Intractable OAB. How to manage it?

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

Start	End	Topic	Speakers
09:00	09:20	Introduction - What is an intractable overactive bladder	• Jacques Corcos
09:20	09:30	Questions	All
09:30	09:45	Alternative treatment 1 : Sacral neuromodulation	• Jerzy Gajewski
09:45	09:55	Questions	All
09:55	10:15	Alternative treatment 2: Tibial nerve neuromodulation	• Gilles Karsenty
10:15	10:30	Questions	All
10:30	11:00	Break	None
11:00	11:15	Alternative treatment 3: Botulinum toxin	• Brigitte Schurch
11:15	11:20	Questions	All
11:20	11:40	Future pharmacology	• Franscisco Cru
11:40	11:45	Questions	All
11:45	11:55	Cases presentation	All
11:55	12:00	Evaluation	All

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

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- *drir*

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

P

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

Harris (Kimberley-Clark) survey 2004
Muller N. Urol Nursing 2005; 25: 109-115

"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

1. Wein AJ. Urology 2003; 62 (Suppl 5B) 20-27

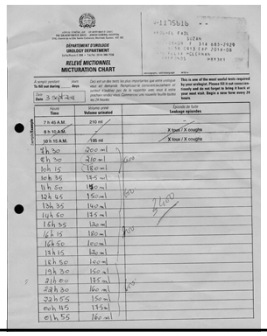
Clinical Significance of QOL Outcomes

- 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?**

Jaeschke R. et al. Control Clin Trials 1991; 12 (Suppl 4) 226S.
Guyatt GH. Et al. Mayo Clin Proc 2002; 77:371-383.

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

Desmopressin, as a "designer-drug," in the treatment of overactive bladder syndrome.
Hashim H, Malmberg L, Graugaard-Jensen C, Abrams P.
Neurourol Urodyn. 2009;28(1):40-6

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

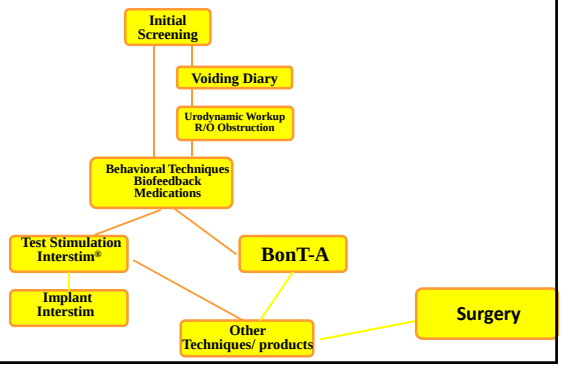
Use a more invasive approach

- **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

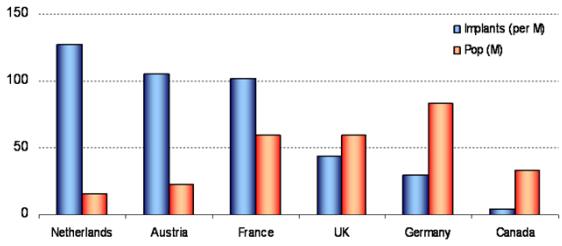
Department Of Urology Dalhousie University

Halifax, N.S. Canada

Definition

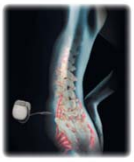
- **Neuromodulation** = stimulation of the intact sacral nerves to modulate the neural reflexes that influence the bladder, sphincter and pelvic floor.
- **Neurostimulation** = Brindley stimulator
- **Electrostimulation** = transvaginal, transrectal or surface stimulation

SNS implants per population

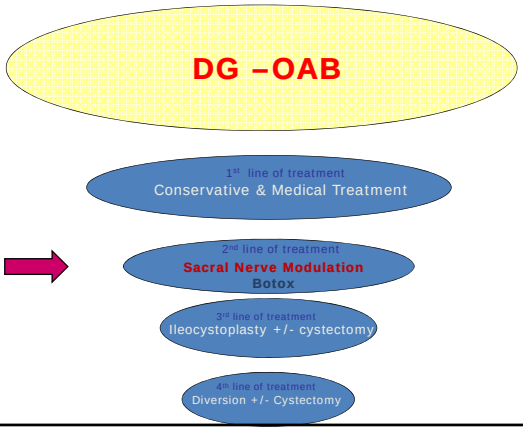


Over 30'000 implants performed worldwide

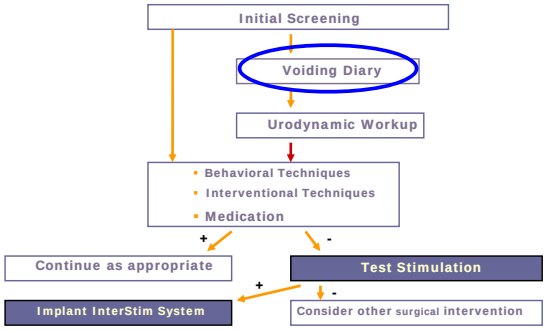
INDICATIONS



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



Selecting Patients for InterStim™ Therapy



Sacral Nerve Modulation
Two step therapy

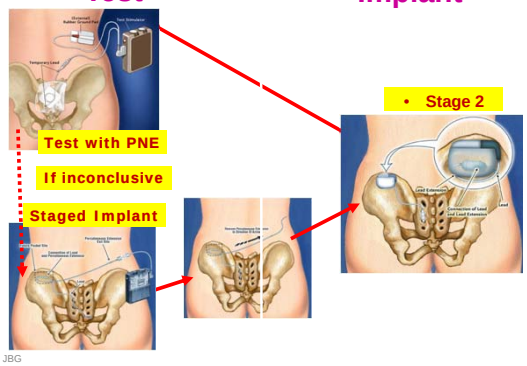
– **Acute**: Test stimulation procedure
- PNE – 3 to 7 days, temporary
- First stage electrode implant

