Neurogenic detrusor overactivity management and indication for botulinum toxin A

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Division of Urology

University of Toronto
Storage and emptying

Storage phase

- Bladder filling
- First sensation to void
- Normal desire to void

Emptying phase
Neural control

- Brain
- Pons
- Thoracic segments (Sympathetic chain)
- Sacral micturition centre
  - Parasympathetic
  - Somatic
Intact neural control

- **Storage (bladder filling):**
  - Inhibition of detrusor reflex by higher centres
  - Urethral contraction

- **Voiding (bladder emptying):**
  - Activation of detrusor reflex
  - Urethral relaxation
Lack of neural control

- **Storage impaired or failure**
  - Decreased bladder capacity
  - Urinary incontinence

- **Voiding impaired or failure**
  - Urinary retention, infection
  - Compromised renal function
Assessment of storage and voiding function

- **Clinical** – history and physical examination, urinalysis, PVR
- **Urodynamic testing**
  - Uroflow, cystometry, urethral pressure, pressure/flow, electrophysiologic studies, video-urodynamics
Detrusor overactivity
Detrusor overactivity

- Urodynamic observation characterized by involuntary detrusor contractions during the filling phase
- Detrusor overactivity incontinence is incontinence due to an involuntary detrusor contraction
- **Neurogenic detrusor overactivity**
  - Relevant neurological condition
- Idiopathic detrusor overactivity
  - No defined cause

Neurologic diseases with detrusor overactivity

- Cerebrovascular accident
- Brain tumour
- Cerebral palsy
- Parkinson’s
- Multi-system atrophy

- Spinal cord injury
- Multiple sclerosis
- Spina bifida
- Diabetes

Wein A. Chapter 59, Campbell-Walsh 2007
Rationale for Treating NDO

- Higher bladder pressures
  - Poor bladder compliance
- Recurrent febrile urinary tract infections
- Autonomic dysreflexia
- Vesicoureteral reflux
- Hydronephrosis

Assessment and Current Management of NDO
# Patient Assessment

## History
- Neurologic diagnosis
  - SCI – American Spinal Injury Association (ASIA) classification
  - MS – Expanded Disability Status Scale (EDSS)
- Duration of condition
- Severity
- Prior treatments

## Physical Examination
- General/Medical
- Abdominal
- Pelvic/rectal exam

## Bladder/Sphincter Function
- Post void residual (PVR)
- Urinalysis
- Frequency volume chart/bladder diary
- Ultrasound of urinary tract
- Urodynamics

Urodynamics

- Objectively assesses filling and storage of urinary tract\(^1\)
  - Directs targeted treatments
  - Assesses diagnosis and prognosis
- May duplicate the patient’s symptoms while observing LUT function\(^1,2\)

LUT=lower urinary tract.

Patient has NDO with intermittent detrusor sphincter dyssynergia

IDC: Involuntary detrusor contraction; MDP: Maximum detrusor pressure; MCC: Maximum cystometric capacity
Current Management of NDO

Management of NDO falls into 3 major categories:

- **Behavioural approaches**
  - Lifestyle interventions
  - Pads, portable urinals
  - Self-stimulated voiding
  - Intermittent, condom or Foley catheterization for patients with abnormal bladder emptying (e.g., elevated PVR levels)

- **Pharmacotherapy**
  - Anticholinergic agents are the standard therapy

- **Surgery***
  - Reserved for those who fail therapy
  - Bladder Reconstruction
  - Urinary Diversion

PVR = post-void residual urine. * Neurostimulation not indicated for the treatment of NDO

Anticholinergics

- Currently considered first-line therapy for NDO\(^1\) with a long history of use (Level 1 evidence)
  - Systemic therapy

- Potential limiting factors:
  - Variable efficacy\(^2\)
  - Systemic anticholinergic effects: adverse events/tolerability\(^1,2\)
  - Drug-drug interactions\(^3,4\)
  - Low adherence rates\(^2\)

- Limited published data on anticholinergics and NDO

Pharmacologic agents for treatment of overactive bladder

**Antimuscarinics**

<table>
<thead>
<tr>
<th>Nonselective for M₃ Receptors</th>
<th>Selective for M₃ Receptors</th>
<th>“Combined”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine</td>
<td>Darifenacin (M₃)</td>
<td>Oxybutynin</td>
</tr>
<tr>
<td>Trospium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solifenacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fesoterodine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Surgical options

- Transurethral sphincterotomy or urolume™ stent in males
  - Need for CIC, late failures

- Major surgery
  - Augmentation cystoplasty ± urethral and stomal procedures (>40% complication rate)
  - Detrusor myectomy – rarely done
  - Urinary diversion – ileal conduit
    - Stomal, ureteral, renal problems

