**Intractable OAB. How to manage it?**

**W26, 16 October 2012 09:00 - 12:00**

<table>
<thead>
<tr>
<th>Start</th>
<th>End</th>
<th>Topic</th>
<th>Speakers</th>
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<tr>
<td>09:00</td>
<td>09:20</td>
<td>Introduction - What is an intractable overactive bladder</td>
<td>Jacques Corcos</td>
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<td>09:20</td>
<td>09:30</td>
<td>Questions</td>
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<td>09:30</td>
<td>09:45</td>
<td>Alternative treatment 1: Sacral neuromodulation</td>
<td>Jerzy Gajewski</td>
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<td>10:15</td>
<td>Alternative treatment 2: Tibial nerve neuromodulation</td>
<td>Gilles Karsenty</td>
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<td>Questions</td>
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<td>11:15</td>
<td>Alternative treatment 3: Botulinum toxin</td>
<td>Brigitte Schurch</td>
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<td>Future pharmacology</td>
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<td>Questions</td>
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<td>Cases presentation</td>
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<td>Evaluation</td>
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**Aims of course/workshop**

To review the current status of conservative, minimal invasive and surgical treatment in the management of intractable overactive bladder symptoms. To address efficacy, mechanism of actions, technical issues, alternative and new techniques, adverse events, the cost-effectiveness, and current considerations on the use of botulinum toxin and SNM as second-line treatments in OAB.

**Educational Objectives**

The overactive bladder syndrome (OAB) negatively affects the daily life of many people. Conservative treatments, such as antimuscarinics, do not always lead to sufficient improvement of the complaints and/or are often associated with considerable side effects resulting in treatment failure. In the case of failure or intolerable side effects, sacral neuromodulation (SNM) and botulinum toxin are minimally invasive and reversible alternatives. Currently, of these alternatives only SNM with InterStim TM therapy has FDA approval for use in OAB patients. This workshop will attempt to provide an update on the current position of new drugs, TNS, SNM and botulinum toxin in the second-line management of adults with intractable idiopathic OAB, based on the available clinical evidence concerning the efficacy and safety. Current surgical procedure will also be discussed.
Intractable OAB

Jacques Corcos MD
Professor of Urology
McGill University

ICS 2012

OAB

• Frequency > 8/day
• Urgency
• Urge incontinence
• Nocturia > 1/night

20% of the population

Corcos et al 2006

8% seek treatment

• But before treating them …..
• Define “THE” most bothersome symptom
• What the patient cannot do because of his OAB
• Establish a “contract” with the patient
• Improve this symptom

8% seek treatment

• Oxybutinine based medication
  - Oxybutinine
  - Ditropan XL (10mg)
  - Uromax (25mg)
  - Oxytrol patches
  - Gelnique
• Other antimuscarinics
  - Tolterodine (Detrol)
  - Derafenacine (Enablex)
  - Trospium (Trosec)
  - Solifenacine (Vesicare)
  - Fesoteridine (Toviaz)

Anticholinergic treatment

• Start with a low dose and increase progressively
• Importance of well explained AE
• Prevention of dry mouth and constipation ++

Responders: 6-12 month of treatment

INTRACTABLE OAB

Summary

• High prevalence of the syndrome
• At least 50% of patient don’t need complex testing
• Behavioral changes + medication
• Rest of patients are the complex cases
Intractable OAB

Failed medical treatment using known oral medications (anticholinergics, antispasmodics, antidepressants, sedatives, calcium channel blockers, adrenergics)

Reason for Lack of Efficacy of Antimuscarinics

- Direct activation of intracellular signaling by pathologic process
- Altered membrane potential of smooth muscle cell
- Lack of pharmacologic levels in bladder tissue

Are patients with OAB well treated?

- 13% of people with symptoms report that they have been diagnosed by a health care provider
- 64% of those with symptoms not currently being treated at all
- Many with co-morbid problems and reluctant to add another pill

“Intractable” OAB: What to do?

