Bridging the Gap

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University of Cambridge Teaching Hospital
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OAB

Aetiology: Unknown!!!

Ideal Treatment: Inadequate
Prevalence = 17%
Increase in Post menopausal women
Major impact on quality of life
70% have low self esteem

COST
$US 31.1 billion in 2000

Hu et al Urology 2004;63:461
OAB – United Kingdom

7 million adults affected
More prevalent than diabetes and angina

Cost €800 million in 2000

Rise by 22% by 2020
OAB – United Kingdom

€ 800 million

Consultations with physicians – 45%
Incontinence Pads - 33%
Prescription medicines - 8%

More prevalent than Diabetes or Asthma
OAB

Lifestyle changes
Bladder retraining
Pelvic floor rehabilitation
Anticholinergics
  Failure to respond
  Side effects
Botulinum Toxin
Sacral neuromodulation
Bladder augmentation
All patients to an MDT
QOL questionnaires
Lifestyle advice
PFE
Behavioral therapies
Anticholanergics
Botox
SNS
Surgery
Options Beyond Anticholinergics

Sacral Nerve Stimulation

Posterior Tibial Nerve Stimulation

Verve Transcutaneous Stimulation

Botulinum toxin A

TENS

Augmentation Cystoplasty
BOTULINUM TOXIN A
Botox® – the evidence

7, 620, 000 entries

Ocular
Upper respiratory
Dystonia disorders
GIT
Urinary
Pain
ANS
Other muscle
Evidence base??

Advertised for at least 12 years

Widely available

Minimal safety concerns

Minimal efficacy concerns

Minimal concern regarding adverse outcomes
Cosmetic
History
Botulinum Toxin

Neurotoxic Protein
Produced by Clostridium Botulinum

Most toxic substance known to mankind
- Ricin
- Anthrax
- Sarin
- Tetrodotoxin
- Cyanide
- Mercury
- Strychnine
- Amotoxin

$L_D{50}$
- $0.005 - 0.05 \mu g/kg$
- $70 \mu g$ per oral
- $0.09 \mu g$ I.V.

1Gm would kill 1,000,000 humans
Botulinum Toxin

150 kDa molecular mass

Seven distinct serological types: - A – G

Two chain polypeptide

Heavy chain - 100kD
Light chain - 50kDA

Light chain = enzyme (protease)

Attacks one of the fusion proteins at a neuromuscular junction preventing vesicles from anchoring to the membrane and releasing Ach

Causes a flaccid paralysis
Botulinum Toxin

Described 1817 – Justinus Kerner
   “sausage poison”

1817 – Botulism – Muller

1897 – Emile van Ermengem identified the bacterium

1928 – Snipe and Sommer purified the toxin

1960’s Scott and Schantz prepared a toxin for therapeutic purposes

1989 – FDA approval for strabismus

2002 – FDA approval for frown lines
<table>
<thead>
<tr>
<th>Botulinum Toxin A</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Apobotulinum Toxin A</td>
<td>150 Kda</td>
</tr>
<tr>
<td>- Botox</td>
<td></td>
</tr>
<tr>
<td>Abobotulinum Toxin A</td>
<td>800 KDa</td>
</tr>
<tr>
<td>- Dysport</td>
<td></td>
</tr>
</tbody>
</table>
Technique

Cystoscopic injection
Flexible / Rigid scope
Anasthesia
Sheath
Disposable needle
Botox

100 to 300 units
Inject over a grid pattern
Injection Controversies

Correct dosage
  Different rates of retention

Dilution

Site of injection
  Trigonal
  Non-trigonal

Handling
Clinical Danger

28 deaths in Dermatology 1989 – 2003

Cote et al J Am Acad Dermatol

28/02/2009

FDA

‘Botox has been linked in some cases to adverse reactions, including respiratory failure and death, muscle weakness, swallowing difficulties….’

No reported deaths in cosmetic cases
Clinical Evidence
Relax
An overactive bladder study

Doug Tincello
Mark Slack
Phil Toozs-Hobson
Patients with refractory OAB
Treated with more than one AcH preparation
Urodynamic evidence of DOI
Randomised to Botox or Placebo
Placebo identical to injection
Grant funded study
n = 240

Randomised placebo controlled trial

Open label extension x two further injections
1:1 randomization

Local / G.A.

