Botox for Overactive Bladder

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Definition

- Urinary urgency
- With or without urge incontinence
- Usually with frequency & nocturia

International Continence Society 2003

Epidemiology

- OAB affects 16% of population
- 33 million adults
- Prevalence: women = men

Prevalence of OAB by Age and Gender in the US

- Men: 16.0%
- Women: 16.9%


How widespread are the symptoms of an overactive bladder and how are they managed? Br J Urol Int. 2001;87:760-766.
Community residents in the United States spend $9.17 billion on Institutionalized costs amount to $2.85 billion. Annual spending for patients with OAB is 5-fold higher compared to patients without the condition, $5018 vs. $1767.

Possible Etiologies for OAB
- **Myogenic**
  - Myogenic activity and distension of the detrusor
- **Neurogenic**
  - Decreased central nervous inhibition
- **Urothelial**
  - Abnormalities in urothelial signaling

The Urothelium: Not Your Ordinary Lining
- Not just a barrier for toxic substances
- Also is a highly metabolic active tissue
- May take an active part in both storage and voiding phases of micturition cycle
- ATP may be involved in sensory signaling in the urinary bladder
- ATP acts on P2x3 receptors on subepithelial sensory nerves to convey information to the CNS
- Effects of ATP inhibited by L-arginine and by neurokinin-2–receptor antagonist

Potential Receptor Targets: Sub-urothelium
- (Diagram showing receptors and signaling pathways involving ATP, NO, and other factors.)
**Alternative Therapies**

- Neuromodulation
  - Posterior tibial
  - Pudendal
  - Sacral
- Botulinum toxin
- Intravesical instillation
  - Anticholinergic agents*
  - Capsaicin*
  - Resiniferatoxin*
- Bladder augmentation *Non-approved

**Technique**

- Botox 100 U diluted in 10 ml NaCl (10 U/ml)
- No bubbles
- 5 Fr injection needle + rigid cystoscopy
- Inject 1 ml/site
- Maximum dose: 100-300 U

**Botox A for Neurogenic Detrusor Overactivity (NDO)**
BoNT-A in NDO: Overview

SAFETY
- BoNT-A (Hall)
  - One case of arm muscle weakness
- BoNT-A (Dysport NCTN-2916)
  - Up to 17% transient muscle weakness in the trunk and/or extremities lasting up to 3 months
  - 5%-8% hypoesthesia
  - Side effects appear to be dose-related: 2 NDO studies using lower doses had different outcomes
- Molecular size may result in migration

EFFICACY
- 2000-2007 review
- 37 studies, >1200 NDO patients
- Predominantly spinal cord injury (SCI), multiple sclerosis (MS), and spina bifida patients
- Most subjects were refractory to, and/or unable to tolerate, anticholinergic therapy
- High rates of continence (73%-90%)

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Botox in NDO: Selected Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reitz et al., 2004</td>
<td>Multicenter, nonrandomized, open-label, retrospective</td>
<td>200</td>
<td>Largest case series with BoNT-A in NDO</td>
</tr>
<tr>
<td>Schurch et al., 2005</td>
<td>Multicenter, randomized, double-blind, placebo-controlled</td>
<td>59</td>
<td>First randomized, double-blind, placebo-controlled trial with BoNT-A in NDO</td>
</tr>
<tr>
<td>Giannantoni et al., 2004</td>
<td>Single-center, randomized, open-label, prospective</td>
<td>25</td>
<td>Only study that compares intravesical resiniferatoxin and BoNT-A injections into the detrusor muscle in NDO</td>
</tr>
</tbody>
</table>

Safety and Efficacy of Botox in NDO With UI (Schurch, 2005)

Methods
- Multicenter, double-blind, randomized, placebo-controlled, N = 59
- Entry criteria: NDO + incontinence from SCI or MS inadequately treated with anticholinergics and performing regular CIC
- Key outcomes: Primary outcome: Incontinence episodes (baseline, weeks 2, 6, 12, 18, 24)
  - Urodyamics (baseline, weeks 2, 6, and 24)
  - Maximum cystometric capacity (MCC), volume at first bladder contraction, maximum detrusor pressure during contraction (MDP)
  - Adverse events
  - QoL (incontinence quality-of-life questionnaire)
- Injection paradigm: Randomized (1:1:1) to single 200 U, 300 U, or placebo dose
- 30 detrusor sites sparing trigone; 1 cc (10 U) per site
- Concomitant anticholinergics allowed

