# Neuro-urology for the Urogynaecologist and urologist

W20, 15 October 2012 14:00 - 18:00

| Start | End | Topic | Speakers |
|---|---|---|---|
| 14:00 | 14:05 | Introduction to the Workshop | • Sohier Elneil |
| 14:05 | 14:25 | Neurology of the Bladder and the Pelvic Floor | • Daniel Engeler |
| 14:25 | 14:45 | Bladder Symptoms and their Assessment in the Neurological Patient | • Michele Spinelli |
| 14:45 | 15:05 | Pelvic Floor Dysfunction and its Assessment in the Neurological Patient | • Alex Digesu |
| 15:05 | 15:20 | Chronic Pelvic Pain in the Neurological Patient | • Daniel Engeler |
| 15:20 | 15:30 | Discussion | All |
| 15:30 | 16:00 | Break | None |
| 16:00 | 16:30 | Indications and Limitations of Botulinum Toxin in the Neurogenic Bladder and Pelvic Floor | • Rizwan Hamid |
| 16:30 | 17:00 | Indications and Limitations Neuromodulations (PTNS) in the Neurogenic Bladder and Pelvic Floor | • Alex Digesu |
| 17:00 | 17:10 | Discussion | All |
| 17:10 | 17:40 | Indications and Limitations of Neurmodulation (SNM) in Neurogenic Bladder | • Michele Spinelli |
| 17:40 | 17:50 | SNM in Pelvic Floor Disorders | • Sohier Elneil |
| 17:50 | 18:00 | Discussion | All |

## Aims of course/workshop

Aims and Objectives: -Current concepts relating to the neurological control of the bladder and the pelvic floor. -Urinary and pelvic floor symptoms in patients with cerebral lesions, multiple sclerosis, Parkinson's disease, spinal cord injury and cauda equina -Urinary and pelvic floor symptoms in bladder pain syndrome/IC and chronic pelvic pain syndromes (neurological basis of disease). -Investigating neurogenic bladder and pelvic floor dysfunction -Innovative therapies in treating neurogenic bladder and pelvic floor disorders: Indications and limitations of botulinum toxin -Innovative therapies in treating neurogenic bladder and pelvic floor disorders: Indications and limitations of neuromodulation

## Educational Objectives

This workshop will provide a fresh approach to the understanding of the neurological basis of bladder and pelvic floor conditions encountered in urogynaecology and urology.

All the speakers have worked extensively in this field and have published widely on the subject matter.

Some knowledge of the neurological causes of bladder and pelvic floor dysfunction is essential for the general urogynaecologist and urologist. Patients with neurological disease are referred to both sets of clinicians for advice regarding their bladder and pelvic floor management.

It is important to have an understanding of the nature of their neurology, especially when planning medical or surgical management. In addition, clinicians need to know what may be the presenting uro-genital symptoms of a patient with a neurological condition, and the minimal neurological examination necessary for recognising an underlying neurological problem.

The areas covered in this workshop will help clinicians understand the neurological patient with bladder and pelvic floor dysfunction better. The speakers will discuss patient assessment, investigations and
provide algorithms for managing this group of complex patients.

## NEURO-UROLOGY FOR THE UROGYNAECOLOGIST AND UROLOGIST

**Chairman: Sohier Elneil**

### Introduction

The pelvic floor is highly complex structure made up of skeletal and striated muscle, support and suspensory ligaments, fascial coverings and an intricate neural network. Its dual role is to provide support for the pelvic viscera (bladder, bowel and uterus) and maintain functional integrity of these organs. In order to maintain good pelvic floor function, this elaborate system must work in a highly integrated manner. When this is system if damaged, either directly or as a consequence of an underlying neurological condition, pelvic floor failure ensues along with organ dysfunction.

The aetiology is inevitably multi-factorial, and seldom as a consequence of a single aetiological factor. It can affect one or all three compartments of the pelvic floor, often resulting in prolapse and functional disturbance of the bladder (urinary incontinence and voiding dysfunction), rectum (faecal incontinence), vagina and/or uterus (sexual dysfunction). This compartmentalisation of the pelvic floor has resulted in the partitioning of patients into urology, gynaecology, colo-rectal surgery or neurology, depending on the patients presenting symptoms. In complete pelvic floor failure, all three compartments are inevitably damaged resulting in apical prolapse, with associated organ dysfunction. It is clear that in this state, the patient needs the clinical input of at least two of the three pelvic floor clinical specialities. Whilst the primary clinical aim is to correct the anatomy, it must also be to preserve or restore pelvic floor function. As a consequence, these patients need careful clinical assessment, appropriate investigations, and counselling before embarking on a well-defined management pathway. The latter includes behavioural and lifestyle changes, conservative treatments, pharmacotherapy, minimally invasive surgery, and radical specialised surgery.

