BOTULINUM TOXIN
IN UROLOGY
Compliance With Oral Therapies

% Still on Therapy

Rx1 Rx2 Rx3 Rx4 Rx5 Rx6 Rx7 Rx8 Rx9 Rx10 Rx11 Rx12

Base: 26,200; New Patients: Oct-Dec 2000

Tolterodine ER
Oxybutynin ER
Tolterodine
Oxybutynin IR

Data on File, Watson Pharma, Inc.
IMS HEALTH LRx.
Botulinum Toxin

- Derived from clostridium botulinum, a anaerobic gram + rod

- **Muscle paralytic by chemodenervation**
  - Blocks Ach release from presynaptic nerve terminal blocking neural transmission
  - Compromises intracellular protein SNAP-25
  - Blocks fusion of synaptic vesicle with presynaptic membrane
  - Recovery of chemodenervation in 3-6 months
    - Due to turnover of presynaptic molecules and nerve sprouting from nerve terminal forming a new functional synapse

- **Therapeutic effects derived from local site-specific injection**
Botulinum Toxin

Seven immunoologically distinct subtypes identified (A-G)
- Botulinum-A toxin isolated in 1920’s and purified in 1946

Dr. David Scott
- 1973 – effect of botulinum toxin on lateral rectus muscle of the monkey
- 1981 – first application in humans treating strabismus

Botulinum-A toxin (BOTOX) approved in 1981 by FDA for treatment of strabismus, benign essential blepharospasm and disorders of cranial nerve VII

Botulinum-B toxin (Myobloc) recently approved by FDA for cervical dystonia
Urological uses of Botulinum over the Years

- 1987 – Detrusor-sphincter dyssynergia
  - *Dykstra, Sidi*
- 1998 – Treatment of prostatitis
  - *Maria G et al*
- 2000 – Neurogenic bladder overactivity (adults)
  - *Schurch, Schmid, Stohrer et al*
- 2001 – Neurogenic bladder (paediatrics)
  - *Shulte-Baukloh et al*
- 2001 – Non-neurogenic voiding dysfunction
  - *Phelan et al*
- 2003 – Idiopathic bladder overactivity
  - *Chancellor et al*
  - *Popat, Fowler et al*
- 2003 – Obstructive uropathy due to prostatic hypertrophy
  - *Maria et al*
- 2003 – Interstitial cystitis
  - *Radziszewski, Chancellor et al*
  - *Smith, Chancellor et al*
Pharmacology
Botulinum Neurotoxin Serotypes Differ by Percent of ToxinNicked

Unnickned
Inactive

Nicked
Active

Nicking → Activation → Efficacy

Mechanism of Action
BoNT-A (Allergan)
Botulinum Toxin: Urological Applications Today

- Sphincteric dysfunction
  - DESD
  - Dysfunctional voiding
  - Fowler’s syndrome

- Detrusor overactivity
  - Neurogenic overactivity
  - Idiopathic overactivity
Botulinum Toxin-A for DESD