50% improvement

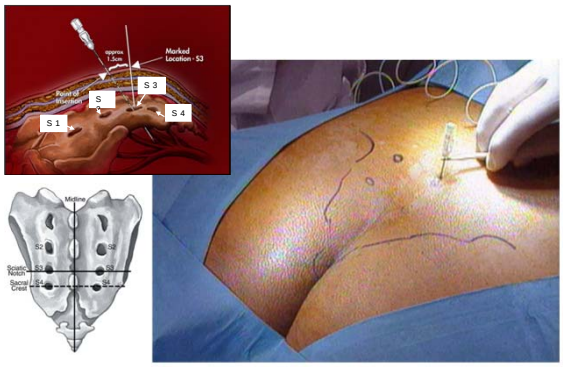
– **Chronic**:
- Implantation of lead, neurostimulator and extension
- Second stage - Implantation of neurostimulator and extension

Procedure Flows

Test **Implant**



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

PNE +Implant v/s 2 stage procedure
42 patients

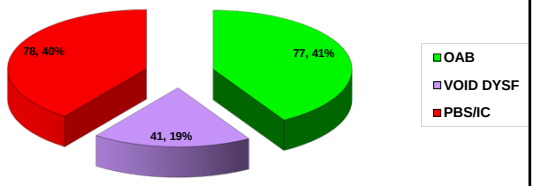
- 33% failed in PNE+Implant
- 14% Failed 2 stage procedure

European Urology 45 (2004) 649–654

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.
J Urol. 2011 Mar;185(3):970-5. Epub 2011 Jan 19

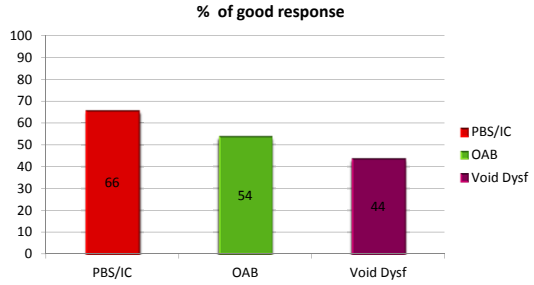
- Medicare patients
  - 358 received percutaneous test stimulation
    - **45.8%** underwent subsequent battery implantation.
  - 1,132 underwent 2-stage lead placement, of who
    - **35.4%**, respectively, underwent subsequent battery implantation.

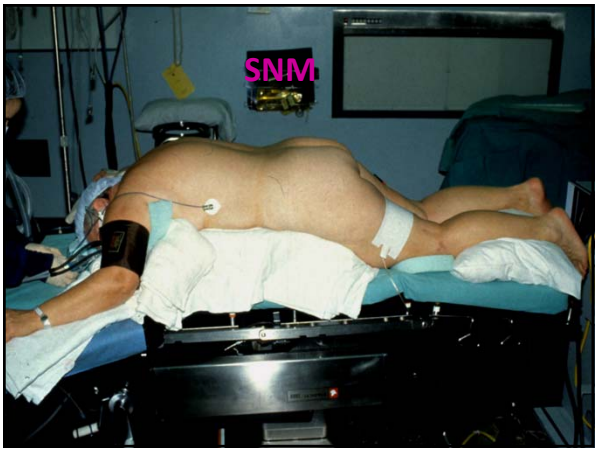
PNE – 196 patients



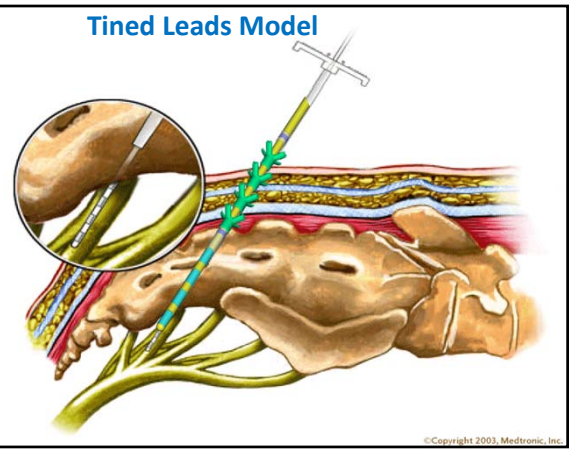
J. Urol. 2-May-08
Vol. 185, 981-986, March 2011

