The role of Botulinum Toxin A in the management of urinary incontinence

Angie Rantell
Senior Nurse, Urogynaecology
King’s College Hospital
London
Aim of session

• To review the initial assessment and management of OAB / DO

• To consider initial treatment pathways

• To discover the history behind the medical use of Botulinum toxin

• To examine its use in the management of urinary incontinence
## Prevalence of OAB

<table>
<thead>
<tr>
<th>A prevalent condition</th>
<th>16.6% of the population in Europe aged 40 years and over suffer from OAB symptoms&lt;sup&gt;1&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Under diagnosed</td>
<td>Most sufferers in Europe do not seek medical attention or remain undiagnosed&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Under treated</td>
<td>In Europe, only 27% of those with OAB who consult a doctor receive treatment&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Increases with age</td>
<td>30-40% of those aged 75 years and over in Europe suffer from OAB&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Significant burden</td>
<td>OAB sufferers in the US reported 20% more physician visits and 138% more UTIs&lt;sup&gt;3&lt;/sup&gt;</td>
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1. Milsom et al, 2001
2. Goepel et al, 2002
3. Wagner et al, 2002
Impact of Incontinence on Quality of Life

**Physical**
- Limitations or cessation of physical activities

**Sexual**
- Avoidance of sexual contact and intimacy

**Occupational**
- Absence from work
- Decreased productivity

**Domestic**
- Requirements for specialized underwear, bedding
- Special precautions with clothing

**Psychological**
- Guilt/depression
- Loss of self-esteem
- Fear of
  - being a burden
  - lack of bladder control
  - urine odour

**Social**
- Reduction in social interaction
- Limiting and planning travel around toilet accessibility
**IUGA / ICS definitions**

**Overactive bladder (OAB) syndrome**

- Urgency usually accompanied by frequency and nocturia with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology.

**Detrusor Overactivity (DO)**

- Detrusor overactivity is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked.
- If a relevant neurological cause is present, then neurogenic detrusor overactivity (NDO) is noted, otherwise idiopathic detrusor overactivity (IDO) should be the term used.
Aetiology of NDO

• Spinal cord injury
• Spina bifida
• Multiple sclerosis
• Cerebral vascular accidents
• Parkinson’s disease
• Spinal surgery
• Other
Urgency and Frequency: Causes

Urological
- Urinary tract infection
- Urethral syndrome
- Detrusor overactivity
- Bladder tumour
- Bladder calculus

Gynaecological
- Cystocele
- Previous pelvic surgery

Genital
- Urethritis
- Vulvovaginitis
- Urethral caruncle

Medical
- Upper motor neurone lesion
- Impaired renal function
- Congestive heart failure

General
- Excessive intake
- Pregnancy

- Urethral diverticulum
- Small capacity bladder
- Interstitial cystitis
- Radiation cystitis / fibrosis
- Chronic residual

- Pelvic mass (Fibroids)

- Atrophy
- Herpes
- Warts

- Diabetes mellitus
- Diabetes Insipidus
- Constipation

- Anxiety
- Habit
Initial assessment

• Review symptoms, impact on QoL
• Assess desire for treatment
• Abdominal / rectal examination
• Associated prolapse, pelvic floor strength
• Bowel symptoms
• Skin condition
• Exacerbating conditions / co-morbidities
• Manual dexterity
• Assess environment / functional ability
Initial treatment

- General lifestyle/ fluid advice
- Implement bladder training regime
- Improve quality/access to toilet facilities and mobility
- PFMT
- Provide pads, continence aids
- Review concurrent medication: Diuretics
- Commence medication: Antimuscarinics
Initial Management of Urinary Incontinence in Women

**HISTORY**
- Incontinence on physical activity
- Incontinence with mixed symptoms
- Incontinence / frequency with urgency

**CLINICAL ASSESSMENT**
- General assessment (see relevant chapter)
- Urinary symptom assessment (including frequency-volume chart and questionnaire)
- Assess quality of life and desire for treatment
- Physical examination: abdominal, pelvic and perineal
- Cough test to demonstrate stress incontinence if appropriate
- Urinalysis ± urine culture -> if infected, treat and reassess if appropriate
- Assess oestrogen status and treat if appropriate
- Assess pelvic floor muscle function
- Assess post-void residual urine

**PRESUMED DIAGNOSIS**
- Stress incontinence presumed due to sphincter incompetence
- Mixed incontinence: treat most bothersome symptom first
- OAB -with or without urgency incontinence presumed due to detrusor overactivity

**TREATMENT**
- Lifestyle interventions.
- Pelvic floor muscle training for SUI, MUI, or OAB
- Bladder retraining for OAB
- Antimuscarinics (OAB ± urgency incontinence) or Duloxetine** (SUI)

**SPECIALISED MANAGEMENT**
- Other adjuncts, such as electrical stimulation
- Vaginal devices

**Complicated incontinence**
- Recurrent incontinence
- Incontinence associated with:
  - Pain
  - Haematuria
  - Recurrent infection
  - Significant voiding symptoms
  - Pelvic irradiation
  - Radical pelvic surgery
  - Suspected fistula

*Subject to local regulatory approval (see black box warning).