Placebo 20mls human serum albumin and NaCl

Trigone sparing
Primary outcome measures:

24 hour diary x two

Secondary outcome measures:

Diary
Urgency
Incontinence episodes
Urge severity

Quality of life

ICIQ-SF
IQOL

Complications, Additional treatments, Interval between voids

Economics

EuroQa 5D
Estimated costs
Recruitment

Screened 415
Eligible 283

Loss before randomisation 43

Randomised to Botox 122
Randomised to placebo 118

6/12 visit 116
Lost 0

Extension study 105

6/12 visit
Lost 2

Extension study 107
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60 (50 – 67)</td>
<td>58 (51 – 69)</td>
</tr>
<tr>
<td>BMI</td>
<td>49</td>
<td>50</td>
</tr>
<tr>
<td>Smoker</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>Parity 1+</td>
<td>112</td>
<td>111</td>
</tr>
<tr>
<td>Prev surgery</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>Voiding Freq.</td>
<td>10 (9 – 12)</td>
<td>10 (9 – 13)</td>
</tr>
<tr>
<td>Incont. / 24 hrs</td>
<td>6 (3-8)</td>
<td>6 (3-9)</td>
</tr>
<tr>
<td>Urgency</td>
<td>8 (6 – 10)</td>
<td>8 (6-9)</td>
</tr>
<tr>
<td>Continent</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>ICIQ</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>I-QOL</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>Anaesthetic - Local</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>- Flexi</td>
<td>43</td>
<td>44</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th></th>
<th>Treatment n=100</th>
<th>Placebo n=90</th>
<th>Difference OR and 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voiding Freq</td>
<td>8 (7-10)</td>
<td>10 (9-12)</td>
<td>1.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Incontinence episodes/24 hours</td>
<td>1.7</td>
<td>6</td>
<td>4.3 (3-6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urgency episodes</td>
<td>4</td>
<td>6</td>
<td>2.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>USS</td>
<td>1.5</td>
<td>1.9</td>
<td>0.4</td>
<td>0.0006</td>
</tr>
<tr>
<td>Continent</td>
<td>31%</td>
<td>12%</td>
<td>3.12 *</td>
<td></td>
</tr>
<tr>
<td>ICIQ score (n=0)</td>
<td>10</td>
<td>15</td>
<td>5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>I-QOL (n = 100)</td>
<td>55</td>
<td>27</td>
<td>-27</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
## Diary outcomes at 3 months

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N=86</th>
<th>N=86</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Void freq /24 hr</td>
<td>8 (6-10)</td>
<td>10 (8-11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Incont episodes/24 hr</td>
<td>1 (0-6)</td>
<td>5 (2-8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urgency/24hrs</td>
<td>3 (0-6)</td>
<td>7 (4-9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IUSS</td>
<td>1.3 (08-2)</td>
<td>1.9 (1.4-2.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Continent n(%)</td>
<td>36 (35)</td>
<td>12 (12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICIQ score</td>
<td>8 (3-14)</td>
<td>15 (9-17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IQOL score</td>
<td>64 (27-90)</td>
<td>25 (14-44)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

A 19 point change in I-QOL correlates with 90% of patients saying they are very much better
## Adverse events at f/u at 6/12

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Treatment</th>
<th>Placebo</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI (%)</td>
<td>36 (31%)</td>
<td>12 (11%)</td>
<td>3.68(1.7-8.2)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Voiding difficulty (%)</td>
<td>10 (9%)</td>
<td>1 (1%)</td>
<td>10.28 (1.4-450)</td>
<td>0.01</td>
</tr>
<tr>
<td>ISC (%)</td>
<td>18 (16%)</td>
<td>4 (4%)</td>
<td>4.8 (1.5-20)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Results
BoNT -A produced:

A 25% reduction in frequency
A 50% reduction in urgency & leakage episodes
A third of women achieving continence at six months after injection.
Background

Botulinum toxin (BoNT-A) established as second line treatment

Neurotoxin from *Clostridium botulinum*

Single treatment provides profound long-term benefits

Improvements in urgency, leakage most marked

Moderate risk of retention (8-15%)

Uncertainties remain

What is the “ideal” dose?