Continence Surgery

Enterocystoplasty
Neuromodulation

- Sacral
- Pudendal
- Posterior tibial nerve stimulation
- Finetech-Brindley posterior/anterior stimulator
- Hemilaminectomy and ventral root microanastomosis, the Xiao procedure
  - L5 ventral root to S2/3 ventral root
  - Skin stimulation results in normal voiding

Burks et al. Urol CI NA 2010; 37:559-565
Kaplan-Meyer graph of persistence with antimuscarinic drugs

Darifenacin
Flavoxate
Solifenacin
Trospium
Emepronium
Oxybutynin
Tolterodine

OnabotulinumtoxinA (Botox)

- Neurogenic Detrusor Overactivity associated with a neurological condition
  - for the treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from neurogenic bladder associated with multiple sclerosis or subcervical spinal cord injury in adults who had an inadequate response to or are intolerant of anticholinergic medications

http://www.allergan.ca/assets/pdf/ca_botox_pm.pdf
Inhibition of ACh Release

1. Botulinum toxin binds to receptor

2. Botulinum toxin endocytosed

3. Light chain cleaves specific SNARE proteins
   Types A, C, E: SNAP-25
   Types B, D, F, G: VAMP

4. SNARE complex does not form: Ach not released
BoNT/A actions

Kanai et al. N & U 2012, 31:300-8
Effect of BoNT/A

- Increase
  - Bladder capacity
  - Volume at first reflex detrusor contraction
  - Compliance

- Decrease detrusor pressures during filling and voiding

- Improvement in urgency – thought to be afferently mediated

Botulinum Toxin A

- Contraindications
  - Myasthenia gravis or Eaton Lambert Syndrome
  - Infected site
  - Known hypersensitivity to any ingredient in the formulation
  - Pregnancy (abortion and fetal malformations observed in rabbits, no reported complications in human pregnancy)

- Approved for use in NDO and incontinence
Botulinum Toxin A
Adverse Effects

Rare (0.1%), generally within the first week
- Erythema muliforme, psoriaform eruption
- Anaphylaxis
- Death (dysphagia, pneumonia, arrhythmia, MI)
- Transient muscle weakness
  - 7 patients for NDO treated with 1000U Dysport or 300U Botox, lasted less than 1 month (Wyndaele and Van Dromme Spinal Cord 2002)
  - 4 patients (Grosse et al. Eur Urol 2005)
  - 4 patients (Pannek et al. BJUI 2009)
  - 2 patients (Herschorn et al. J Urol 2011)
  - 1 patient (Cruz et al. Eur Urol 2011)
- May be potentiated by drugs that interfere with neuromuscular transmission including aminoglycosides
Method of administration

- Local anaesthetic
  - Aqueous Lidocaine (4%) left in bladder for 20-30 minutes
  - Topical urethral lidocaine
- Neuroleptic
- Regional
- General
Rigid or Flexible Cystoscope Bladder Injection Technique

- Dilute 100-300 U of Botox into 10-30 ml of saline
- Inject (targeting the trigone), base of the bladder and lateral walls
- **Rigid cystoscope**: 25 Gauge needle, inject approximately 0.5-1.0 ml into 20-30 sites
- **Flexible cystoscope**: flexible cystoscopy injection needle

Smith et al. Urology, 2005; 65:37-41
Botox needles

- **Cook**
  - Williams - rigid
  - Flexible (adjustable tip)
- **Coloplast (Porges)**
  - Rigid and flexible (adjustable tip)
- **Laborie**
  - Rigid and flexible (adjustable tip)
- **Olympus**
  - Flexible
Clinical Studies
Refractory
Idiopathic & Neurogenic Detrusor Overactivity
Botulinum toxin for refractory patients
Systematic review for NDO

- 18 studies with 698 patients
- 3 retrospective with series with >75 patients
- 3 prospective studies
- Majority were small open-label studies
- Overall botulinum toxin provides clinically significant improvements in refractory NDO

Percent continent

Change in QOL

Efficacy of Botulinum Toxin A Injection for Neurogenic Detrusor Overactivity and Urinary Incontinence: A Randomized, Double-Blind Trial

Sender Herschorn,*,† Jerzy Gajewski,‡ Karen Ethans, Jacques Corcos,§ Kevin Carlson,‖ Gregory Bailly, Robert Bard, Luc Valiquette,¶ Richard Baverstock,** Lesley Carr†† and Sidney Radomski‡‡

From the University of Toronto (SH, LC, SR), Toronto, Ontario, Dalhousie University (JG, GB), Halifax, Nova Scotia, University of Manitoba (KE, RB), Winnipeg, Manitoba, McGill University (JC) and University of Montreal (LV), Montreal, Quebec, and University of Calgary (KC, RB), Calgary, Alberta, Canada
Daily mean frequency of leakage episodes

Herschorn et al. J Urol 2011; 185:2229-2235
Volume at maximum detrusor pressure

Herschorn et al. J Urol 2011; 185:2229-2235
Anticholinergic use

Anticholinergics were discontinued at Week 3, and could be resumed at 50% of the previous dosage at Week 4 and full dose at Week 6.