It is not surprising that in this complex group of patients, a multidisciplinary approach is not

only necessary, but critical, if good clinical care and governance is to be ensured. But it is of significant import that one has a good understanding of the neurology of the pelvis and its organs.

***Neural control of uro-genital system***

Voluntary control over the uro-genital system is critical to our social existence. Since its peripheral innervation derives from the most distal segments of the spinal cord, integrity of the long tracts of the central nervous system for physiological function is immediately apparent. In a survey of the site of the underlying neurological disease affecting a sample of patients referred to the department with bladder symptoms, spinal cord involvement of various pathologies was found to be the commonest cause of bladder symptoms.
Because of the commonality of innervation shared by the bladder and genital organs, it might be expected that abnormalities of these two systems inevitably occur together. This however is not the case because although the organs share the same root innervation and have common peripheral nerves within the pelvis, each is controlled by its own unique set of central nervous system reflexes.

In this workshop, a brief account of the neurophysiological control of the bladder and pelvic is given initially, followed by a description of the effect that neurological disease at different levels of the nervous system may have and finally the management of those conditions.

The bladder performs only two functions - storage and voiding of urine- and the modern view of the control of these two mutually exclusive activities is that whereas storage is organised within the spinal cord, micturition results from activation by suprapontine influences of a centre in the dorsal tegmentum of the pons, the pontine micturition centre (PMC). In neurological disease, this delicate interaction can be severely disrupted, and manifests as a disorder of voiding or storage depending on the condition such as multiple sclerosis,

Parkinson's disease, multiple system atrophy and others. But commonly, it is direct injury to pelvic nerves that can give rise to quite marked bladder and pelvic floor dysfunction.

The peripheral innervation of the pelvic organs can be damaged by extirpative pelvic surgery such as resection of rectal carcinoma, radical prostatectomy, or radical hysterectomy. The dissection necessary for rectal cancer is likely to damage the parasympathetic innervation to the bladder and genitalia, as the pelvic nerves take a medio-lateral course through the pelvis either side of the rectum and the apex of the prostate. The nerves may either be removed together with the fascia which covers the lower rectum or may be damaged by a traction injury as the rectum is mobilized prior to excision.

Urinary incontinence following a radical prostatectomy or a radical hysterectomy which includes the upper part of the vagina, is probably also due to damage to the parasympathetic innervation of the detrusor and in the case of a radical prostatectomy, there may be additional direct damage to the innervation of the striated urethral sphincter

The focus in the literature tends to focus on the effects of neurological disease on the bladder tends, but other pelvic floor effects should not be ignored, such as pelvic organ prolapse, pain syndromes and sexual dysfunction.

Therapies to manage these conditions depend on a multi-disciplinary approach. This workshop will help guide practitioners on how to maximise the therapeutic options for their patients.

**Aims and Objectives of the Workshop**

- Current concepts relating to the neurological control of the bladder and the pelvic floor.
- Urinary and pelvic floor symptoms in patients with cerebral lesions, multiple sclerosis, Parkinson's disease, spinal cord injury and cauda equine
- Urinary and pelvic floor symptoms in bladder pain syndrome/IC and chronic pelvic pain syndromes (neurological basis of disease).
- Investigating neurogenic bladder and pelvic floor dysfunction
- Innovative therapies in treating neurogenic bladder and pelvic floor disorders: Indications and limitations of botulinum toxin
- Innovative therapies in treating neurogenic bladder and pelvic floor disorders: Indications and limitations of neuromodulation

**Neurology of the bladder and the pelvic floor (Daniel Engeler)**

Voluntary control of micturition is based on a complex neural circuitry highly distributed on different levels of the nervous system. A variety of neurotransmitters are involved in signalling of neural control. Understanding the pathways involved at the level of the brain, the spinal cord and the peripheral nervous system as well as the peripheral organ is important for the physician diagnosing and treating patients with neurogenic bladder and pelvic floor dysfunction. Diseases or injuries to this complex system may lead to abnormal function of the end organs, i.e. leading to pathologic storage or release of urine. Disruption of the normal neural pathways has different specific functional consequences in the lower urinary tract as well as the pelvic floor. Cerebral lesions, multiple sclerosis, Parkinson’s disease and trauma to the nervous system at different levels, such as the brain, spinal cord, or cauda equina are therefore followed by a variety of functional disturbances, which can be derived from the pathways involved. Both, current concepts relating to the normal neurological control of the bladder and the pelvic floor, as well as disease or trauma specific pathologies are discussed here.