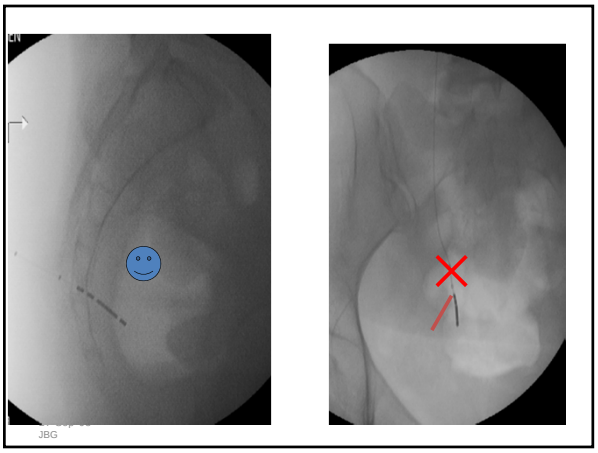
PNE





Tined Leads Model





Long-Term Outcome and Surgical Interventions After Sacral Neuromodulation Implant for Lower Urinary Tract Symptoms: 14-Year Experience at 1 Center

J. Urol
Vol. 185, 981-986, March 2011

Ali A. Al-zahrani,* Ehab A. Elzayat and Jerzy B. Gajewskiŧ

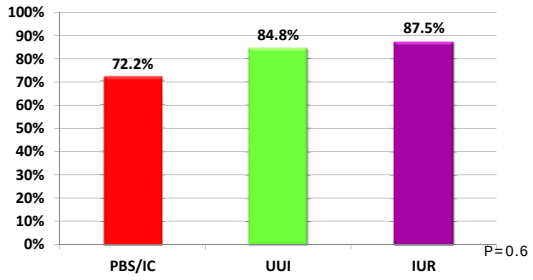
- Retrospective review
- Between 1994 and 2008.
- Objective:
  - Incidence and cause of surgical re-intervention after SNM implant.
  - long-term efficacy
- Outcome: Global Response Assessment Scale

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)



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%).

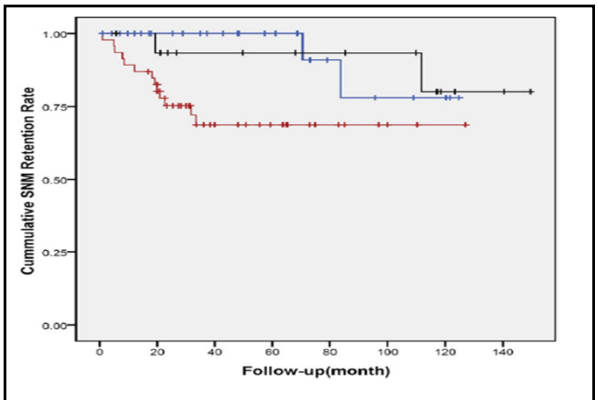
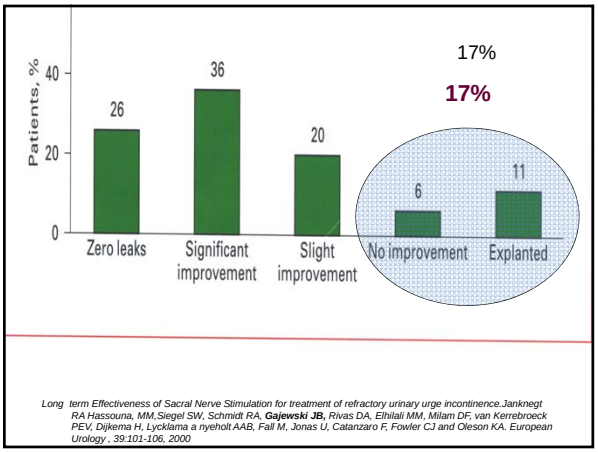
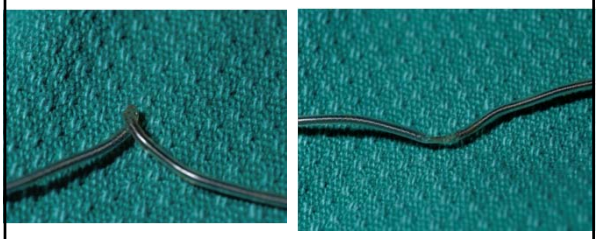


Figure 2. Kaplan-Meier graph of SNM retention rate. Blue curve indicates UUI. Red curve indicates BPS. Black curve indicates IUR.



*Long term Effectiveness of Sacral Nerve Stimulation for treatment of refractory urinary urge incontinence.Janknegt RA Hassouna, MM,Siegel SW, Schmidt RA, **Gajewski JB,** Rivas DA, Elhilali MM, Milam DF, van Kerrebroeck PEV, Dijkema H, Lycklama a nyeholt AAB, Fall M, Jonas U, Catanzaro F, Fowler CJ and Oleson KA. European Urology , 39:101-106, 2000*

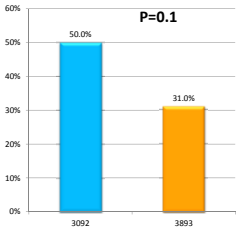
Lead breakage 4 years after implant



J.B.G

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%).