Patients on anticholinergics

<table>
<thead>
<tr>
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<th>Placebo</th>
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</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>21/28 (75%)</td>
<td>18/29 (62%)</td>
<td>0.3950</td>
</tr>
<tr>
<td>6 weeks</td>
<td>14/21 (67%)</td>
<td>17/18 (94%)</td>
<td>0.0489</td>
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<td>Resumed at 50% of baseline dose</td>
<td>7/14 (50%)</td>
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Patients on anticholinergics

Herschorn et al. J Urol 2011; 185:2229-2235
## Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Botulinum toxin A (n=28) No. pts. (%)</th>
<th>Placebo (n=29) No. pts. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>16 (57)</td>
<td>16 (55)</td>
</tr>
<tr>
<td>Voiding difficulty/retention</td>
<td>6 (21)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Headaches</td>
<td>6 (21)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Nausea +/- vomiting</td>
<td>6 (21)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>3* (11)</td>
<td></td>
</tr>
</tbody>
</table>

* 1 unrelated

Herschorn et al. J Urol 2011; 185:2229-2235
Conclusions

- BoNT/A had a beneficial effect on diary outcomes measures, urodynamics, and QoL.
- Following open-label treatment, improvements were also seen in patients initially randomized to placebo.
- Improvements lasted up to 9 months

Herschorn et al. J Urol 2011; 185:2229-2235
Neuro-urology

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

Francisco Cruz\textsuperscript{a,*}, Sender Herschorn\textsuperscript{b}, Philip Aliotta\textsuperscript{c}, Mitchell Brin\textsuperscript{d,e}, Catherine Thompson\textsuperscript{d}, Wayne Lam\textsuperscript{d}, Grace Daniell\textsuperscript{d}, John Heesakkers\textsuperscript{f}, Cornelia Haag-Molkenteller\textsuperscript{d}

\textsuperscript{a} Department of Urology & IBMC, Hospital S\~ao Jo\~ao & Universidade Do Porto, Porto, Portugal; \textsuperscript{b} Division of Urology, University of Toronto, Toronto, Canada; \textsuperscript{c} Center for Urologic Research of Western New York, Williamsville, NY, USA; \textsuperscript{d} Allergan, Inc., Irvine, CA, USA; \textsuperscript{e} Department of Neurology, University of California, Irvine, CA, USA; \textsuperscript{f} Radboud University Nijmegen Medical Centre, the Netherlands

Design of Phase 3 Pivotal NDO Study

- Multicentre (global), randomized, double-blind 52-week study sponsored by Allergan, Inc
- 275 SCI or MS patients with UI due to NDO
  - Not adequately managed by anticholinergics
- Up to 2 treatments of 300 U, 200 U or placebo
- Primary Endpoint: Number of UI episodes at week 6
- Secondary Endpoints: Urodynamics, Incontinence Quality of Life (I-QOL)

### Patient Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (N=92)</th>
<th>200 U (N=92)</th>
<th>300 U (N=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.9 yrs (± 13.4)</td>
<td>46.0 yrs (± 13.1)</td>
<td>44.4 yrs (± 13.9)</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>46.7 %</td>
<td>41.3 %</td>
<td>42.9 %</td>
</tr>
<tr>
<td>Time since diagnosis of MS</td>
<td>14.1 yrs (± 7.6) (N=50)</td>
<td>14.8 yrs (± 9.8) (N=53)</td>
<td>14.0 yrs (± 8.6) (N=51)</td>
</tr>
<tr>
<td>Time since diagnosis of SCI</td>
<td>11.8 yrs (± 9.9) (N=42)</td>
<td>8.3 (± 7.1) (N=39)</td>
<td>8.9 (± 7.9) (N=40)</td>
</tr>
<tr>
<td>Time since diagnosis of NDO</td>
<td>8.1 yrs (± 7.1)</td>
<td>7.6 yrs (± 6.7)</td>
<td>8.2 yrs (± 7.2)</td>
</tr>
<tr>
<td>Using anticholinergics at baseline</td>
<td>62.0 %</td>
<td>58.7 %</td>
<td>56.0 %</td>
</tr>
<tr>
<td>MS %</td>
<td>54.3 %</td>
<td>57.6 %</td>
<td>56.0%</td>
</tr>
<tr>
<td>SCI %</td>
<td>45.7 %</td>
<td>42.4 %</td>
<td>44.0%</td>
</tr>
</tbody>
</table>