**Bladder Symptoms and its Assessment in the Neurological Patient (Michele Spinelli)**

To be discussed in the workshop

**Pelvic Floor Dysfunction and its Assessment in the Neurological Patient (Alex Digesu)**

To be discussed in the workshop

**Neurological Aspects in Chronic Pelvic Pain (Daniel Engeler)**

A number of well-defined conditions may cause chronic pelvic pain in women, such as endometriosis, infection, or gynaecological malignancies. Indeed, many of the patients suffering from chronic pelvic pain (CPP) will not be found to have well-defined conditions as a treatable cause. The main focus for CPP in the past has been on pelvic end-organs, whereas research on chronic pain states has shown, many of the important mechanisms involved are based within the central nervous system. In this part of the workshop, urinary and pelvic floor symptoms in bladder pain syndrome/interstitial cystitis and chronic pelvic pain syndromes are discussed and relevant neurological aspects of the disease are highlighted.

**Indications and Limitations of Botulinum Toxin in Neurogenic Bladder and Pelvic Floor Disorders (Rizwan Hamid)**

# Botulinum Toxin therapy in neuropathic bladder

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Consultant Urological Surgeon
National Hospital for Neurology & Neurosurgery, UCLH
&
London Spinal Injuries Unit, Stanmore, RNOHT

## Overactive Bladder

OAB defined based on symptoms (ICS 2002)

- Urgency, with or without urge incontinence, usually with frequency and nocturia
- In the absence of pathologic or metabolic conditions that might explain these symptoms
- These symptoms with any neurologic diagnosis - NDO

Abrams P et al. Neurourol Urodyn 2002

## Treatment options

- Behavioural Therapy
- Antimuscarinic medications
- Sacral neuromodulation
- Botulinum toxin therapy
- Augmentation cystoplasty

Reyblat P, Ginsberg DA et al. Curr Urol Rep 2010

## Botulinum toxin therapy

- What is botulinum toxin
- Who introduced it / when
- How it works
- Technique of procedure
- Efficacy
- Duration
- QoL
- Safety profile
- Future

## The development of BOTOX® for therapeutic use

| | |
|---|---|
| 2010 | BOTOX® injection therapy is the only product specifically licensed for the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine) |
| 2002 | BOTOX® received UK approval for treatment of ocular and hand disability due to upper limb spasticity associated with stroke in adults |
| 2001 | BOTOX® approved for the treatment of axillary hyperhidrosis (excessive sweating) in the UK |
| 1998 | BOTOX® received UK approval for dynamic equinus foot deformity due to spasticity in paediatric cerebral palsy patients aged 2 years and older |
| 1997 | BOTOX® approved for the treatment of the symptomatic relief of idiopathic cervical dystonia in the UK |
| 1994 | BOTOX® approved in the UK for the treatment of hemifacial spasm (a neuromuscular disorder characterised by unpredictable and involuntary twitching of the facial muscles on one side of the face) and blepharospasm |
| 1989 | Allergan, Inc., receives approval from the Food & Drug Administration (FDA) for the name BOTOX® (botulinum toxin type A, Oculinum) and gets FDA approval to market BOTOX® for strabismus and blepharospasm (uncontrollable eye blinking) associated with dystonia |
| 1988 | Allergan acquires rights to distribute Dr Scott's botulinum toxin type A, Oculinum |
| 1980s-70s | Purification process of botulinum toxin type A optimised. Alan. B. Scott, M.D., Smith Kettlewell Eye Research Foundation, San Francisco, tests efficacy of toxin as treatment for crossed eyes (strabismus). Dr Scott forms company, Oculinum Inc. to conduct human testing |
| 1960s | Dr Vernon Brooks proves botulinum toxin blocks acetylcholine release from motor neuron endings, inducing a temporary 'relaxation' of the targeted muscle |
| 1946 | Botulinum toxin type A isolated in crystalline form by Edward J. Schantz, Ph.D., University of Wisconsin-Madison |
| 1920s | Botulinum toxin type A isolated in purified form by Doctor H. Sommer, University of California, San Francisco, USA |
| 1896 | Bacterium Bacillus botulinum (later renamed Clostridium botulinum) identified by Prof E. P. van Ermengem, a bacteriology professor at the University of Ghent, Belgium |

## Botulinum Toxin A


## Mechanism of action

- Seven subtypes (A,B,C1,D,E,F,G)
- Clinically A & B used. (A more potent)
- Enters pre-synaptic endplate of cholinergic neurons by receptor mediated endocytosis.
- Selectively cleaves SNAP-25- prevents normal vesicle docking & fusion to the presynaptic plasma membrane
- Inhibits the release of neurotransmitters (no effect on production and storage of transmitters)
- It reduces the level of sensory receptors (TRPV1 & P2X3) in suburothelium. Hence decreased sensitivity of the aberrant unmyelinated C fibres
- BTX cannot cross the blood-brain barrier
- Doesn't- alter detrusor structure, induce muscle cell degeneration,induce axonal sprouting