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

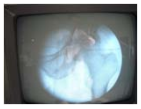
- three independent studies of efficacy.
- incontinent episodes per day and pad usage significantly decreased after SNS therapy.
- there was a significant decrease in mean incontinent episodes per day (2–3) and mean daily pad use (1–3).
- About 45% of patients reported "cure," or lack of daily incontinence 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

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 tined 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,
  - urgency/frequency or urge incontinence,
  - nonobstructive urinary retention, and
  - pelvic/bladder pain without interstitial cystitis.
- 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

Deterministic Analysis

COST-EFFECTIVENESS OF SACRAL NERVE STIMULATION IN REFRACTORY OVERACTIVE BLADDER: A CANADIAN PERSPECTIVE

Hassouna MM, Gajewski J ,Tu LM, Corcos J, Dwyer NE, Gray G,Robert M,Sadri HB

INTERSTIM vs. BOTOX

	Incr. Cost			Incr. QALY			C/QALY		
	Mean	Low Range	High Range	Mean	Low Range	High Range	Mean	Low Range	High Range
1 year	$7,237	$7,574	$6,709	0.05	0.05	0.05	$144,067	$150,769	$133,558
2 years	$4,318	$4,884	$3,591	0.09	0.09	0.09	$44,837	$50,708	$37,288
4 years	-$651	$277	-$1,691	0.19	0.19	0.19	Interstim Dominant	$1,436	Interstim Dominant
5 years	-$2,775	-$1,701	-$3,941	0.24	0.24	0.24	Interstim Dominant	Interstim Dominant	Interstim Dominant
10 years	-$9,402	-$7,698	-$11,129	0.51	0.51	0.51	Interstim Dominant	Interstim Dominant	Interstim Dominant

INTERSTIM vs. OMT

	Incr. Cost			Incr. QALY			C/QALY		
	Mean	Low Range	High Range	Mean	Low Range	High Range	Mean	Low Range	High Range
1 year	$8,878	$8,812	$9,008	0.19	0.19	0.19	$45,999	$45,655	$46,672
2 years	$5,888	$5,847	$6,029	0.38	0.38	0.38	$15,130	$15,024	$15,491
4 years	$348	$335	$523	0.76	0.76	0.76	$455	$438	$684
5 years	-$2,233	-$2,236	-$2,039	0.94	0.94	0.94	Interstim Dominant	Interstim Dominant	Interstim Dominant
10 years	-$11,447	-$11,347	-$11,246	1.76	1.76	1.76	Interstim Dominant	Interstim Dominant	Interstim Dominant

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.

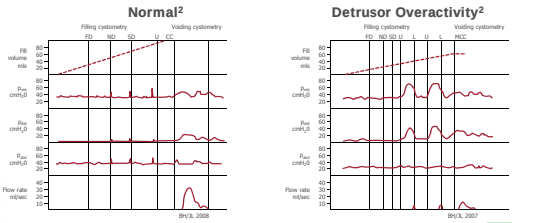
Botulinum toxin and intractable overactive bladder

Prof. Brigitte Schurch
Service de Neuropsychologie et Neuroréhabilitation

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

Detrusor Overactivity:
Characterised by involuntary detrusor contractions during the filling phase,
which may be spontaneous or provoked[1]



Figures adapted from Haylen BT et al 2010
CC=cystometric capacity (permission to void given); FD=first desire to void; L=leakage;
MCC=maximum cystometric capacity; ND=normal desire to void; SD=strong desire to void; U=urgency.

1. Abrams P et al. *Neurourol Urodynamics.* 2010;29:213-240. 2. Haylen BT et al. *Neurourol Urodynamics.* 2010;29:4-20.

Common bladder storage symptoms and definitions

Increased Daytime Frequency[1]	Increased voiding episodes during the day (NIH: *the patient voids eight or more times in a day)*
Nocturia[1]	Individual has to wake at night ≥1 time to void
Urgency (if intact sensation)[1]	A sudden compelling desire to pass urine that is difficult to defer (NIH: *the patient feels a strong need to pass urine for fear of leakage)*
Urinary Incontinence[1]	Any involuntary leakage of urine

1. Pannek J. European Association of Urology. Guidelines on neurogenic lower urinary tract dysfunction. 2011. http://www.uroweb.org/gls/pdf/17_Neurogenic%20LUTS.pdf. Accessed June 2011

Current management of DO/NDO

Management of NDO falls into 3 major categories:

- Behavioral approaches
  - Lifestyle interventions
  - Pads, portable urinals
  - Intermittent, condom or Foley catheterization 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
  - Neurostimulation
  - Urinary Diversion
  - Bladder Reconstruction (to improve bladder functionality)

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

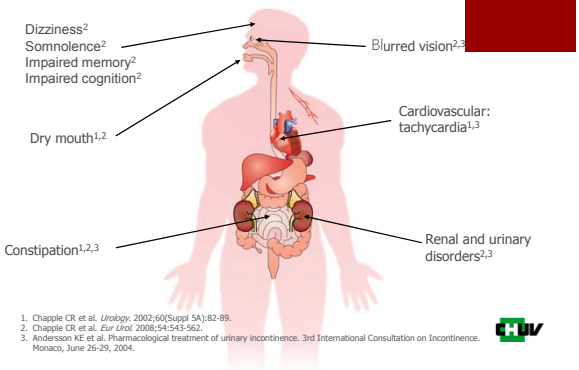
Committees 8,10,12. In: Incontinence, 4th Edition; Abrams P et al, eds. From the 4th ICI; Health Publication Ltd; 2009.