No significant difference among treatment groups

## Baseline Diary Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (N=92)</th>
<th>200 U (N=92)</th>
<th>300 U (N=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly urinary incontinence</td>
<td>36.7 (±30.7) (5.2 per day)</td>
<td>32.5 (±18.4) (4.6 per day)</td>
<td>31.2 (±18.1) (4.5 per day)</td>
</tr>
<tr>
<td>Use of CIC at baseline</td>
<td>54.9 %</td>
<td>52.2 %</td>
<td>48.9 %</td>
</tr>
<tr>
<td>Volume per void (CIC or spontaneous voids)</td>
<td>147.4 mL (±94.2)</td>
<td>158.8 mL (±113.0)</td>
<td>167.9 mL (±118.4)</td>
</tr>
</tbody>
</table>

CIC: Clean intermittent catheterization

No significant difference among treatment groups

Significant Decrease in Urinary Incontinence

Change in urinary incontinence episodes/week

Baseline | Week 2 | Week 6 | Week 12
---|---|---|---
Placebo | 0 | -5 | -10
200 U | -10 | -15 | -20
300 U | -15 | -20 | -25

* p = <0.001 in pairwise comparison versus placebo

Mean baselines:
Placebo = 36.7/wk, 200 U = 32.5/wk, 300 U = 31.2/wk

Significant Increase in MCC

Change in MCC at 6 weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>Change from baseline (mL)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.5</td>
<td>92</td>
</tr>
<tr>
<td>200 U</td>
<td>157</td>
<td>92</td>
</tr>
<tr>
<td>300 U</td>
<td>157.2</td>
<td>91</td>
</tr>
</tbody>
</table>

* p = <0.001 in pairwise comparison versus placebo

MCC: Maximum cystometric capacity

Significant Improvement in UI Episodes

Percent of patients with ≥ 50% decrease in urinary incontinence

Percent of patients with 100% decrease in urinary incontinence (‘DRY’)

* *

* p = <0.001 in among-group comparison

Data on file.
Duration of Symptom Relief in Bladder Was Approximately 9 Months

Based on time to patient request for re-treatment


12 weeks was the earliest time point when patients were allowed to request treatment.
## Adverse Events ≥ 5% in Any Treatment Group

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (N=90)</th>
<th>200 U (N=91)</th>
<th>300 U (N=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>74.4 %</td>
<td>86.8 %</td>
<td>88.8 %</td>
</tr>
<tr>
<td>UTI</td>
<td>40.0 %</td>
<td>56.0 %</td>
<td>64.0 %</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>3.3 %</td>
<td>19.8 %</td>
<td>31.5 %</td>
</tr>
<tr>
<td>Hematuria</td>
<td>4.4 %</td>
<td>5.5 %</td>
<td>10.1 %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.1 %</td>
<td>8.8 %</td>
<td>3.4 %</td>
</tr>
<tr>
<td>Dysuria</td>
<td>2.2 %</td>
<td>5.5 %</td>
<td>7.9 %</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3.3 %</td>
<td>6.6 %</td>
<td>6.7 %</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.2 %</td>
<td>5.5 %</td>
<td>6.7 %</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.7 %</td>
<td>3.3 %</td>
<td>6.7 %</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>1.1 %</td>
<td>4.4 %</td>
<td>6.7%</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>1.1 %</td>
<td>6.6 %</td>
<td>4.5 %</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3.3 %</td>
<td>6.6 %</td>
<td>1.1 %</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5.6 %</td>
<td>3.3 %</td>
<td>1.1 %</td>
</tr>
<tr>
<td>Influenza</td>
<td>0</td>
<td>5.5 %</td>
<td>1.1 %</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>2.2 %</td>
<td>5.5 %</td>
<td>1.1 %</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3.3 %</td>
<td>5.5 %</td>
<td>2.2 %</td>
</tr>
</tbody>
</table>

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 §

From the University of Southern California (DG), Los Angeles and Allergan, Inc. (CT, WL, BJ, CHM) and University of California-Irvine, Irvine (MFB), California, Herbert Wertheim College of Medicine, Florida International University (AG), Miami, Florida, Université de Liège (VK), Liège, Belgium, and University of Tübingen (KDS), Tübingen, Germany.