* At any stage of the patient's care pathway, management may need to include continence products.
Drugs and OAB

- Antimuscarinics
- B3 agonist
- Oestrogens
- Antidepressants
- Vasopressin analogues
Antimuscarinic Agents

After lifestyle changes, antimuscarinic agents are the most common and currently the most widely used therapy for OAB syndrome. 

Andersson, 2004

Antimuscarinics

- reduce intra-vesical pressure
- increase compliance
- raise volume threshold for micturition
- reduce uninhibited contractions

Abrams et al, 2002
Antimuscarinic Side Effects

- Dry mouth
- Constipation
- Blurred vision
- Somnolence
Antimuscarinics
Achieving the optimal balance

Efficacy
- Relieves symptoms

Tolerability
- Minimal side effects

Adherence
- Persistence

Optimal Balance
- Maximises duration of therapy
β3-adrenoceptor agonists: Mode of Action

Activation of parasympathetic pathway causes detrusor muscle contraction and micturition
Activation of sympathetic pathway inhibits detrusor contraction and contracts the bladder outlet
Mirabegron for treating symptoms of overactive bladder

What has NICE said?

NICE recommends mirabegron as a possible treatment for the symptoms of overactive bladder in some people (see below).

Who can have mirabegron?

You should be able to have mirabegron if drugs called ‘antimuscarinics’ do not work, if they are not suitable for you, or their side effects are unacceptable.
Specialised Management of Urinary Incontinence in Women

HISTORY/SYMPTOM ASSESSMENT
- Incontinence on physical activity
- Incontinence with mixed symptoms
- Incontinence with urgency / frequency

CLINICAL ASSESSMENT
- Assess for pelvic organ mobility / prolapse
- Consider imaging of the UT/pelvic floor
- Urodynamics (see notes)

URODYNAMIC STRESS INCONTINENCE (USI)
MIXED INCONTINENCE USI/DOI Treat. most bothersome symptom first
DETRUSOR OVERACTIVITY INCONTINENCE (DOI)

INCONTINENCE associated with poor bladder emptying

If initial therapy fails:
- Stress incontinence surgery
- bulking agents
- tapes and slings
- colposuspension

If initial therapy fails:
- Botulinum toxin
- Neuromodulation
- Bladder augmentation

Bladder outlet obstruction
Underactive detrusor

If initial therapy fails:
- Correct anatomic bladder outlet obstruction (e.g. genito-urinary prolapse)
- Intermittent catheterization

“Complicated” incontinence:
- Recurrent incontinence
- Incontinence associated with:
  - Pain
  - Haematuria
  - Recurrent infection
  - Voiding symptoms
  - Pelvic irradiation
  - Radical pelvic surgery
  - Suspected fistula

Consider:
- Urethrocystoscopy
- Further imaging
- Urodynamics

DIAGNOSIS

TREATMENT *

At any stage of the patient’s care pathway, management may need to include continence products

5th ICI, 2012
Botulinum Toxin
The ‘Sausage’ Poison
History of Botulinum toxin

- Dr. Justinus Kerner (poet & physician) first studied ‘sausage poisoning’ in the early 19th century
- Described the clinical symptoms of botulism – referred to then as ‘sausage poisoning’
- Malaise, nausea, vomiting, diarrhoea, double vision, dilated pupils, fatigue, swallowing difficulty, unconsciousness, cramps, rigor & death.
- Kerner deduced that botulinum toxin acts by interrupting signal transmission within the peripheral motor & nervous systems
  - Sensory signal transmission was intact
EARLY SPECULATION

“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

- Botulinum toxins are produced by the bacterium *Clostridium botulinum*:
  - An anaerobic bacterium whose spores are commonly found in soil
  - Grows into a rod-shaped bacterium if a spore contaminates food under the right conditions:
    - Temperature of $>10^\circ$C
    - Anaerobic (lack of oxygen)
    - pH of 4.6 or above
  - Will then produce more bacteria, or implode, dissolving its cell wall and releasing the toxin *Clostridium botulinum*
Botulinum Neurotoxins