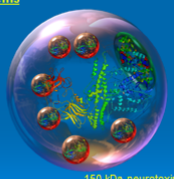
## Botulinum Toxin:
## *Unique Molecular Structure*

Clostridium botulinum is a gram positive, anaerobic, rod-shaped bacterium that produces seven serologically distinct neurotoxins (A, B, C1, D, E, F, G)

Non-Toxic Accessory Proteins

Non-toxic, non-hemaglutinin (NTNH)

Hemaglutinin (HA)

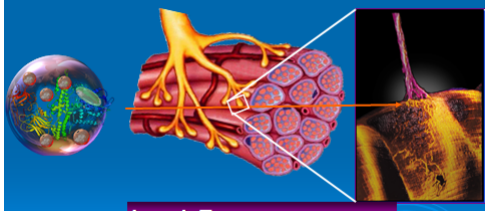


150 kDa neurotoxin protein

Modular Design Imparts Activity

Schantz EJ Gasper E (1975) Jpn J Med Sci Biol 28:65-69

## BTX has high affinity for the Neuromuscular Jn



**Local, Temporary, Muscle Relaxation**

## Botulinum Toxin Type A Mechanism: *alpha* Motor Neuron Inhibition

- BTX-A binds to acceptors on cholinergic terminals
- Internalization

- Release of light chain
- Cleavage of SNAP-25 and blockage of ACH release


EUROPEAN UROLOGY 49 (2006) 644–650

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

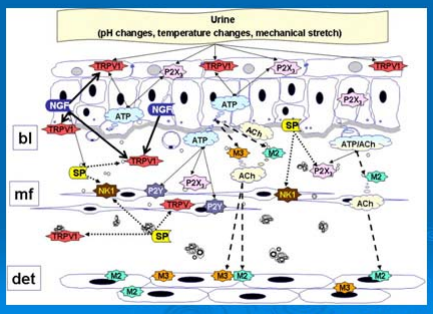
European Association of Urology

Review - Neuro-urology – Voiding Dysfunction

**Proposed Mechanism for the Efficacy of Injected Botulinum Toxin in the Treatment of Human Detrusor Overactivity**

Apostolos Apostolidis [a], Prokar Dasgupta [a,b], Clare J. Fowler [a,*]

[a] Department of Uro-Neurology, the National Hospital for Neurology and Neurosurgery, London, UK
[b] Department of Urology, Guys' and St. Thomas' Hospitals and GKT Medical School, London, UK




Apostolidis Aet al. Eur Urol 2006

0022-5347/00/1643-0692/0
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Vol. 164, 692–697, September 2000
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BOTULINUM-A TOXIN FOR TREATING DETRUSOR HYPERREFLEXIA IN SPINAL CORD INJURED PATIENTS: A NEW ALTERNATIVE TO ANTICHOLINERGIC DRUGS? PRELIMINARY RESULTS

B. SCHURCH,* M. STÖHRER, G. KRAMER, D. M. SCHMID, G. GAUL AND D. HAURI

*From the Swiss Paraplegic Centre, University Hospital Balgrist and Departments of Urology, University Hospital, Zurich and BG Unfallklinik, Murnau, Switzerland*

'Penicillin for the 21st century'

## Botulinum toxin A

- Popularised by Schurch
- Unlicensed indication
- 2nd line (refractory to medications)
- Temporary (ave 8-9 months)
- Repeated injections are effective
- Need for self catheterization
- Local / GA
- Number / site / dose not well defined

## Points of Technique

A minimally invasive technique for outpatient local anaesthetic administration of intradetrusor botulinum toxin in intractable detrusor overactivity

M. HARPER, R.B. POPAT, R. DASGUPTA, C.J. FOWLER and P. DASGUPTA*

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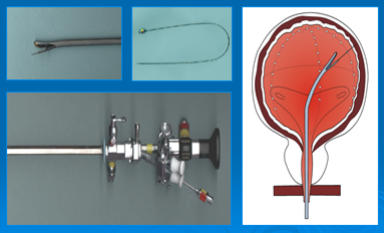
Accepted for publication 31 March 2003

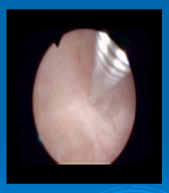
## Surgical Procedure



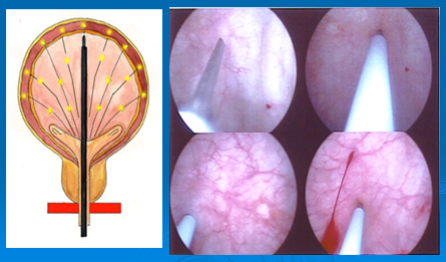
## Technique of injection

Via flexible cystoscope

- Dose
  - Botox 200IU
- Site of injections
  - Avoid the trigone
- Number of injections
  - Vary in number, but usually 20