- Understand what really bother the patient
- Reconsider diagnosis (SUI, IC)
- Treat a reversible cause
- Changes in life style, when? How? For how long?
- Reconsider same medication
- Consider adding meds (DDAVP)
- Intensify the follow up (nurse continence advisor)
- Use alternative treatments

What bother the patient: Clinical Efficacy

Combination of efficacy, tolerability, and compliance

- Efficacy:
  - Traditional OAB outcome measures
  - QoL
  - Global assessment of impact
  - Combinations
- Tolerability: side effects
- Compliance and persistence

Clinical Significance of QOL Outcomes

- How much change in HRQOL is enough to evaluate the treatment or to consider one treatment better than another?
- Clinically meaningful change in HRQOL
  - Minimal importance difference (MID)
    - Smallest difference in the score of the domain of interest which patients perceive as beneficial (or harmful) which would mandate, in the absence of troublesome side effects or excessive cost, a change in patient’s management
  - How much is enough?

### Reconsider diagnosis

- Clinical evaluation
- Voiding diaries

### Treat a reversible cause

**Treat associated conditions**
- Bladder outflow obstruction
- Stress UI

**Treat reversible conditions**
- Urinary Tract Infection
- Congestive Heart Failure
- Diabetes
- Spinal stenosis

### Behavioral management

**Fluid management:**
- Limit diuretics, caffeine, soda, alcohol
- Avoid to drink in evening

**Schedules voids**
- Regularly timed intervals
- Increase time between voids

**Use pelvic floor**
- Kegels, PFMT, vaginal cones

### Reconsider same medication

- Why the patient stopped it?
- Restart it at lower dose and slowly increase to maximum dosage
- Use mouth moisteners / gums / candies
- Use laxatives
- Consider use of tricyclic antidepressants associated to anticholinergics

### Consider the use of DDAVP

- Depending on the most bothersome symptom
- DDAVP 0.1 to 0.2 mg (or 60-120 μg of Melt)
- Alone or with anticholinergics

### Intensify the follow up

- These patients need close monitoring
- Frequent visit if problem with medication
- Counselling and phone follow up by nurses continence advisors
- Hot lines

---

Desmopressin, as a "designer-drug," in the treatment of overactive bladder syndrome.
Hashim H, Mülmenberg L, Graugaard-Jensen C, Abrams P.
Use a more invasive approach

- Neuromodulation
- Botulinum Toxine A intra detrusor inject

How to chose between alternative treatments?
1. Availability of therapy
2. Patient’s understanding of the long term treatment plan
3. Invasiveness of the procedure
4. Drug and technique related adverse effects
5. Drug efficacy
6. Cost

Management Algorithm for OAB

Thank you
Secral Neuromodulation for Refractory OAB

Jerzy B Gajewski
Department Of Urology Dalhousie University
Halifax, N.S. Canada

Definition

- **Neuromodulation** = stimulation of the intact sacral nerves to modulate the neural reflexes that influence the bladder, sphincter and pelvic floor.

- **Neurostimulation** = Brindley stimulator

- **Electrostimulation** = transvaginal, transrectal or surface stimulation

INDICATIONS

1. Overactive bladder
2. Voiding dysfunction
3. Painful Bladder Syndrome
   Interstitial Cystitis

SNS implants per population

Over 30,000 implants performed worldwide

DG – OAB

Conservative & Medical Treatment

- Sacral Nerve Modulation
- Botulinum toxin +/- Cystectomy

Selecting Patients for InterStim™ Therapy

- Initial Screening
- Voiding Diary
- Urodynamic Workup
- Behavioral Techniques
- Interventional Techniques
- Medication
- Test Stimulation
- Consider other surgical intervention

+ Continue as appropriate
Sacral Nerve Modulation
Two step therapy

- Acute: Test stimulation procedure
  - PNE – 3 to 7 days, temporary
  - First stage electrode implant
  
  50% improvement

- Chronic:
  - Implantation of lead, neurostimulator and extension
  - Second stage - Implantation of neurostimulator and extension

Testing for Motor & Sensory Responses

Predictor of Success of First Stage in OAB

- 95% with (+) motor response went on to 2nd stage
- Only 4.7% with only (+) sensory response went to 2nd stage

Cohen et al. J Urol 175, 2178-2181 June 2006

Procedure Flows

- Test
  - PNE
  - 3 to 7 days, temporary
  - First stage electrode implant
  - 50% improvement

- Implant
  - First stage implant: Electrode implant
  - Second stage implant: Neurostimulator and extension

PNE + Implant v/s 2 stage procedure

- 42 patients
- 33% failed in PNE+Implant
- 14% Failed 2 stage procedure

National trends in the usage and success of sacral nerve test stimulation.
Cameron AP, Anger JT, Madison R, Saigal CS, Clemens JQ; Urologic Diseases in America Project.