- Described by Dykstra in 1988
- 9 studies (total 121 pts), only two small RTC’s
  - PVR decreased in 6, unchanged in 3
  - Bladder pressure decreased in 5
- Largest study used 50-100 units
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Toxin Dose</th>
<th>Outcome</th>
<th>Patient Population</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schurch et al.</td>
<td>2000</td>
<td>21</td>
<td>200 or 300 Units</td>
<td>89% completely continent</td>
<td>Spinal Cord Injury</td>
<td>CS</td>
</tr>
<tr>
<td>Schulte-Baukloh et al.</td>
<td>2002</td>
<td>17</td>
<td>85 to 300 Units</td>
<td>Incontinence decreased 39.4% UDS improved</td>
<td>Children with MMC</td>
<td>CS</td>
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<tr>
<td>Loche et al.</td>
<td>2003</td>
<td>30</td>
<td>200 Units</td>
<td>67% had improved continence</td>
<td>Refractory DO</td>
<td>CS</td>
</tr>
<tr>
<td>Radzieszweski and Borkowski</td>
<td>2002</td>
<td>12</td>
<td>300 Units</td>
<td>100% reported improvement in DO symptoms</td>
<td>Refractory DO</td>
<td>CS</td>
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<tr>
<td>Yokoyama et al.</td>
<td>2002</td>
<td>10</td>
<td>300 Units</td>
<td>80% improved symptoms</td>
<td>Neurogenic voiding dysfunction</td>
<td>CS</td>
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<tr>
<td>Abdelmalak et al.</td>
<td>2004</td>
<td>18</td>
<td>300 Units</td>
<td>100% had improved UDS and frequency</td>
<td>Refractory DO</td>
<td>CS</td>
</tr>
<tr>
<td>Grosse et al.</td>
<td>2004</td>
<td>35</td>
<td>N/A</td>
<td>53% improved UDS</td>
<td>Congenital spinal cord</td>
<td>CS</td>
</tr>
<tr>
<td>Corcos et al.</td>
<td>2004</td>
<td>20</td>
<td>5 U/Kg up to a max of 300 Units</td>
<td>65% improved UDS</td>
<td>Children with MMC</td>
<td>CS</td>
</tr>
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</tr>
<tr>
<td>Chancellor et al.</td>
<td>2004</td>
<td>41</td>
<td>100 to 300 Units</td>
<td>67% continent or improved</td>
<td>Neurogenic DO</td>
<td>CS</td>
</tr>
<tr>
<td>Grosse et al.</td>
<td>2004</td>
<td>49</td>
<td>300 Units Botox® or 750-1000 UI Dysport®</td>
<td>65% had 30% to 90% clinical and UDS improvement</td>
<td>Mixed, mostly spinal cord injury</td>
<td>CS</td>
</tr>
<tr>
<td>Kuo*</td>
<td>2004</td>
<td>20</td>
<td>200 Units</td>
<td>73% continent or improved</td>
<td>Mixed population</td>
<td>CS</td>
</tr>
<tr>
<td>Rapp et al. *</td>
<td>2004</td>
<td>35</td>
<td>300 Units</td>
<td>60% partial or complete symptom improvement</td>
<td>Refractory DO</td>
<td>CS</td>
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<tr>
<td>Reitz et al.</td>
<td>2004</td>
<td>231</td>
<td>300 Units</td>
<td>Of 180 patients with incontinence, 73% continent, remainder improved</td>
<td>Neurogenic DO</td>
<td>CS</td>
</tr>
<tr>
<td>Giannantoni et al.</td>
<td>2004</td>
<td>25</td>
<td>300 Units</td>
<td>BtxA &gt; RTX for DO, 50% BtxA treated group continent</td>
<td>Refractory Neurogenic DO</td>
<td>RCT</td>
</tr>
<tr>
<td>Schurch et al.</td>
<td>2004</td>
<td>59</td>
<td>200 or 300 Units</td>
<td>32-58% reduction in IEF versus placebo</td>
<td>Neurogenic DOI</td>
<td>RCT</td>
</tr>
<tr>
<td>Werner et al. *</td>
<td>2004</td>
<td>21</td>
<td>100 Units</td>
<td>90% improved UDS and QoL</td>
<td>Refractory idiopathic DOI</td>
<td>CS</td>
</tr>
<tr>
<td>Schurch et al. *</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Under development</td>
<td>Idiopathic DOI</td>
<td>RCT</td>
</tr>
</tbody>
</table>
Neurogenic DO: Botulinum Toxin – A

- 19 SCI patients with refractory neurogenic overactivity
  - All IC dependent, all incontinent
- 200-300 units Botulinum Toxin-A injected at 20-30 sites sparing trigone
  - 100 units/10ml NS
- Follow up at 6 weeks
  - 17/19 completely continent
  - UDS parameters improved significantly (compliance and pdetmax)
  - Persistent results at 36 weeks (minor regression)
<table>
<thead>
<tr>
<th>Time</th>
<th>Reflex Vol.</th>
<th>PVR</th>
<th>MCC</th>
<th>Compl.</th>
<th>pdet max</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>216 ml</td>
<td>261 ml</td>
<td>296 ml</td>
<td>32.6</td>
<td>65.6 cmH2O (n=19)</td>
</tr>
<tr>
<td>6 wks</td>
<td>416 ml</td>
<td>491 ml</td>
<td>481 ml</td>
<td>62.1</td>
<td>35 cmH2O (n=19)</td>
</tr>
<tr>
<td>12 wks</td>
<td>320 ml</td>
<td>413 ml</td>
<td>458 ml</td>
<td>50.2</td>
<td>37 cmH2O (n=11)</td>
</tr>
</tbody>
</table>

Mean values
Neurogenic DO: Botulinum Toxin – A
Schurch et al J ICS, 2004

• Randomized, multicenter, double-blind, placebo controlled study
• 59 patients with NDO refractory to anticholinergics
  – 53 SCI, 6 MS
  – 57 completed
• Randomized to:
  – BOTOX 200 units
  – BOTOX 300 units
  – Placebo
• Evaluated up to 24 wks.
Botulinum Toxin – A
Schurch et al ICS, 2004

• Significant reductions in incontinence episodes for both BOTOX groups, but not placebo
  – 200 units  32-54%
  – 300 units  42-58%

• Significant improvement in UDS parameters in both BOTOX groups, but not placebo at all time points
  – Increased MCC
  – Decreased in MDC
Significant (p≤0.05) within-group improvements in bladder function from baseline associated with BOTOX® treatment at all time points.