## Botox injection technique



## Pubmed search

| | 2000 | 2002 | 2004 | 2006 | 2008 | 2010 |
|---|---|---|---|---|---|---|
| BTX | 1 | 3 | 6 | 35 | 44 | 57 |
| Anti-choli | 3 | 15 | 13 | 32 | 24 | 28 |
| SNS | 1 | 3 | 3 | 5 | 14 | 19 |

## European Consensus Report

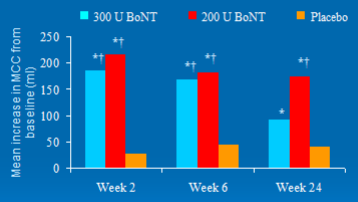
- 200 IU BTX
- Mostly intradetrusor injections
- Efficacy 36-89% (mean 69%)
- Complete continence 32-86% (mean 58%)
- Duration of effect 4-10 mo (mean 6 mo)

- MCC – increased (11-242%)
- Pdet – decreased (9-56%)

- PVR (4-45%)
- UTI's (6-35%)
- Haematuria (3-5%)
- Malaise (5%) / Flu-like symptoms
- Hyposthenia
- No fibrosis

Apostolides A et al. Eur Urol 2009

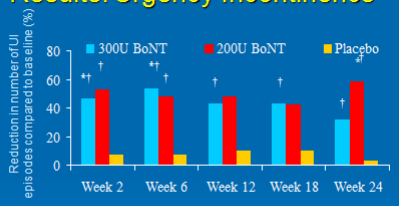
## Results: Urodynamics – MCC




*p<0.05 for within-group changes from baseline
†p<0.05 for pairwise contrasts between BoNT groups versus placebo

Schurch. J Urol, 2005

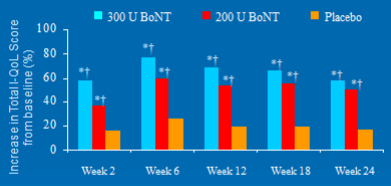
## Results: Urgency Incontinence




*p<0.05 for differences between BoNT group and placebo
†p<0.05 for difference within-group changes from baseline

Schurch. J Urol, 2005

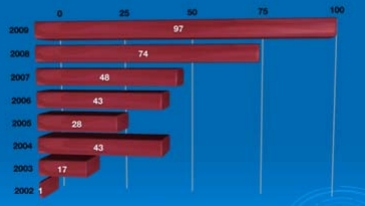
## Results: Quality of Life



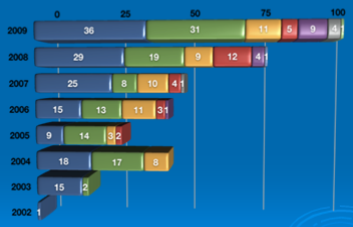

*p<0.05 for pairwise contrasts between BoNT groups and placebo
†p≤0.002 for within-group differences from baseline

Schurch. J Urol, 2005

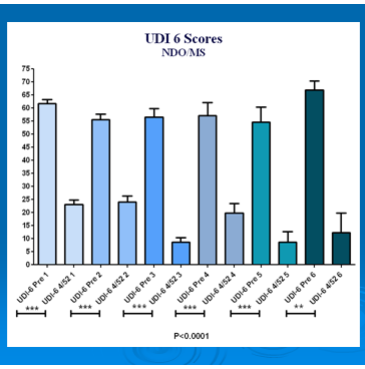
## Number of NDO/MS patients treated by BoNT-A

