if
- Bladder outflow obstruction
- Anticoagulants
- Bladder pathology eg fibrosis, tcc, DXT etc…
- Pregnancy / planning pregnancy
Equipment
Injection technique

Key Points-Technique
- LA; prophylactic antibiotics;
- Day Case
- Don’t shake vial!
- 10 U/mL/site
- Mapping of posterior, lateral walls and dome - trigone sparing!!

Harper et al., 2003; Sahai et al., 2006; Schulte-Baukloh et al., 2005

Techniques-variations
- Rigid cystoscope using a collagen-flexible needle
- Flexi cystoscope using ultra fine 4mm flexible needle
- Trigonal vs trigone sparing techniques
- Detrusor vs suburothelium
- Number of injections; Volume of injection
- Mode of delivery

Variations in technique and research
- Indigo carmine injection
  Schulte-Baukloh et al., BJU 2005;
- Focused bladder base
  and trigonal injections
  (left NDO; right IDO / IC)
  Smith & Chancellor
  J Endourol 2005;
- MRI study post injection
  with contrast;
  18% outside detrusor
  rigid scope technique
  Mehnert et al., World J Urol 2009

Does technique matter??
-Majority of experts- No; Others –Yes
-Maneksha et al Eur Urol 2012
-RCT – Trigone sparing vs Trigone + Bladder
-Combined showed better subjective efficacy but no change in UDS
-Small numbers/ Performed under GA; Feasibility of trigonal LA injection
Evidence-Summary

Trigone inclusive injections appear to be more efficacious with slightly increased risk of CISC

Trigone alone - inferior in efficacy but less risk of CISC

BTA-instillation does not work & effect if any very short lived

Animal experiments with combination of liposomes and botox (lipotoxin) have shown some promise!!
Notes
Record your notes from the workshop here