- 416 pts. – 227 MS, 189 SCI and DO
- 14+ UI episodes/wk
- 1º endpoint – ΔUI episodes/wk,
- 2º endpoints – MMC, MDP, IQOL; AEs
  - 200U and 300U reduced UI episodes by 21 and 23/wk vs. 9 in placebo (P<0.001)
  - Median time to retreatment was 256 and 254 days vs. 92 in placebo
  - Most common AEs were UTI and retention
  - IC initiated in 10% placebo, 35% 200U, and 42% 300U
Summary of BOTOX® Phase 3 Trials

- Studies demonstrated BOTOX® provided sustained benefits to patients with NDO in terms of:
  - UI, urodynamic parameters, QOL
- 300 U dose provided no additional clinically relevant benefits compared with 200 U, but:
  - 300 U associated with increase in PVR and more patients initiating catheterization
  - Higher incidence of UTI and retention in 300 U group

→ Approved dose is 200 U

UTI: Urinary tract infection
PVR: Post-void residual
Repeat BoNT/A injections

- Review of multiple studies
  - Overall objective and subjective (patient reported) efficacy outcomes after first injection sustained after repeated injections

Dowson et al. Nat Rev Urol 2010; 7:661-667
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients receiving each number of injections</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Total 10 studies</strong></td>
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<tr>
<td><em>Neurogenic detrusor overactivity</em></td>
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<tr>
<td>Grousse et al. (2005)³</td>
<td>187</td>
</tr>
<tr>
<td>Karsenty et al. (2006)⁹</td>
<td>NR</td>
</tr>
<tr>
<td>Akbar et al. (2007)⁴</td>
<td>NR</td>
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<tr>
<td>Kalsi et al. (2007)⁵</td>
<td>43</td>
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<tr>
<td>Reitz et al. (2007)⁶</td>
<td>NR</td>
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<tr>
<td>Del Popolo et al. (2008)⁷</td>
<td>199</td>
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<tr>
<td>Giannantoni et al. (2009)⁸</td>
<td>NR</td>
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<td>Ghalayini et al. (2009)⁹*</td>
<td>NR</td>
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<tr>
<td>Pannek et al. (2009)¹⁰</td>
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<tr>
<td><em>Idiopathic detrusor overactivity</em></td>
<td></td>
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<tr>
<td>Sahai et al. (2009)¹¹</td>
<td>34</td>
</tr>
<tr>
<td>Khan et al. (2009)¹²</td>
<td>81</td>
</tr>
</tbody>
</table>

*119 injections in 17 patients over the 6-year period. Injections only reported up to this point. Abbreviation: NR, not reported.

Dowson et al. Nat Rev Urol 2010; 7:661-667
Botulinum toxins

- OnabotulinumtoxinA (Botox/Botox Cosmetic),
- AbobotulinumtoxinA (Dysport)
- RimabotulinumtoxinB (Myobloc)
- IncobotulinumtoxinA (Xeomin)

- All are different pharmacologically and are not interchangeable

Systematic review of Botox and Dysport

73 articles

Mangera et al. Eur Urol 2011; 60:784-795
Systematic review of Botox and Dysport

- **NDO**
  - High level data for both
  - Botox better studied than Dysport
  - Only Botox has high level data in children; Dysport not recommended for routine use

- **IDO**
  - High level data for Botox in adults
  - Botox better investigated than Dysport
  - Only Botox has 1 level 3 study in children; Dysport not recommended for routine use

Mangera et al. Eur Urol 2011; 60:784-795
Trigone+ vs. trigone-

- 22 pts. RCT with AbobotulinumtoxinA (500 U) for IOAB
- After 6-24 weeks larger improvement in outcomes of trigone+ vs. trigone- (P<0.05)
- No difference in PVR, CMG, no reflux,

Practical issues related to Botulinum toxin

- Approval and funding
  - Approval only for neurogenic disease, not yet funded
  - Approved by CDR

- Patient selection
  - Refractory, prepared to do IC
  - Urodynamics not necessary for IOAB
  - Urodynamics necessary to diagnose NDO

- Method of administration, dose, follow-up
  - 100 U to be recommended for IOAB
  - 200 U recommended for NDO/NOAB
  - Follow-up after 1-2 weeks to R/O retention
  - Duration of effect ~5-9 months
Practical issues related to Botulinum toxin

- Repeated injections
  - No tachyphylaxis yet

- Other toxins
  - AbobotulinumtoxinA (Dysport) and RimobotulinumtoxinB (Myobloc) reported but not approved
  - Only OnabotulinumtoxinA (Botox) approved