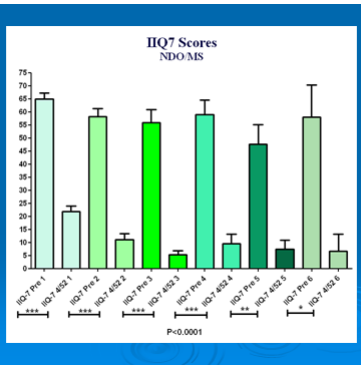


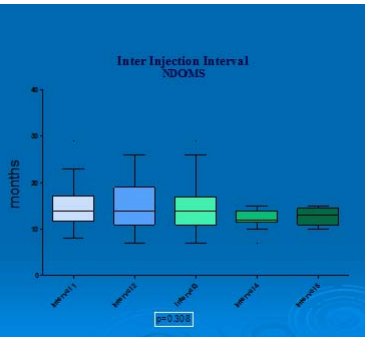
## New v/s repeat injections

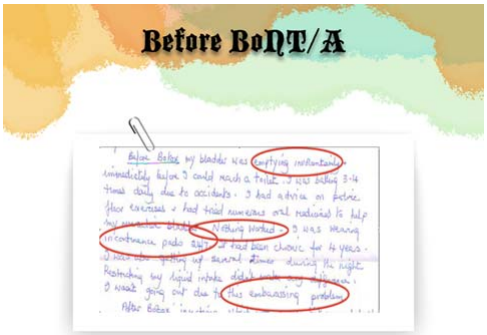


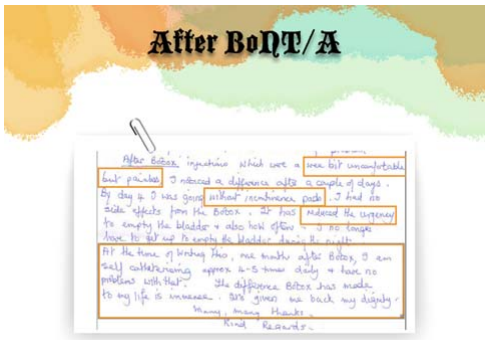

## Pain Perception

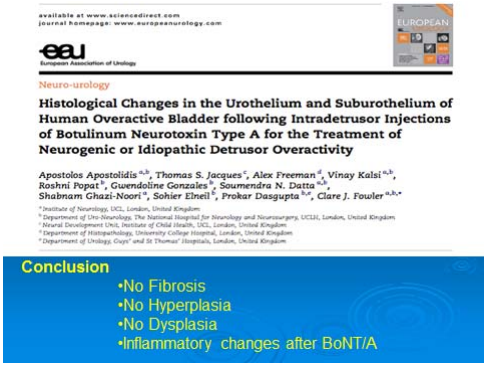



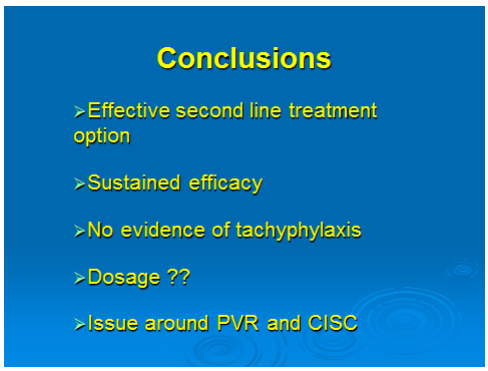



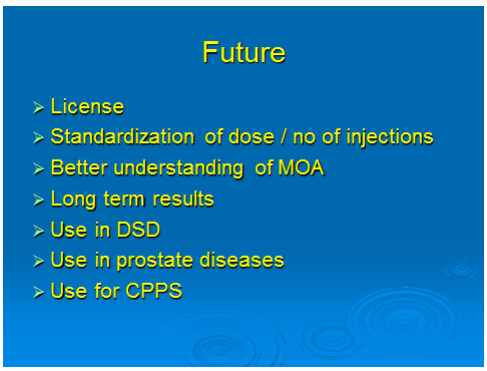






**Indications and Limitations Neuromodulation (PTNS) in the Neurogenic Bladder and Pelvic Floor (Alex Digesu)**

Pelvic floor disorders such as lower urinary tract symptoms (LUTS), anal incontinence and sexual dysfunctions are common disorders occurring in about 80% of neurogenic patients. Urgency represents the most bothersome LUTS and severely affects the quality of life (QOL). Neurogenic detrusor overactivity, detrusor sphincter dyssynergia and/or detrusor underactivity are the most common cause of LUTS in neurogenic patients. These bladder abnormalities tend to become more severe with the progression of the disease leading to voiding difficulties, urinary retention, recurrent urinary tract infections and need of clean intermittent self catheterization. Drugs, surgery and repeated intradetrusor injections of botulinum toxin have been suggested as therapeutic options. However, neurological patients

often fail to respond to drug therapy, report intolerable side effects and/or are reluctant to invasive surgical treatment.

Neuromodulation is a mechanism by which the nervous system regulates electrical impulses flowing through neural tissues. Percutaneous tibial nerve stimulation (PTNS), a new minimally invasive neuromodulation technique, is able to modify the lower urinary tract behaviour by inhibiting involuntary detrusor contractions in patients with both neurogenic and idiopathic detrusor overactivity in an outpatient setting.
PTNS has been demonstrated to be an effective, safe and well tolerated treatment in neurogenic patients affected by LUTS and unresponsive to anticholinergic drugs. Both subjective and objective improvement have been reported. A statistically significant improvement of patient perception of bladder condition, overactive bladder (OAB) symptoms, mean voided volume per micturition, post micturition residual and QOL parameters have been reported.

Previous studies have also showed that PTNS is effective to suppress detrusor overactivity in MS patients.