Anticholinergics

- Currently the most widely used therapy for DO/NDO[1] 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[2]
- Higher doses of anticholinergics can be related to higher rate of side-effects[3]
- Potential limiting factors:
  - Systemic anticholinergic effects: adverse events/tolerability[1,2]
  - Drug-drug interactions[4]
  - Low adherence rates[2]
- Limited published data on anticholinergics and DO/NDO

1. Chapple CR et al. *Urology.* 2002;60(Suppl 5A):82-89.
2. Chapple CR et al. *Eur Urol.* 2008;54:543-562.
3. Stohrer M et al. *European Urology.* 2009;56:81- 88.
4. Andersson KE et al. Pharmacological treatment of urinary incontinence. 3rd International Consultation on Incontinence. Monaco, June 26-29, 2004.

Systemic impact of anticholinergics



1. Chapple CR et al. *Urology*. 2002;60(Suppl 5A):82-89.
2. Chapple CR et al. *Eur Urol*. 2008;54:543-562.
3. Andersson KE et al. Pharmacological treatment of urinary incontinence. 3rd International Consultation on Incontinence. Monaco, June 26-29, 2004.

Why botulinum toxin?

DO + BoNT

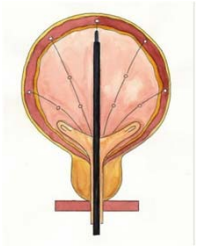
1998

Antimuscarinics

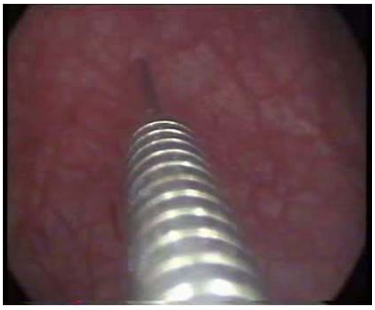
Neurostimulation / Neuromodulation

Surgery / Augmentation

Techniques of application



Technique of application



Placebo controlled study

Table 1 – Baseline characteristics of study groups

	Treatment group (*n* = 122)	Placebo group (*n* = 118)
Age, yr (range)	60.7 (50.8–67.8)	58.2 (51.5–69.2)
Body mass index >30	49 (40.2)	50 (43.5)
Ethnic group		
White	118 (96.7)	109 (93.9)
Other	4 (3.3)	7 (6.2)
Smoking	30 (24.6)	24 (20.5)
Parity		
0	10 (8.2)	6 (5.1)
1+	112 (92.8)	111 (94.9)
Previous continence surgery	44 (36.1)	46 (39)
Voiding frequency per 24 h	10.3 (9.3–12.7)	10.7 (9.3–13.3)
Incontinence episodes per 24 h	6.2 (3.7–8.3)	6.2 (3.0–8.7)
Urgency episodes per 24 h[†]	8.0 (5.7–10.3)	7.7 (6.0–9.7)
Urgency severity score (IUSS)	2.1 (1.7–2.4)	2.1 (1.7–2.3)
Maximum voided volume	350 (275–450)	300 (250–420)
Mean voided volume	165.8 (122.0–203.7)	164.4 (121.8–198.0)
Continent	6 (4.9)	8 (6.8)
ICIQ score	17.0 (14.0–19.0)	16.0 (13.0–18.0)
I-QOL score	24.4 (11.4–38.6)	23.3 (12.5–34.1)
Treated with flexible cystoscope	43 (35.2)	44 (37.3)
Treated under local anaesthesia	58 (47.5)	60 (50.8)

IUSS = Indevus Urgency Severity Scale; ICIQ = International Consultation on Incontinence Questionnaire; I-QOL = Incontinence Quality of Life (questionnaire).
[*] Data are displayed as medians (interquartile range) or number (%).
[†] Defined as severity of moderate or severe from the urgency severity score in the urinary diary.

Tincello et al. 2012: Denys et al. 2011

Botox and OAB: placebo controlled study

Table 2 – Primary outcome and other 6-mo data[*]

	Treatment group (*n* = 100)	Placebo group (*n* = 99)	Difference/OR and 95% CI	*p* value
Primary outcome				
Voiding frequency per 24 h	8.33 (6.83–10.00)	9.67 (8.37–11.67)	1.34 (1.00–2.33)	0.0001
Secondary outcomes				
Incontinence episodes per 24 h	1.67 (0.00–5.33)	6.00 (1.33–8.33)	4.33 (3.33–5.67)	<0.0001
Urgency episodes per 24 h	3.83 (1.17–6.67)	6.33 (4.00–8.67)	2.50 (1.33–3.33)	<0.0001
Urgency severity score (IUSS)	1.50 (1.00–2.00)	1.90 (1.50–2.30)	0.40 (0.20–0.60)	0.0006
Continent	31 (31.3)	12 (12.0)	3.12 (1.49–6.52)[†]	0.002
ICIQ score	10.00 (4.00–15.00)	15.00 (11.00–18.00)	5.00 (3.00–7.00)	<0.0001
IQOL score	55.11 (23.30–78.41)	27.27 (18.18–46.59)	−27.84 (−31.82 to −12.50)	<0.0001

OR = odds ratio; CI = confidence interval; IUSS = Indevus Urgency Severity Scale; ICIQ = International Consultation on Incontinence Questionnaire; IQOL = Incontinence Quality of Life (questionnaire).
This analysis includes only those women who returned a minimum of 2 d of valid data "in window." Only 23 of 199 women (11.6%) returned data >2 wk each side of the 6-mo date.
Inclusion of "out of window" data did not affect the results (data not shown).
[*] Data are displayed as medians and interquartile ranges (IQR), with *p* values calculated using the Mann-Whitney *U* test. The difference between medians is displayed with 95% confidence intervals.
[†] For continence the OR with 95% CI is displayed.