*Clostridium botulinum* produces seven distinct neurotoxin serotypes:

- A, B, C1, D, E, F and G only types A and B are in clinical use
- Each has different biochemical properties
What is Botox

- BOTOX® (botulinum toxin type A) is a toxin produced by the bacterium *Clostridium botulinum* under rigorous laboratory conditions

- BOTOX® (BoNT-A) is a purified protein complex comprising a multi-subunit, zinc-dependent toxin core surrounded by accessory proteins that stabilise and protect the core toxin
Clinical Uses of Botulinum Toxin

1994 – symptomatic relief of blepharospasm and hemifacial spasm
1997 – symptomatic relief of cervical dystonia
1998 – management of dynamic equinus foot
2002 – cosmetic indications
2003 – management of axillary hyperhidrosis
2010 – prophylaxis of headaches in patients with chronic migraines
2011 – treatment of NDO
2013 – treatment of iOAB
Inhibition of interaction of synaptic vesicles with nerve terminal membranes is key to the sensorimotor action of BoNT-A.

1. BoNT-A binds to receptor
2. BoNT-A endocytosed
3. Light chain cleaves specific SNARE proteins
4. SNARE complex does not form
Botulinum Toxin

• Blocks the release of acetylcholine and other transmitters from presynaptic nerves
  Yokoyama et al, 2002; Smith et al, 2003; Smith and Chancellor, 2004

• Results in reversible decreased muscle contractility and muscle atrophy at the injection site

• Axons are regenerated in about 3 to 6 months
Types of Botulinum Toxin

Botulinum toxin type A
(Onabotulinumtoxin A: BOTOX®)

Botulinum toxin type A
(Abobotulinumtoxin A: Dysport®)

Botulinum toxin type A
(Incobotulinumtoxin A: Xeomin®)

Botulinum toxin type B
(Rimabotulinumtoxin B: Myobloc®)
Botox

• Only licensed botulinum toxin for therapeutic use in urology

• **Dignity Study** - Ginsberg D, J Urol 2012; 187:2131-9
  Cruz F, Eur Urol, 2011; 60:742-50

• **Embark Study** - Nitti VW, J Urol 2012; 189:2186–93.

• **Licensed Doses**
  200IU - NDO
  100IU – iOAB
BOTOX® (botulinum toxin type A) is a recommended treatment for refractory idiopathic overactive bladder (iOAB) and NDO

- European Association of Urology (EAU) guidelines: Grade A recommendation 2013
- International Consultation on Incontinence (ICI) guidelines: Grade A recommendation from 2012
Eligibility for Botox®

- Confirm diagnosis of OAB / DO
- Exclude any bladder malignancy
- Exclude obstruction – especially in men
- Inadequately controlled on anticholinergic therapy
- No recent (within 12 weeks) BOTOX® injection for any indication
- Patients should be willing and able to learn clean intermittent catheterisation
Communication is key to patient acceptance of treatment

- Explain catheterisation and the process involved

ISC rates

33.7% - NDO
6.5% - iOAB
Eligibility for Botox®

• No urinary tract infection at the time of treatment
• Confirm absence of urinary retention
• Do not use BOTOX® in pregnant or breast feeding women
• Confirm no allergy to BOTOX®
Managing patient expectations

• Set treatment goals and ensure patients have realistic expectations of the outcomes that can be achieved

• Inform patients that onset of treatment effect can be up to 3 weeks

• If patient is on anticholinergics, stop treatment 2 weeks after BOTOX® injection
Injection: a simple procedure

- Prophylactic antibiotics should be administered in accordance with local standard
- Cold chain has to be observed (refrigerator 2–8°C or freezer ≤–5°C)
- Reconstitution shortly before injection: No shaking!
- Injection using local anaesthesia, sedation or general anaesthesia
- Injection via rigid or flexible cystoscope and injection needle
Instill bladder with enough saline to visualise bladder wall

Perform 20 injections of 0.5 mL of reconstituted BOTOX®, spaced ~1 cm apart

Needle should be inserted ~2 mm into detrusor

Avoid injection of the trigone
  - Theoretical risk of causing vesicoureteric reflux
  - No reported difference in efficacy and tolerability of trigone-including vs. trigone-sparing intradetrusor injections in patients with iOAB
After injection

Post-procedure care

- **Discuss** with your patient when they can go home
- **Describe** potential side effects including urinary tract infection and urinary retention, and when and where to seek medical advice
- **Reassure** your patient that the following are normal:
  - Blood in the urine initially after treatment (24 hours)
  - Burn or stinging when passing urine (2–3 days)
  - Slower urinary flow