- Significant improvements were observed following BOTOX® treatment in all key urodynamic parameters and I-QoL scores throughout the study.
- Treatments were well-tolerated – no drug-related AEs reported.
• Available in 100 unit vials

• Crystallized

• Kept in freezer

• Cost approx $500-600/vial
BOTOX Injection

- 40 ml 1% lidocaine intravesically 10 minutes prior to procedure
- Rigid cystoscope with fixed needle
  - May use flexible scope
- Approx 30 injection sites
Controversies

• Amount injected
  – Based on literature/experience we use 200-300 units

• Concentration (100 units diluted in 1-10 ml)
  – Based on literature we use 100U/10 ml

• # of infections

• Site of injection
Our Protocol

• Bladder emptied
  – 40 cc 1% lidocaine instilled in bladder
  – 20 cc of 2% lidocaine gel injected into urethra
  – Left for 10 minutes

• Injections done with a 21 Fr. Rigid scope
  – BOTOX 100 units in 10 ml
  – 200-300 units injected at 20-30 sites
Injection

- Bladder emptied and partially filled
- 20-30 infections of 0.75 – 1 ml depending on amount used (usually 200 or 300 units)
- Cover posterior wall and posterior and lateral dome
- Anterior dome spared
- Trigone is optional – we do
Post Procedure

• Monitor patient to void
  – Hematuria
• 3 days of prophylactic abx usually quinolone
• Monitor PVR at 10 days
• May take 7-14 days for results
• Call MD:
  – if difficulty voiding or inability to void
  – Significant hematuria
  – Fever/chills
• If retention/ elevated PVR
  – Initiate CIC
  – May take several months to resolve
Re Injection

• Usually based on return of sx’s
• Usually 6-9 months
  – Sometimes earlier
BOTOX Injection
Summary

Idiopathic OAB Studies

- Usually refractory to PO cholinergics
- Btx-A (Allergan) doses: 50-200u
- Injection sites: 10-20; some include trigone
- Effect around 1 week
- Duration: 3-6 months
Botulinum Toxin A Compounds are not Equal

- Onabotulinum toxin A – BOTOX (Allergan)
  - 50, 100 & 200 U vials

- Abobotulinum toxin A – Dysport (Ipsen/Medicis)
  - 300 U vial

- Incobotulinum toxin A – Xeomin (Merz)
  - 50 & 100 U vials

THESE DOSES BETWEEN DRUGS ARE NOT INTERCHANGEABLE!!
Botulinum Toxin - Activity

Three steps leading to paralysis

1. Toxin binding by heavy chain
2. Translocation of light chain into cytosol
3. Cleavage of docking proteins \(\Rightarrow\) Inhibition of neurotransmitter release (Ach and others)
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Three steps leading to paralysis
1. Toxin binding by heavy chain
2. Translocation of light chain into cytosol
3. Cleavage of docking proteins ➔ Inhibition of neurotransmitter release (Ach and others)
Methods

- Patients with idiopathic OAB and urinary incontinence
  - ≥3 urinary urgency incontinence episodes in 3-day diary*
  - ≥8 micturitions/day

- Inadequately managed by anticholinergics (insufficient efficacy or intolerable side effects)
  - No concomitant anticholinergics

- 20 intradetrusor injections of onabotulinumtoxinA or placebo
  - 0.5 mL per site, sparing the trigone

*no more than one urgency incontinence-free day
Methods

Co-primary endpoints (measured at week 12)
- Daily frequency of incontinence episodes
- Proportion of patients with positive response on TBS

Secondary endpoints
- Daily frequency of micturition episodes
- Daily frequency of urgency episodes
- Volume voided per micturition
- Incontinence Quality of Life (I-QoL) total score
- King's Health Questionnaire (KHQ) domain scores (role limitations and social limitations)
OnabotulinumtoxinA – UUI Results

![Graph A: Time Post-treatment (Weeks)](image1)
- **Time Post-treatment (Weeks):**
  - 0, 2, 4, 6, 8, 10, 12
  - UI Episodes 24 Hours
  - **Placebo: -1.09, -1.07, -0.87**
  - **OnabotA 100U: -2.85*, -3.05*, -2.65* (significant)**

![Graph B: Time post-treatment, wk](image2)
- **Time post-treatment, wk:**
  - 0, 2, 4, 6, 8, 10, 12
  - Mean change from baseline (UI episodes per day)
  - **Placebo: -1.34, -1.37, -1.03**
  - **OnabotA 100 U: -2.85*, -3.18*, -2.95* (significant)**

![Graph C: Patients with Positive Treatment Response](image3)
- **Patients with Positive Treatment Response (%):**
  - Placebo: 32.6, 34.7, 29.2
  - OnabotA 100U: 64.5*, 66.9*, 69.8*

![Graph D: Patients, %](image4)
- **Patients, %:**
  - Time post-treatment, wk: 2, 6, 12
  - **Placebo: 36.8, 30.9, 26.8**
  - **OnabotA 100 U: 64.2, 69.3, 62.8 (significant)**

Nitti, VW  J Urol 2013; 189: 2186-93
Chapple C  Eur Urol 2013; 64: 249-56
Duration of Effect & Retreatment

- Duration of effect defined by patient request for re-treatment*
  - Median time to re-treatment request was 166 days (~24 weeks)

- Efficacy sustained for up to 5 treatments

- Maintained efficacy with repeat injection seen in literature
  - OAB
  - NDO

*Patients could be retreated if:
- They requested it
- They had ≥2 UUI episodes on a 3 day diary
  - PVR <100 ml

Nitti, AUA, 2013
Sahai, et al, Urology, 2011
Khan, et al, J Urol, 2011
Assessment of Outcomes

- Voiding diary
- Patient-related global response scales
  - Urgency
  - Urgency incontinence
  - Frequency
  - Nocturia
- Validated OAB-specific questionnaires
- Query of adverse events