Tincello et al. 2012: Denys et al. 2011

Botox and OAB: placebo controlled study

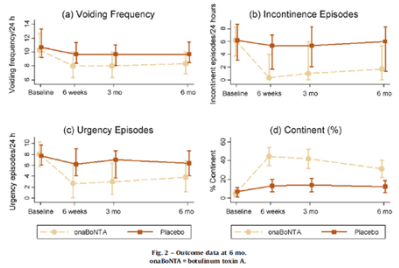


Fig. 2 – Outcome data at 6 mo.
onaBoNTA = botulinum toxin A.

Tincello et al. 2012: Denys et al. 2011

Botox and OAB: placebo controlled study

Table 3 – Diary and other outcomes at 6 wk and 3 mo

6-wk outcomes	Treatment group n = 97	Placebo group n = 98	p value
Voiding frequency per 24 h	8.00 (6.33–10.00)	9.67 (8.37–11.67)	<0.0001
Incontinence episodes per 24 h	0.33 (0.00–4.00)	5.33 (1.67–7.00)	<0.0001
Urgency episodes per 24 h	2.67 (0.00–6.33)	6.17 (4.00–9.00)	<0.0001
Urgency severity score (IUSS)	1.30 (0.7–1.90)	1.90 (1.40–2.20)	<0.0001
Continent, n (%)	43 (41.8)	13 (13.1)	<0.0001
ICIQ score	7.00 (1.00–14.00)	14.00 (1.00–18.00)	<0.0001
IQoL score	55.68 (22.72–85.23)	30.68 (17.05–51.14)	0.0001
3-mo outcomes	**n = 86**	**n = 86**	
Voiding frequency per 24 h	8.00 (6.30–10.00)	9.67 (8.00–11.00)	<0.0001
Incontinence episodes per 24 h	1.00 (0.00–6.00)	5.33 (2.00–8.33)	<0.0001
Urgency episodes per 24 h	3.00 (0.67 –6.33)	7.00 (3.67–8.67)	<0.0001
Urgency severity score (IUSS)	1.30 (0.80–2.00)	1.90 (1.40–2.30)	0.0001
Continent, n (%)	36 (35.0)	12 (12.0)	<0.0001
ICIQ score	8.00 (3.00–14.00)	15.00 (9.00–17.00)	<0.0001
IQOL score	64.77 (27.27–90.91)	25.00 (14.77–44.32)	<0.0001

IUSS = Indevus Urgency Severity Scale; ICIQ = International Consultation on Incontinence Questionnaire; I-QOL = Incontinence Quality of Life (questionnaire).
The *p* values in this table are from secondary analyses and should be interpreted with due caution.

Tincello et al. 2012: Denys et al. 2011

Botox and OAB: phase 2 Study

Table 4 – Adverse events during follow-up

Adverse events	At 6 wk				At 6 mo			
	Treatment (n = 118)	Placebo (n = 113)	OR (95% CI)	p	Treatment (n = 116)	Placebo (n = 110)	OR (95% CI)	p
Urinary tract infection, n (%)	35 (30)	10 (9)	4.34 (1.95–10.37)	0.0001	36 (31)	12 (11)	3.68 (1.72–8.25)	0.0003
Voiding difficulty, n (%)	19 (16)	5 (4)	4.1 (1.42–16.70)	0.004	10 (9)	1 (1)	10.28 (1.41–450.19)	0.01
ISC, n (%)	16 (14)	5 (4)	3.39 (1.13–12.20)	0.02	18 (16)	4 (4)	4.87 (1.52–20.33)	0.003
Use of additional treatment, n (%)	8 (7)	22 (20)	0.30 (0.11–0.75)	0.006	16 (14)*	35 (32)	0.34 (0.16–0.69)	0.001

OR = odds ratio; CI = confidence interval; ISC = intermittent self-catheterisation.
Reported events since discharge at each follow-up visit; urinary tract infection was reported by the patient (microbiological confirmation was not required). Routine ultrasound screening for retention was not part of the study protocol. Voiding difficulty was diagnosed, and ISC commenced on the basis of symptoms (voiding difficulty and/or incomplete emptying) and confirmed by ultrasound and/or catheterisation. Threshold volume for ISC was 100 ml (three centres) or 150 ml (four centres).
* Three patients in the active group had received two different drugs.