- Medicare patients
  - 358 received percutaneous test stimulation
    - 45.8% underwent subsequent battery implantation.
  - 1,132 underwent 2-stage lead placement, of who
    - 35.4%, respectively, underwent subsequent battery implantation.

PNE – 196 patients

<table>
<thead>
<tr>
<th>% of good response</th>
<th>PBS/IC</th>
<th>OAB</th>
<th>Void Dysf</th>
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<tr>
<td>100</td>
<td>66</td>
<td>54</td>
<td>44</td>
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PBS/IC OAB Void Dysf

Tined Leads Model

(C)opyright 2012, Meritron, Inc.
• Retrospective review
• Objective:
  – Incidence and cause of surgical re-intervention after SNM implant.
  – long-term efficacy
• Outcome: Global Response Assessment Scale

**RESULTS**

- 96 SNM device.
  – 88 women (91.7%) and 8 men (8.3%).
- Mean age at implantation was 45 years (SD ± 12.5).
- The indications for implantation were:
  – Painful Bladder Syndrome/ Interstitial Cystitis (PBS/IC) (47.9%).
  – Urge Urinary Incontinence (UUI) -34 (35.4%).
  – Idiopathic Urinary Retention (IUR) (16.7%).

**Success**

- Median follow up was 50.7 months (SD ± 38.1)

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<tr>
<th>PBS/IC</th>
<th>UUI</th>
<th>IUR</th>
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<tr>
<td>72.2%</td>
<td>84.8%</td>
<td>87.5%</td>
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</table>

Explantation

- Explantation rate was 20.8%.
  – median time till removal was 18.5 months (SD ± 31.7).
  - PBS/IC: 27%
  - UUI: 14.7%
  - IUR: 12.5% (P=0.2)
- The reasons for the explantation:
  - Poor result in 12 patients (12.5%)
  - Painful stimulation in 6 patients (6.25%)
  - Feeling the stimulation along the leg in 2 patients (2%).

Figure 2. Kaplan-Meier graph of SNM retention rate. Blue curve indicates UUI. Red curve indicates PBS. Black curve indicates IUR.
Efficacy and adverse events of sacral nerve stimulation for overactive bladder: A systematic review.
Siddiqui NY, Wu JM, Amundsen CL. Neurourol Urodyn. 2010;29:S18–S23

- three independent studies of efficacy.
- incontinent episodes per day and pad usage significantly decreased after SNS therapy.
- there was a significant decrease in mean incontinent episodes per day (2–3) and mean daily pad use (1–3).
- About 45% of patients reported “cure,” or lack of daily incontinence episodes, up to 3 years after implant.
- 54% of patients maintained improvements in daily incontinence episodes after implant. Subjective outcomes were also assessed and shown to be beneficial.

Revision

- 39% of the patient needed revision of the SNM implant.
- Reason for revision:
  - loss of stimulation in 24 procedures (58.5%).
  - Pain from the pulse generator in 7 procedures (17%).
  - Painful stimulation in 5 procedures (12.2%).
  - Positive stimulation in the leg in 5 procedures (12.2%).

Posterior Tibial Nerve Stimulation

- Posterior tibial nerve stimulation (PTNS) was first introduced by McGuire et al. in 1983.
- Peters et al. (2009) reported on the global response assessments (OrBIT)
  - PTNS 79.5% cure or improvement rate,
  - compared with 54.8% of those on tolterodine (P<0.01).
- Ridout and Yoong (2010) reported on a review article 60% to 81% response rate to PTNS.
- Van der Pal et al. (2006) showed greater than 50% worsening in frequency and incontinence episodes after a 6-week pause in 64% of patients.

Pudendal Neuromodulation

- Peters et al. (2001) review of patients undergoing lead placement at the pudendal nerve via the ischial rectal approach for chronic pudendal neuromodulation.
- 84 patients with different diagnoses, including interstitial cystitis/painful bladder syndrome, benign prostatic hyperplasia, and post-radical prostatectomy urinary incontinence.
- Almost all who failed sacral neuromodulation responded to the pudendal lead stimulation (93.2% [41 of 44]).
- Overall, positive pudendal response (≥50% improvement on the pudendal lead) was achieved in 60 of 84 participants (71.4%).