Patient Profiles
- Neurogenic basis: N = 59; spinal cord injury (53); American Spinal Injury Association Class (A = 33, B = 10, C = 5, D = 4, E = 1)
- Multiple sclerosis (6)
- Mean NDO history 63 months (range 3 months - 24 years)
- Withdrawals: 2 patients in the 200 U group
  - AE (urethral stricture) prior to study drug administration
  - Lack of efficacy at week 6; protocol violation
- Demographics: Mean age, 41 years (range 20-72)
  - 91% male, 90% female; 93% Caucasian
- Baseline measures: No differences between groups
**Safety and Efficacy of Botox in NDO With UI: Results**

**SAFETY**
- No differences between groups in overall AE incidence
- No drug-related AEs
- No injected patients withdrew due to an AE
- No cases of autonomic dysreflexia or systemic effects
- No clinically relevant changes in other safety assessments observed

**EFFICACY**
- Improvements in UI management
  - Rapid and sustained decrease in number of daily UI episodes: 49.2% reported no incontinence at some point
  - Improvements in all urodynamic parameters (MCC and MDP)
  - Marked increase in I-QoL scores


**Botox in NDO: Gaps in Knowledge**
- Data from large randomized, controlled clinical trials—phase II and III trials (ongoing)
- Long-term safety data on single and multiple administration of BoNT-A in NDO
- Data on dose-ranging and optimal administration of BoNT-A
- Better definition of duration of effect to compare studies and guide in retreatment
- Studies in other NDO patient populations (eg, MS, MMC, children)
- Separate evaluation of different commercially available BoNT agents and formulations

**BoNT-A Therapy for Idiopathic Overactive Bladder (IOAB)**

**Botox and IOAB Overview of Clinical Studies**
- Medline search 1999 to 3/2007\(^1,2\)
- 26 studies, 14 published clinical studies in full
  - 1 RCT (evidence level I)
  - 24 prospective studies (evidence level II)
  - 1 retrospective study (evidence level III)
- >500 patients studied with IOAB unable to tolerate or refractory to anticholinergic therapy
- BoNT-A formulations studied
  - 18/26 studies investigated the efficacy of BoNT-A (Hall) exclusively
  - 1 BoNT-A (NCTC-2916)
  - 1 BoNT-A (Hall) and BoNT-A (NCTC-2916)
  - 6 studies did not specify a particular formulation

BoNT-A and IOAB
Selected Clinical Studies

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<th>Study</th>
<th>Design</th>
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<th>Description</th>
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<tbody>
<tr>
<td>Sahai et al, 2007</td>
<td>Single-center, randomized, double-blind, placebo-controlled</td>
<td>34</td>
<td>BoNT-A &lt;br&gt;• Only randomized, double-blind, placebo-controlled trial with BoNT-A in IDO &lt;br&gt;• Clinical evidence level I</td>
</tr>
<tr>
<td>Schmid et al, 2006</td>
<td>Multicenter, nonrandomized, open-label, prospective</td>
<td>100</td>
<td>BoNT-A &lt;br&gt;• Largest case series with BoNT-A in IOAB &lt;br&gt;• Clinical evidence level II</td>
</tr>
<tr>
<td>Ghei et al, 2005</td>
<td>Single-center, randomized, double-blind, placebo-controlled, crossover</td>
<td>20</td>
<td>BoNT-B &lt;br&gt;• Examined in mixed population (NDO + IDO) &lt;br&gt;• Clinical evidence level I</td>
</tr>
</tbody>
</table>


Overview of Efficacy in Published Clinical Studies: BoNT-A (Hall) in IOAB

- 1/2000 to 7/2006: 25 studies and 22 abstracts documenting use of BoNT-A in IOAB
- Only one randomized, placebo-controlled study
- >500 IOAB patients refractory to or unable to tolerate anticholinergic therapy
- All IOAB studies showed improvements in symptoms and/or urodynamic parameters
- Duration of effect with BoNT-A ranged from 5 to 10 months


Overview of Safety in Published Clinical Studies: BoNT-A and IOAB

- No systemic adverse events following BoNT-A treatment
- Local side effects
  - Transient urinary retention that may require clean intermittent catheterization (CIC)
  - Post-procedure urinary tract infection (6%-31%)