Tincello et al. 2012: Denys et al. 2011

Other palcebo 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)

Neurogenic Detrusor Overactivity:
defined as overactivity due to a relevant neurological condition

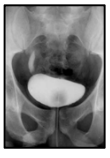
- **Aetiologies:**
  - Spinal cord injury[1,2]
    - Spina bifida[2]
  - Multiple sclerosis[2]
  - Stroke[1]
  - Parkinson's disease[1]
  - Cerebrovascular accidents[1]
  - Other[1]

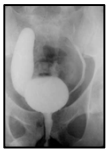
1. Abrams P et al. *Neurourol Urodynamics.* 2010;29:213-240.
2. Pannek J. European Association of Urology. Guidelines on neurogenic lower urinary tract dysfunction. 2011. http://www.uroweb.org/gls/pdf/17_Neurogenic%20LUTS.pdf. Accessed June 2011.

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

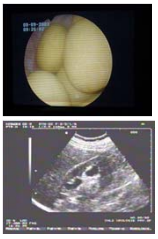




Reynard JM et al. *Spinal Cord.* 2003;41:1-11.

Consequences of untreated NDO: High detrusor pressures

- Urinary tract infections
- Lithiasis
- Reflux
- Hydronephrosis
- Renal failure



de Sèze M. *Mult Scler.* 2007;13:915-928.

Consequences of untreated NDO: Impact on quality of life

Physical
- Limitations or cessation of physical activities

Intimacy
- Avoidance of sexual contact and intimacy

Psychological
- Guilt/depression
- Loss of self-esteem
- Fear of:
  - Lack of bladder control
  - Urine odour

QUALITY OF LIFE

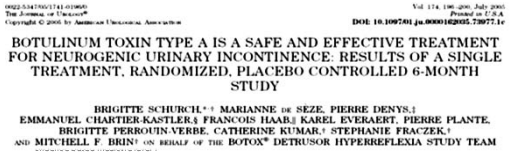
Occupational
- Absence from work
- Decreased productivity

Social
- Reduced social interaction
- Planning travel around toilet accessibility

Domestic
- Requirements for specialized underwear
- Precautions with clothing

Tubaro A. *Urology.* 2004;64(Supp 6A):2-6.

NDO: Phase 2 Study

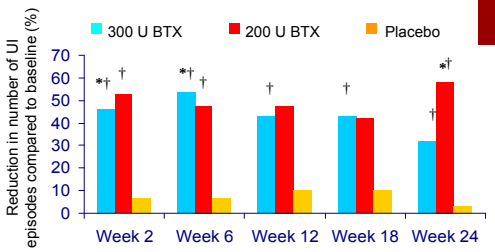


BOTULINUM TOXIN TYPE A IS A SAFE AND EFFECTIVE TREATMENT FOR NEUROGENIC URINARY INCONTINENCE: RESULTS OF A SINGLE TREATMENT, RANDOMIZED, PLACEBO CONTROLLED 6-MONTH STUDY

BRIGITTE SCHURCH,*† MARIANNE DE SÈZE, PIERRE DENYS,‡ EMMANUEL CHARTIER-KASTLER,§ FRANÇOIS HAAB,‖ KAREL EVERAERT, PIERRE PLANTE, BRIGITTE PERROUIN-VERBE, CATHERINE KUMAR,† STEPHANIE FRACZEK,† AND MITCHELL F. BRIN† ON BEHALF OF THE BOTOX® DETRUSOR HYPERREFLEXIA STUDY TEAM

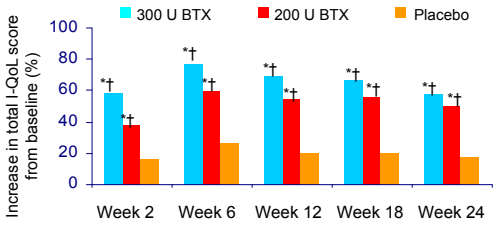
- N=59 (57 endete); 90%QL, 10%MS
  - 19 BOTOX® 300 E., 19 BOTOX® 200 E., 21 placebo
- Alle Patienten mit neurogener Detrusorhyperaktivität und Harninkontinenz unter selbst-intermittierendem Katheterismus

Incontinence episodes



*p<0.05 for differences between BTX (BOTOX®) group and placebo
†p<0.05 for within-group changes from baseline **Schurch et al. J Urol 2005**

IQol-score



*p<0.05 for pairwise contrasts between BTX-A (BOTOX®) groups and placebo
†p≤0.002 for within-group differences from baseline **Schurch et al. J Urol 2005**

NDO Phase 3 Study: Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, 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 %

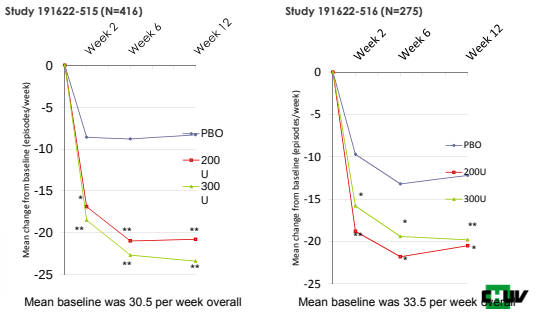
Cruz et al. Eur Urol 2011
Ginsberg et al. J. Urol. 2012

Baseline Diary Parameters
(Pooled 515/516 ITT population)