Usually pharmacological agents with a predominant anticholinergic action are widely used as first line treatment of LUTS in patients with neurogenic bladder**.** However, the effectiveness of these treatments has been evaluated in non-neurogenic patients and their applicability to patients with OAB syndrome and neurogenic patients is not known. In neurogenic patients OAB symptoms more difficult to manage and the symptoms themselves can exacerbate fatigue and increase disability. In addition, placebo controlled trials in more disabled populations where multiple factors can contribute to the production of urinary symptoms have not found the older anticholinergic agents to be effective due to side effects. Peters et al. compared in a randomized, multicenter, controlled study the effectiveness of PTNS to extended-release tolterodine. The study demonstrated that subject assessment of OAB symptoms compared to baseline was statistically significant in the PTNS arm with 79.5%

reporting cure or improvement compared to 54.8% of subjects on tolterodine ($p < 0.01$), without significant side effects. Based on these results,-PTNS may be considered a clinically significant alternative therapy for OAB in those patients who do not respond to pharmacological therapy.

The mechanism of action of PTNS is not completely understood yet. Long-latency somatosensory evoked potentials (LL-SEP) are well known to reflect information processing in the brain after stimulation of peripheral somatosensory system. Some authors found a modification of brain activity after PTNS and speculated that its efficacy is mediated by sacral and suprasacral centres of stimulus elaboration involving cortical associative areas. Considering its high safety, ease of use, lack of side effects and office-based convenience, PTNS could be consider as an ideal alternative treatment for neurogenic patients suffering from LUTS, expecially taking into account the lack of scientific evidence of anticholinergic efficacy in this group of patients.

PTNS has been also demonstrated to be clinically effective in the treatment of Anal incontinence which is commonly associated to LUTS in neurogenic patients.
The role of PTNS in the treatment of sexual dysfunctions has been suggested and speculated by some authors but it has not been demonstrated yet.
The main limitation of PTNS is the longevity of action. In addition it is a time consuming treatment which requires dedicated personnel.

**Indications and Limitations in Neuromodulation (SNM) in Neurogenic Bladder (Michele Spinelli)**

The pelvic floor plays an important role in the urine storage, voiding, urine continence, anal continence to gas and feces, defecation and sexual activity. All these pelvic organ functions

are controlled by nervous pathways that involve neurons in the motor cortex of the brain, spinal cord and peripheral ganglia.

In neurological diseases the alteration of these nervous pathways are responsible of the lack of coordination between the urinary bladder, urethra, rectum and pelvic floor muscle (PFM) leading to pelvic floor dysfunction (PFD).

Symptoms commonly reported by patients with neurological diseases include urinary incontinence (37–70%), constipation (29–67%), and in men erectile dysfunction (40–60%). This indicates that the central nervous system is involved both in motor and autonomic pelvic functions.

The pathogenesis of PFD in patients with neurological lesions is an active area of research. However, it is still unknown whether PFD are caused by lesions of the central nervous system or peripheral nerves.

It has also been demonstrated that the prevalence of bladder and bowel dysfunction increased with the severity of the illness. Sakakibara et al., showed that the majority of patients with Parkinson’s disease experienced pelvic organ dysfunction onset after the appearance of motor disorder.

The most striking feature of bladder dysfunction in the Parkinson’s disease patients is filling phase disorder and urinary incontinence. It has been suggested that in those patients, the decrease in central dopaminergic neurons (D1), which regulate the pontine micturition center, is responsible of detrusor hyperreflexia.

Voiding phase disorder is another feature seen in Parkinson's disease patients due to detrusor-sphincter dyssynergia. This disorder may be caused by peripheral a-adrenergic stimulation by anti-parkinsonian drugs such as levodopa or its metabolites.

However, the effect of dopaminergic drugs on parkinsonian bladder shows conflicting results. In some reports, the use of apomorphine, levodopa, pergolide produced a lessening of detrusor hyperreflexia whereas in others, it provided amelioration of voiding difficulty.

The most common bowel dysfunction in Parkinson's disease patients are constipation and prolonged colorectal transit time, difficulty in expulsion and paradoxical contraction of the puborectal muscle. These symptoms probably, reflect abnormalities in the colon and ano-rectum. Experimental study findings showed that a decreased intestinal motility occurs when there is a reduction in the number of central dopaminergic neurons, which modulate the pontine defecation centre. Other possible causes are peripheral nerve lesions or overextension injury secondary to faecal impaction.

Sexual dysfunction is also very common in both men and women with Parkinson's disease. However, the mechanism of sexual dysfunction is less clear than that of bladder and bowel dysfunction. Whereas motor disorder, pain, and depression may affect sexual function, there is little evidence that autonomic dysfunction contributes to sexual dysfunction in those patients. Experimental studies have shown that the key area for sexual function is in the hypothalamus and particularly the medial preoptic area and paraventricular nucleus.