Technical improvement

- InterStim II
- iCon patient’s programmer
- Compatible with both Interstim devices: InterStim and InterStim II
- Interactive display
### Benefits of InterStim Therapy

- Marked Reduction or elimination of incontinence
- Improvement in Quality of Life
- Safe, reversible & compatible with alternative treatments
- Minimally invasive procedure
- Use of test stimulation as an accurate and low-cost predictor of clinical success
- Improved economic management of patients
- Real opportunities to treat many pelvic floor disorders

### Conclusions

- Sufficient new evidence in the literature continues to prove that Interstim therapy provides a unique and exiting treatment option that the physician can offer to patients in whom conventional treatment options have failed.

- The SNM is a minimal invasive procedure with a very good outcome and long-term result.

- Lower re-operation rate of SNM with the improvement of the surgical skill as well as the latest modification in the surgical technique and technology.
Tibial nerve stimulation as a treatment of OAB

Gilles Karsenty, MD 1,2

1 Aix-Marseille Univ. 13284, Marseille, France
2 APHM, La Conception Hospital, Urology and Kidney Transplantation department, 13385, Marseille, France

Posterior tibial nerve stimulation (PTNS) to treat lower urinary dysfunction has been described for more than 10 years. Its principle of action is based on a neuromodulative effect on micturition/continence reflexes. This effect has been described in animals and humans after peripheral stimulation of afferent fibers conveyed in somatic nerves such as, ventral branch of 3rd sacral spinal nerve (sacral neuromodulation), pudendal nerve, dorsal nerve of penis or clitoris. Modulation of micturition/continence reflexes by somatic nerves stimulation represents the singular situation of a somatovisceral reflex. Although the actual organization of such reflex is still matter of debate there is a good body of evidence to support the efficacy of neuromodulation by electric stimulation as a treatment of lower urinary tract dysfunction. It is for overactive bladder (OAB) that clinical trials supporting the efficacy of posterior tibial nerve stimulation are the most convincing. In the 2 last available meta analyses by Moossdorff-Steinhauser et al. and Burton et al. four RCTs were identified and demonstrated a significant superiority to PTNS over sham treatment. The pooled subjective and objective success rates were estimated to be over 60%. Two other RCTs compared PTNS to anticholinergics and failed to demonstrate a superiority of drugs over PTNS. A Medium term follow up study by young et al. published in September 2012 suggests durability of effect over 24 months.

Efficacy, non-invasive nature, and absence of complication strongly support to include PTNS in the therapeutic algorithm of OAB treatment. Its actual place in such algorithm, either before or after introduction of anticholinergic drugs, as well as its efficacy as an adjuvant therapy deserve to be discussed at the light of larger comparative studies.
Botulinum toxin and intractable overactive bladder

Prof. Brigitte Schurch
Service de Neuropsychologie et Neuroréhabilitation

Overactive bladder (OAB) syndrome is defined as storage LUTS of urgency, with or without urge incontinence (UI), usually with frequency and nocturia in the absence of infection or other obvious pathology.

Common bladder storage symptoms and definitions

- Increased Daytime Frequency
- Nocturia
- Urgency of micturition
- Urinary Incontinence

OAB: definition

- Overactive bladder (OAB) syndrome is defined as storage LUTS of urgency, with or without urge incontinence (UI), usually with frequency and nocturia in the absence of infection or other obvious pathology.

Current management of DO/NDO

Management of NDO falls into 3 major categories:

- Behavioral approaches
  - Lifestyle interventions
  - Pads, portable urinals
  - Intermittent, condom or Foley catheterisation for patients with abnormal bladder emptying (e.g. elevated PVR levels)

- Pharmacotherapy
  - Anticholinergic agents are the standard therapy

- Surgery
  - Reserved for those who fail conservative therapy

Anticholinergics

- Currently the most widely used therapy for DO/NDO with a long history of use
- Systemic therapy
- Evidence to date suggests they are an efficacious therapeutic option for overactive bladder, which also improve quality of life
- Higher doses of anticholinergic can be related to higher rate of side effects
- Potentially limiting factors:
  - Systemic anticholinergic effects: adverse events/interactions
  - Drug-drug interactions
  - Low adherence rates
- Limited published data on anticholinergics and DO/NDO

Published 1-2-2011, Updated 3-2-2011


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

Systemic impact of anticholinergics

- Dry mouth
- Antimuscarinics
- Surgery / Augmentation
- DO + BONT
- Neurostimulation / Neuromodulation

Why botulinum toxin?