Parameter	Overall (N=691)	MS (N=381)	SCI (N=310)
Weekly urinary incontinence	**31.7 (4.5 per day)**	32.7 (4.7 per day)	30.5 (4.4 per day)
Use of CIC at baseline	**55.0 %**	35.4 %	82.8 %
Weekly CIC voids (patients using CIC)	**32.9 (N=373) (4.7 per day)**	27.4 (N=112) (3.9 per day)	35.2 (N=261) (5.0 per day)
Weekly spontaneous voids (patients not using CIC)	**66.4 (N=305) (9.5 per day)**	66.7 (N=263) (9.5 per day)	63.9 (N=42) (9.1 per day)

Cruz et al. 2011

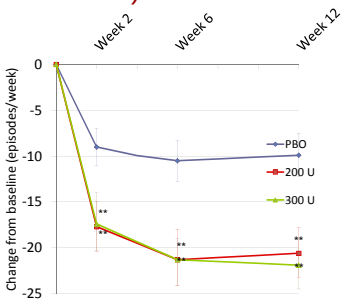
Change from Baseline in Weekly Urinary Incontinence Episodes



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

* p= <0.05; ** p= <0.001 in pairwise comparison versus placebo

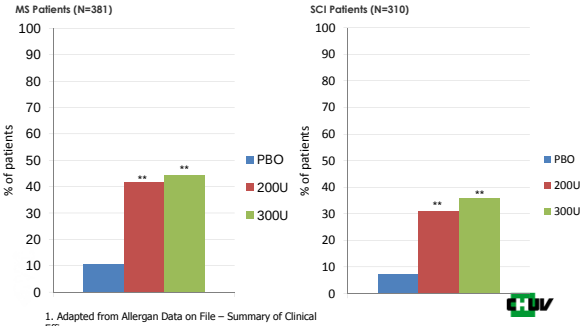
Change from Baseline in Weekly Urinary Incontinence Episodes (pooled 515/516)



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

** p= <0.001 in pairwise comparison versus placebo 95% CI plotted

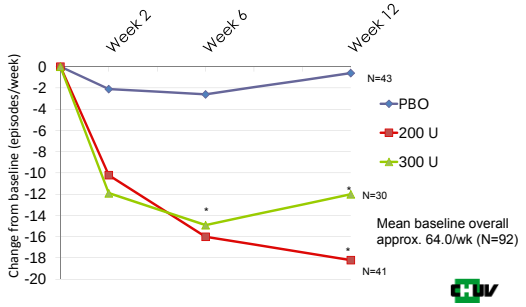
Proportion of 'Dry' patients at Week 6 by Etiology (pooled 515/516)



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

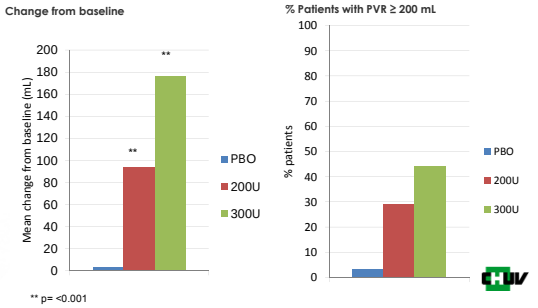
** p= <0.001 in among-group comparison

Change from Baseline in Weekly Micturition Episodes in MS Patients (pooled 515/516) (patients not using CIC pre- or post-treatment)



* p= <0.05 in pairwise comparison versus placebo

PVR Urine Volume at Week 2 (in patients not using CIC at baseline)



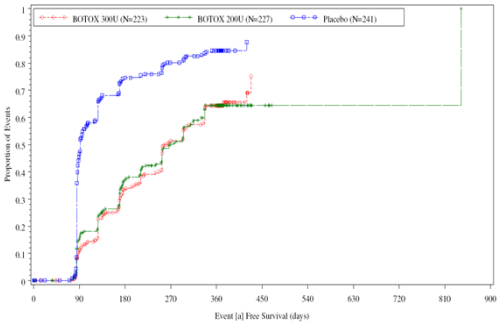
** p= <0.001

UTI (first 12 weeks of Tx cycle 1)

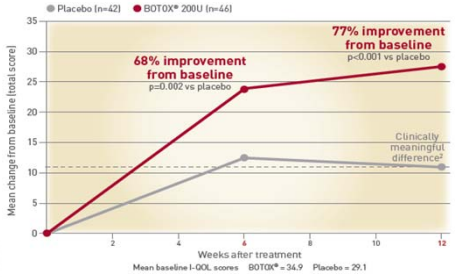
CIC Status		Dose		
Pre-Tx	Post-Tx	Placebo	200 U	300 U
Using	Using	20.7 % (29/140)	22.0 % (29/132)	29.2 % (33/113)
Not Using	Using	11.9 % (5/42)	40.4 % (19/47)	42.6 % (23/54)
	Not Using	16.4 % (10/61)	21.3 % (13/61)	26.1 % (12/46)
	Not using and PVR ≥ 200 mL	0.0 % (0/5)	32.0 % (8/25)	42.9 % (9/21)
	Not using and PVR < 200 mL	17.9 % (10/56)	13.9 % (5/36)	12.0 % (3/25)

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



Change from baseline in total I-QOL score in patients with de novo catheterisation[1]

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

MS Exacerbation: Annualized Exacerbation Rates

	Placebo	200 U	300 U
Study 515	0.22	0.14	0.37
Study 516	0.19	0.36	0.20
Pooled 515/516	0.20	0.23	0.29

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