BoNT-A for Patients With IDO (Sahai, 2007)

<table>
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<tr>
<th>Methods / Demographics</th>
<th>Design</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Single-center, randomized, double-blind, controlled</td>
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<tr>
<td></td>
<td>34 randomized (1:1); placebo = 18; BoNT-A = 16</td>
</tr>
<tr>
<td></td>
<td>Blind for 12 weeks; open-label extension for 12 weeks</td>
</tr>
</tbody>
</table>

| Inclusion criteria     | Age 18-80; symptoms of OAB, DO by urodynamics |
|                       | Failed anticholinergic therapy, can perform CISC |

| Key outcome parameters | Primary outcome: change in MCC |
|                       | Clinical, urodynamics (baseline, weeks 4, 12, and 24) |

| Injection paradigm     | 20 injections of 200 U BoNT-A or placebo, 10 U/mL per injection site in the bladder wall, sparing the trigone |

| Baseline characteristics | Baseline characteristics comparable except for urgency (more severe in the BoNT-A group) |

BoNT-A for Patients With IDO: Results

- BoNT-A treatment compared to placebo
- Significant improvements in urodynamics
- ↓ in MCC and PVR, ↓ in MDP
- Reductions in frequency, urgency, and urgency incontinence
- Discontinuation in anticholinergic use in several patients
- Improvements in QoL (IIQ-7 and UDI-6)
- In the open-label extension study, some patients experienced improvements in urodynamics, clinical parameters, and QoL for up to 24 weeks
- No systemic AEs; symptomatic >150 mL PVR (6/16, 38%, all requiring CIC); UTI (7/16, 44%), rash (1/16, 6%)

BoNT-A is better than placebo or no tx
- Less incontinent episodes
- Reduced frequency
- Increase voided volume
- Reduced urgency
- Decrease in detrusor pressure
- Increase mean cystometric capacity

Cochrane Review

- Randomized or quasi-randomized controlled trials
- 8 studies included
- N = 14 to 59
- Majority with neurogenic detrusor overactivity
- F/U range 6 weeks to 24 months…ongoing


Cochrane Review

- Intravesical Botox is better than instillation of resiniferatoxin
- No statistical significance between different doses of Botox
- No longterm data
- Rare adverse effects may only declare themselves with increased use
Where? How Deep?

- N=45 with Idiopathic Detrusor Overactivity
  - 15 into detrusor (2mm)
  - 15 suburothelial
  - 15 bladder base
- All 100U Botox A (Allergan®)


Success Rates

<table>
<thead>
<tr>
<th>Time</th>
<th>Detrusor</th>
<th>Suburothelial</th>
<th>Bladder Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>93%</td>
<td>80%</td>
<td>67%</td>
</tr>
<tr>
<td>6 months</td>
<td>67%</td>
<td>47%</td>
<td>13%</td>
</tr>
<tr>
<td>9 months</td>
<td>20%</td>
<td>20%</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

Success = > 50% improvement in symptoms

Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Detrusor</th>
<th>Suburothelial</th>
<th>Bladder Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention (3 months)</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dysuria</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>UTI</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bladder/ Urethral pain</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Botox for OAB and NDO: Summary

- Antimuscarinic agents are limited by lack of efficacy and tolerability issues, which significantly reduce long-term compliance
  1, 2
- The use of BoNT-A for the treatment of OAB and DO is currently not approved by the FDA
- Defining the optimal use of BoNT-A in OAB is difficult given the variation in dosage, dilution, injection sites, number of injections in small patient numbers reported in the literature

Botox Therapy for OAB and NDO: Summary (continued)

- BoNT-A has shown promise in NDO patients refractory to conventional systemic therapy
- Treatment with BoNT-A can at least temporarily restore full continence and reduce catheter use in a high proportion of NDO patients
- BoNT-A is safe and well tolerated in NDO


Online Resources

- The Neurotoxin Institute (http://www.neurotoxininstitute.org)
  - Information related to the basic science and the clinical applications of neurotoxin therapies
- National Spinal Cord Injury Association (http://www.spinalcord.org)
  - Dedicated to improving QoL for spinal cord injury patients and their families
- National Association for Continence (http://www.nafc.org)
  - Consumer advocacy group for public education on the causes, prevention, diagnosis, treatment, and management of incontinence

Thank You
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