Why do some patients not report benefit?

Aim of study

Do any patient factors predict failure to respond?

Pre-specified secondary analysis of primary data from RELAX

Methods

RELAX was a 1:1 randomised trial (B0NT-A 200u or placebo)

Single treatment, flexible or rigid cystoscopy

Follow up at 6 weeks, 3 & 6 months

Pre-planned secondary analysis

Data from women receiving active drug (n=122)

Outcome data at 6 weeks to avoid confounding of benefit

Five different criteria for “treatment failure”

Stepwise logistic regression of baseline factors and demographics

  Univariate analysis

  Multivariate analysis where multiple factors achieved p <0.10

Multiple imputation to manage missing data
Methods

Failure

10% or lower improvement in leakage, urgency episodes, frequency
Failure to achieve continence
“no change” or worse on the PGI-I scale

Clinical factors

age; ethnicity; parity; previous continence surgery; BMI
baseline leakage episodes, urgency episodes & voiding frequency

Urodynamic variables

volumes at first sensation & capacity
maximum detrusor pressure during filling, voiding & max flow
volume at first contraction
amplitude of first contraction
Conclusions

Few predictive factors

Non-smokers more likely to have benefit in urgency
Greater initial leakage predicts failure to achieve continence

Published data

No regression data
Small bladder capacity/low compliance
High maximum detrusor pressure
Ineffective anticholinergic medication

Factors worth further exploration

Increasing age associated with worse overall improvement
Increasing BMI associated with worse overall improvement

Sahai Urol 2008¹; 71:455; Schmid J Urol 2006²; 176:177; Mackovey N & U 2011; 30:1538³
BOTOX® EMBARK clinical study: Overactive bladder
EMBARK: two phase III pivotal trials with BOTOX® 1-3

BOTOX® 100 U

Placebo

BOTOX® 100 U

Placebo

Pre-screen/randomisation

Efficacy and safety assessment: Weeks 2, 6, 12
Quality-of-life assessment: Week 12

Study 095 (N=557)

Study 520 (N=548)

Long-term extension: Study 096

Up to 3 additional years

Primary endpoint
Earliest time for re-treatment

Weeks

Study exit unless re-treatment occurred

*Placebo-controlled comparison period.

2. BOTOX® Summary of Product Characteristics. Allergan
EMBARK: Study endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>• Number of urinary incontinence episodes</td>
</tr>
<tr>
<td></td>
<td>• Proportion of patients with positive treatment response on the Treatment Benefit Scale</td>
</tr>
<tr>
<td>Secondary</td>
<td>• Number of daily urgency episodes</td>
</tr>
<tr>
<td></td>
<td>• Number of daily micturition episodes</td>
</tr>
<tr>
<td></td>
<td>• Volume voided per micturition</td>
</tr>
<tr>
<td></td>
<td>• I-QOL total summary score</td>
</tr>
<tr>
<td></td>
<td>• KHQ domains (role limitations and social limitations)</td>
</tr>
</tbody>
</table>

Patients randomised in a 1:1 ratio:

**BOTOX® 100 U; or**

**Placebo**

Administered via:

- Rigid or flexible cystoscope
- 20 intradetrusor injections, sparing trigon
- 0.5 mL per site

Optional instillation of local anaesthesia and/or sedation

Re-treatment:

**BOTOX® 100 U permitted after ≥12 weeks**

After two incontinent episodes in the 3 day diary

**PVR <200 mL**

PVR, post-void residual

Patient request

---

1. BOTOX® Summary of Product Characteristics, Allergan
2. Allergan Data on File Summary of clinical Efficacy
Demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BOTOX® 100 U (N=557)</th>
<th>Placebo (N=548)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.6</td>
<td>60.1</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11.0</td>
<td>13.5</td>
</tr>
<tr>
<td>Female</td>
<td>89.0</td>
<td>86.5</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>89.8</td>
<td>92.0</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>10.2</td>
<td>8.0</td>
</tr>
<tr>
<td>BMI (mean, kg/m²)</td>
<td>29.9</td>
<td>30.9</td>
</tr>
<tr>
<td>Duration of OAB (years)</td>
<td>6.04</td>
<td>6.14</td>
</tr>
<tr>
<td>Number of prior anticholinergics used (mean)</td>
<td>2.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Urinary incontinence episodes (per 24 hours)</td>
<td>5.49</td>
<td>5.39</td>
</tr>
<tr>
<td>Urgency episodes (per 24 hours)</td>
<td>8.82</td>
<td>8.31</td>
</tr>
<tr>
<td>Micturition episodes (per 24 hours)</td>
<td>11.99</td>
<td>11.48</td>
</tr>
<tr>
<td>Nocturia episodes (per 24 hours)</td>
<td>2.17</td>
<td>2.04</td>
</tr>
<tr>
<td>Volume voided per micturition (mL)</td>
<td>150.4</td>
<td>156.9</td>
</tr>
</tbody>
</table>

Groups were well balanced with no significant differences between treatment groups.
BMI, body mass index; OAB, overactive bladder.

1. Allergan Data on File Baseline Patient Characteristics
Change in daily urinary incontinence episodes versus placebo

At Week 12, BOTOX® led to a 50% reduction from baseline in UI episodes versus 17.6% with placebo (p<0.001)

Baseline values
Placebo: 5.39/day
BOTOX® 100 U: 5.49/day

**p<0.001 vs. placebo.

UI, urinary incontinence.

Adapted from: BOTOX® Summary of Product Characteristics, Allergan
Change in urinary incontinence versus placebo

Patients with ≥50% or ≥75% decrease in urinary incontinence

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=548)</th>
<th>BOTOX® 100 U (n=557)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% reduction</td>
<td>31.0</td>
<td>60.5</td>
</tr>
<tr>
<td>≥75% reduction</td>
<td>17.7</td>
<td>46.0</td>
</tr>
</tbody>
</table>

*Patients must have had no incontinence episodes in the 3 days preceding the 12-week time point.

Adapted from: BOTOX® Summary of Product Characteristics, Allergan
Change in daily urgency episodes versus placebo

At Week 12, BOTOX® led to a 37% reduction from baseline in daily urgency episodes versus 15% with placebo (p<0.001)

Baseline values
Placebo: 8.31/day
BOTOX® 100 U: 8.82/day

**p<0.001 vs. placebo.

1. Adapted from: BOTOX® Summary of Product Characteristics, Allergan
2. Allergan Data on File: Summary of clinical efficacy
Change in daily micturition frequency versus placebo

At Week 12, BOTOX® led to a 20% reduction from baseline in daily micturition frequency versus 8% with placebo (p<0.001)

Baseline values:
Placebo: 11.48/day
BOTOX® 100 U: 11.99/day

*p≤0.05; **p<0.001 vs. placebo.

Adapted from BOTOX® Summary of Product Characteristics, Allergan
Allergan Data on File Summary of clinical Efficacy
Episodes During Treatment Cycle 1
Over 60% of BOTOX® patients were "Greatly improved" or "Improved"

Significantly more BOTOX® patients reported their symptoms as "Greatly improved" or "Improved"

**p<0.001 vs. placebo.

Adapted from: BOTOX® Summary of Product Characteristics, Allergan
Median time to patient request for re-treatment is ~6 months

The median duration of response following BOTOX® treatment, based on patient request for re-treatment, was 166 days (~24 weeks)
Patients with absolute PVR at different thresholds at Week 12

- Majority of BOTOX®-treated patients with urinary retention had PVR ≤100 mL

Patients (%)

- Placebo
- BOTOX® 100 U

PVR, post-void residual.

PVR, post-void residual.

Main from Allergan Data on File PVR Tables
The majority of patients did not require CIC.

CIC rates are low and predominantly transient.

CIC = 6.5% (36/552 patients)*

*Patients requiring CIC at any point during treatment cycle 1. CIC, clean intermittent catheterisation.
Clinically meaningful improvements in all I-QOL domains

Change from baseline in I-QOL domain scores at Week 12

Mean change from baseline

Avoidance and limiting behaviour

Psychosocial impact

Social embarrassment

Total summary score

Placebo (n=548)

BOTOX® 100 U (n=557)

Clinically important difference = + 10 points

**p<0.0001 vs. placebo.

I-QOL, Incontinence quality-of-life questionnaire.