Follow up

- **Schedule** an appointment to assess post-void residual urine within 2 weeks or ask patient to self catheterise to assess
- **Re-treatment** should be based on patient request due to return of symptoms (no sooner than 12 weeks from prior injection)
Retreatment with Botox

- Average time to re-injection

  NDO – 36 - 42 weeks

  iOAB – 24 weeks

- Anticholinergics can be restarted as symptoms start to recur

- Treatment efficacy maintained with repeat injections
Developing a Nurse Led Botox Injection Service

• **Benefits:**
  - Cost effective
  - Continuity of care

• **Requirements:**
  - Experienced nurse specialist
  - Consultant training and supervision
  - Initial training as a nurse cystoscopist
  - Development of a protocol, PGD’s and consent forms
OAB: Intractable OAB

Peripheral
(PTNS)

Neuromodulation
(SNS)

Sacral

Patient-managed
(PMNS)

Withdrawn
Overactive Bladder: Surgery

- Augmentation Cystoplasty
- Detrusor Myectomy
- Urinary Diversion
Summary

• BOTOX® is now licensed for iOAB and NDO in adult patients who have an inadequate response to, or are intolerant of, anticholinergic medication.

• BOTOX® treatment is a quick and simple procedure that can be performed in an ambulatory setting by nurse specialists.

• Studies show Botox is a well tolerated treatment that can significantly improve patients QoL.
Study design

• To evaluate the efficacy and safety of onabotulinumtoxinA in patients with OAB and urinary incontinence who have been inadequately managed with anticholinergics

• Two identical, pivotal, multicentre, randomised, double-blind, placebo-controlled Phase 3 trials¹⁻⁶
  — Patients randomised to onabotulinumtoxinA 100 U or placebo in 1:1 ratio
  — N=1,105 (onabotulinumtoxinA 100 U=557; placebo=548)

• 24 weeks duration, primary time point Week 12

• Long-term, 3-year extension study to assess the safety and efficacy of repeat onabotulinumtoxinA treatment⁶
Results: Significant reduction in daily urinary incontinence episodes versus placebo

Baseline values
Placebo: 5.39/day
OnabotA 100 U: 5.49/day

*p<0.001 vs. placebo using an analysis of covariance model.

Postvoid residual

**Baseline values**
- Placebo = 19.3 mL
- BoNT-A 100 U = 22.4 mL

![Graph showing mean change from baseline in mL over weeks](chart)

**Mean change from baseline (mL)**

- **Placebo**
- **BoNT-A 100 U**

Week 2:
- Placebo: 5.6 mL
- BoNT-A 100 U: 48.2 mL

**Week 6**:
- Placebo: 3.9 mL
- BoNT-A 100 U: 36.2 mL

**Week 12**:
- Placebo: 4.2 mL
- BoNT-A 100 U: 29.3 mL

**Significant differences marked with**: **

Week 2:
- Placebo vs BoNT-A 100 U: **

Week 6:
- Placebo vs BoNT-A 100 U: **

Week 12:
- Placebo vs BoNT-A 100 U: **
Results: Initiation of clean intermittent catheterisation

6.5%

CIC=6.5% (36/552 patients)*

Patients (%)
- Did not initiate CIC - 93.5%
- Used CIC ≤6 weeks - 2.5%
- Used CIC >6 and ≤12 weeks - 1.3%
- Used CIC >12 and ≤18 weeks - 0.4%
- Used CIC >18 and ≤24 weeks - 1.4%
- Used CIC >24 weeks - 0.9%

CIC rates are low and predominantly transient

*Patients requiring CIC at any point during treatment cycle 1.
CIC = clean intermittent catheterisation.
Data presented here reflect data submitted for licensing application in Spain.
Efficacy over repeat treatment cycles: Treatment Benefit Scale

Proportion of patients with positive treatment response on the Treatment Benefit Scale* at Week 12 after each treatment cycle.

*Patients select one option from the 4-point Treatment Benefit Scale: ‘greatly improved’, ‘improved’, ‘not changed’ or ‘worsened’. A positive treatment response is indicated when a patient selects ‘greatly improved’ or ‘improved’.

Data presented are from a pre-specified interim analysis of the long-term extension study of the two pivotal Phase 3 trials. This interim analysis covers up to 5 treatment cycles of this ongoing study.

Significant improvements in all multi-item KHQ domains versus placebo

Change from baseline in KHQ domain scores at Week 12

*\(p \leq 0.05\); **\(p \leq 0.001\) vs. placebo


Data presented here reflect data submitted for licensing application in Spain.