Antimuscarinics

1998

Techniques of application

- Placebo controlled study

<table>
<thead>
<tr>
<th>Table 2 - Results of application technique</th>
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<tr>
<td>Technique group (n = 103)</td>
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<tr>
<td>Improvement of OAB symptoms</td>
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<tr>
<td>Improvement of QoL</td>
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<tr>
<td>Improvement of ICIQ-SF</td>
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<tr>
<td>Improvement of IPSS</td>
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<tr>
<td>Improvement of QoL</td>
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Botox and OAB: placebo controlled study

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Botox and OAB: placebo controlled study

Tincello et al. 2012; Denys et al. 2011

Botox and OAB: placebo controlled study

Table 1 - Impact and other outcomes at each visit in 12 weeks

<table>
<thead>
<tr>
<th>Study</th>
<th>Impact</th>
<th>Other Outcomes</th>
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<tbody>
<tr>
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<td>Botox</td>
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<tr>
<td>Impact</td>
<td>Placebo</td>
<td>Botox</td>
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Tincello et al. 2012; Denys et al. 2011

Other placebo controlled studies

- Dmochowski et al. 2010 (Allergan dose finding; clinical phase 2)
- Denys et al. 2011 (independent study, dose finding)
- Sahai et al. 2007
- Brubaker et al. 2008
- Flynn et al. 2010

All same conclusions

Neurogenic Detrusor Overactivity (NDO)

Rationale for treating NDO

To avoid complications such as:
- Higher bladder pressures
- Poor bladder compliance
- Recurrent febrile urinary tract infections
- Autonomic dysreflexia
- Vesicoureteral reflux
- Hydronephrosis

Consequences of untreated NDO:
High detrusor pressures
- Urinary tract infections
- Lithiasis
- Reflux
- Hydronephrosis
- Renal failure

NDO: Phase 2 Study

Incontinence episodes

IQol-score

Consequences of untreated NDO:
Impact on quality of life

Physical
- Limitations or cessation of physical activities

Psychological
- Guilt/depression
- Loss of self-esteem
- Fear of: Lack of bladder control, urine smell

Intimacy
- Avoidance of sexual contact and intimacy

Domestic
- Requirements for specialized underwear
- Precautions with clothing

Occupational
- Absence from work
- Decreased productivity

Social
- Reduced social interaction
- Planning travel around toilet accessibility

Physical
- Limitations or cessation of physical activities

Domestic
- Requirements for specialized underwear
- Precautions with clothing

Occupational
- Absence from work
- Decreased productivity

Social
- Reduced social interaction
- Planning travel around toilet accessibility

NDO Phase 3 Study: Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomized, double-blind, placebo-controlled trial (515/516)

Parameter Overall (N=691) MS (N=381) SCI (N=310)

Age 45.9 yrs 49.9 yrs 41.0 yrs

Sex, % female 57.9 % 81.6 % 28.7 %

Race, % Caucasian 85.8 % 92.9 % 77.1 %

Time since diagnosis of MS/SCI 11.9 yrs 14.0 yrs 9.5 yrs

Time since diagnosis of NDO 7.7 yrs 7.9 yrs 7.3 yrs

Using anticholinergics at baseline 54.8 % 50.7 % 60.0 %

Cruz et al. Eur Urol 2011
Schurch et al. J. Urol 2005
Baseline Diary Parameters (Pooled 515/516 ITT Population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall (N=691)</th>
<th>MS (N=381)</th>
<th>SCI (N=310)</th>
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<tbody>
<tr>
<td>Weekly urinary incontinence</td>
<td>31.7 (4.5 per day)</td>
<td>32.7 (4.7 per day)</td>
<td>30.5 (4.4 per day)</td>
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<tr>
<td>Use of CIC at baseline</td>
<td>50.6 %</td>
<td>50.6 %</td>
<td>50.6 %</td>
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<tr>
<td>Weekly spontaneous voids (patients not using CIC)</td>
<td>66.4 (9.5 per day)</td>
<td>66.7 (9.5 per day)</td>
<td>63.9 (9.1 per day)</td>
</tr>
<tr>
<td>Use of CIC at baseline</td>
<td>55.0 %</td>
<td>35.4 %</td>
<td>82.8 %</td>
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Cruz et al. 2011