Adapted from Data on File 001 – Incontinence Quality of Life Domain & Total summary Score (2).
BOTOX® 100 U significantly improves OAB symptoms in patients who had inadequate response to anticholinergic therapy

The EMBARK studies demonstrated significant reduction in daily urinary incontinence episodes

27.1% of BOTOX® patients achieved 100% dry rates vs. 8.4% of patients on placebo

All primary and secondary endpoints showed significant improvements

In all OAB symptoms
In patient perception of benefit/QoL

BOTOX® median duration of response was 166 days (~24 weeks)

OAB, overactive bladder; QoL, quality of life.
1. BOTOX® Summary of Product Characteristics, Allergan.
2. Allergan Data on File: Summary of clinical Efficacy
Primary DIGNITY study results
Significant reduction in weekly urinary incontinence episodes versus placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=241)</th>
<th>BOTOX® 200 U (n=227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline (episodes/week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td><strong>-16.8</strong></td>
<td><strong>-20</strong></td>
</tr>
<tr>
<td>Week 6*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td><strong>-19.8</strong></td>
</tr>
</tbody>
</table>

Mean baseline values:
Placebo: 31.5 episodes/week
BOTOX® 200 U: 32.4 episodes/week

* Week 6 = Primary timepoint
**p<0.001 in pairwise comparison vs. placebo.

Adapted from: BOTOX® Summary of Product Characteristics, Allergan.
High proportion of patients had significant improvements in urinary incontinence 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

63% of patients achieved a ≥75% reduction from baseline in incontinence episodes

Percentage of dry patients (without incontinence) throughout week 6 was 37%

Adapted from: BOTOX® Summary of Product Characteristics, Allergan.
Tachyphylaxis

Neurogenic DOA (spinal cord lesions)
N=27
Mean No of treatments - 7.1
Long term every fourth Pt. needed surgery
  Pannek et al BJU Int Epub ahead of print

Neutralizing antibody formation
  clinical trial database
Formation of nAb < 0.5%
  Naumann et al Mov Disord 2009;24(Suppl 1)
Alternative methods:-

Instillation with Gap junction modulators

Liposomes as a delivery vehicle?

Previously used for capsaisin

Intravesical lipotoxin cleaved SNAP-25 and inhibited CGRP release – blocking acetic acid cystometric changes.
Pilot Study of Liposome Encapsulated Onobotulinumtoxin A to Patients with OAB

Kuo et al, Eur Urol 2014

Randomised trial
N = 25
Reduction in frequency
A Human Touch

What matters the most
Monday, 16th November 2009

TO: Helen Bowyer & Mr Slack,

I am writing to thank you for adding me to your Botox programme for an overactive bladder. It has given me my normal life back.

Before, I suffered for 3yrs, not being able to go out without special protective underwear, then always having to know where toilets were. I could never sleep overnight anywhere. Not even sleeping in the same bed as my husband. With also being so 'wet' all the time, I had exzema throughout the groin, which was very painful. All this and much more, made me severely depressed. Thanks to the Botox treatment my life has improved so much... and set me free.

I so hope the treatment can be funded, for, without it, I would hate to go back to how I was.

Again, I thank-you sincerely for putting my life back on track, and my husband back in my bed, as it should be.

Yours Sincerely,

Sen Staff Conference 2009
Conclusion

Anticholinergics should still be first line?

Botox in bladder disorders is effective

Scientific studies need to be engaged

Random introduction ahead of licensing unethical!??
Systematic review:

16 studies
50% had no daily incontinence
Revision rates 6 – 16%

Siddiqui et al Int Urogynecol J 2012
PTNS
VERV™ Percutaneous SNS
**VERV™**

Replaced every 7 days

Transdermal Amplitude Modulated Signal

Placed by patient

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>UUI</td>
<td>2.2</td>
<td>4.9</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Freq</td>
<td>9.4</td>
<td>11.3</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Urgency</td>
<td>7.8</td>
<td>10.0</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>
TENS Machines
Thank You