Change from Baseline in Weekly Urinary Incontinence Episodes

<table>
<thead>
<tr>
<th>Study 191622-515 (N=416)</th>
<th>Study 191622-516 (N=275)</th>
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<tbody>
<tr>
<td>Mean change from baseline (episodes/week)</td>
<td>Mean change from baseline (episodes/week)</td>
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<tr>
<td>PBO</td>
<td>200U</td>
</tr>
<tr>
<td>-25</td>
<td>-20</td>
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<tr>
<td>-10</td>
<td>-5</td>
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<tr>
<td>* p= &lt;0.05; ** p= &lt;0.001 in pairwise comparison versus placebo</td>
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Proportion of ‘Dry’ patients at Week 6 by Etiology (pooled 515/516)

<table>
<thead>
<tr>
<th>MS Patients (N=681)</th>
<th>SCI Patients (N=680)</th>
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<tbody>
<tr>
<td>% Patients</td>
<td>% Patients</td>
</tr>
<tr>
<td>PBO</td>
<td>200U</td>
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<td>30%</td>
<td>70%</td>
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<tr>
<td>40%</td>
<td>90%</td>
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PVR Urine Volume at Week 2

<table>
<thead>
<tr>
<th>Change from baseline</th>
<th>% Patients with PVR ≥ 200 mL</th>
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<tbody>
<tr>
<td>Mean PVR baseline</td>
<td>N=43</td>
</tr>
<tr>
<td>0</td>
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<td>10%</td>
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<td>100</td>
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<tr>
<td>120</td>
<td>10%</td>
</tr>
<tr>
<td>140</td>
<td>10%</td>
</tr>
<tr>
<td>160</td>
<td>10%</td>
</tr>
<tr>
<td>180</td>
<td>10%</td>
</tr>
<tr>
<td>200</td>
<td>10%</td>
</tr>
</tbody>
</table>

* p= <0.05 in pairwise comparison versus placebo
** p= <0.01 in pairwise comparison
**UTI (first 12 weeks of Tx cycle 1)**

<table>
<thead>
<tr>
<th>CIC Status</th>
<th>Pre-Tx</th>
<th>Post-Tx</th>
<th>Placebo 200 U</th>
<th>Placebo 300 U</th>
<th>Placebo 500 U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using</td>
<td>26.4 % (29/113)</td>
<td>22.0 % (22/100)</td>
<td>26.8 % (29/113)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Using</td>
<td>21.9 % (23/105)</td>
<td>15.5 % (13/83)</td>
<td>20.6 % (23/113)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Using and PVR ≥ 200 mL</td>
<td>6.9 % (5/72)</td>
<td>13.3 % (6/45)</td>
<td>10.9 % (5/46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Using and PVR &lt; 200 mL</td>
<td>11.4 % (10/89)</td>
<td>7.8 % (5/64)</td>
<td>9.5 % (3/32)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Adapted from Allergan Data on File – Summary of Clinical Efficacy

**Kaplan Meier Plot for Time to Patient Request for Re-treatment (pooled 515/516)**

**QOL improvement was not affected by initiation of CIC**

**MS Exacerbation: Annualized Exacerbation Rates**

<table>
<thead>
<tr>
<th></th>
<th>Placebo 200 U</th>
<th>Placebo 300 U</th>
<th>Placebo 500 U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 515</td>
<td>0.22</td>
<td>0.14</td>
<td>0.28</td>
</tr>
<tr>
<td>Study 516</td>
<td>0.14</td>
<td>0.36</td>
<td>0.20</td>
</tr>
<tr>
<td>Pooled 515/516</td>
<td>0.24</td>
<td>0.23</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Reported MS exacerbation rates are:
- Between 0.27 and 1.28 in MS clinical studies
- Between 0.2 and 1.2 in general MS population

* Tyry et al. 2008, Tyry et al. 2008a, Tyry et al. 2008b, Tyry et al. 2008c, Betaseron® Label; Avonex® Label; Rebif® Label; Johnson et al, 1995; Tysabri® Label

**Summary Botulinum toxin and intractable OAB**

- Overall, consistent efficacy and safety results
- Efficacy: Clinical benefit demonstrated
  - Reduction in urinary incontinence
  - Improvement in urodynamic parameters
  - Long duration of effect
- Safety:
  - Well tolerated overall
  - Most common adverse event was UTI and CIC
  - Similar rates between BOTOX® and placebo groups
Notes
Record your notes from the workshop here