People with multiple sclerosis experience high levels of sexual dysfunction which are mainly represented by hypoactive sexual behaviour, lack of sexual interest, decreased libido, often with problems in orgasmic capacity. Fatigue, spasticity, muscular weakness, bladder problems, pain, cognitive and behavioural changes also has an important impact on sexual dysfunction.

Different neurophysiological tests have been proposed in order to assess the direct and reflex responses to the pelvic floor. These include: the pudendoanal reflex, the bulbocavernosus reflex, the pudendal nerve terminal motor latency (PNTML). The cutaneoanal reflex and other somatosomatic and viscero-somatic reflexes have limited usefulness in pelvic floor investigations due to a large variability in the latency of these responses.

The more commonly used electrophysiological investigations to investigate the integrity of the sacral reflex arc supplying pelvic floor muscle function are the PNTML and the sacral reflexes. These last tests can be elicited by mechanical, electrical or magnetic stimulation and involve the whole reflex arc, but do not differentiate the afferent and efferent branch of the reflex.

The PNTML only explores the more distal portion of pudendal nerve, not looking at the portion of the nerve proximal to the site of the stimulation induced by the St. Mark’s electrode.

More recently, Fowler et al. described direct and reflex responses after S3 root stimulation, introducing wire electrode close to S3 sacral root. Direct motor and reflex responses from the external anal sphincter (EAS) by S3 electrical stimulation can provide valuable information on the functional integrity of the sacral reflex pathway, but differently from the pudendoanal and bulbocavernosus reflexes, can distinguish the efferent limb of the reflex pathway from the whole arc.

EAS responses during S3 percutaneous electrical stimulation are easy to perform, not invasive neither too painful thus representing a useful electrophysiological technique for the selection of candidates to sacral nerve modulation (SNM). The EAS responses following the

stimulation of the same S3 fibres used for SNM, contribute to evaluate the functional integrity of the efferent branch of pudendal nerve and to exclude lesions at the sacral S2-S4 central cord levels.

## SNM in Pelvic Floor Disorders (Sohier Elneil)

Electrical neuromodulation of the lower urinary tract began over a century ago, but it was the pioneering work of Tanagho and Schmidt at the University of California in the late 1980s that demonstrated electrical activation of efferent fibres to the striated urethral sphincter inhibited detrusor contractions [1]. Stimulation of the third sacral root (S3) has been shown to be effective in stimulating the urethral sphincter [2]. A large multicentre (Medtronic MDT-103 - USA, Canada and Europe) prospective randomised clinical trial was set up to look at efficacy and safety of chronic neuromodulation to the S3 nerve. Results of this study led to approval by the Food and Drugs Administration in October 1997. Over 25,000 neuromodulators (Interstim® and Interstim II®, Medtronic Inc, Minnesota, Minneapolis, USA) have so far been implanted for approved urinary indications, including functional non-neurogenic urinary retention or chronic urinary retention and voiding dysfunction secondary to urethral sphincter overactivity (Fowler's syndrome) [3, 4]. . Indeed, SNM has been shown to be the only effective therapy in women with these conditions.

### *Mechanism of Action in Urinary Retention*

Sacral neuromodulation restores voiding in women with chronic urinary retention [5], probably by resetting brainstem function [6]. SNM was first described as a treatment for urinary retention in the mid-1990s. At the time, SNM was introduced for the management of bladder dysfunction, paradoxically both intractable incontinence and retention. The first stage of SNM was an initial test procedure, known as a percutaneous nerve evaluation test (PNE) which if found to be positive and restore voiding ability, was followed by the implantation of a permanent sacral electrode. Success rates for women with retention for this

method were reported at 40 – 50% for the PNE, with approximately 60% voiding to completion with formal implantation [7], [8]. In the Department of Uro-neurology at the National Hospital for Neurology and Neurosurgery in London, the author's experience has been comparable, with two thirds of patients continuing to void without need for catheterization at a follow up of 5 years [9].

A retrospective study of 247 women referred to our Department, with urinary retention over a 4-year period showed that Fowler's syndrome is the commonest diagnosis although this only accounts for 58 %. In 32% no diagnosis could be made but in 2% there was a history of chronic opiate ingestion [10]. In 3% of the patients there appeared to be a relationship with chronic idiopathic pseudo-obstruction (CIPO), a rare disorder characterised by severe and chronic constipation without any demonstrable anatomical or mechanical lesion but thought to be due to a visceral neuropathy or myopathy (in infants or children) [11]. In men, there is an uncommon condition where painless urinary retention is present but it is not associated with constipation, and sexual function is preserved, but in whom extensive investigation fails to reveal any underlying abnormality. It has been speculated that this disorder is due to some abnormality of the intrinsic afferent innervation, possibly loss of the "myofibroblast" or interstitial cell, thought to be an integral part of the bladder stretch sensing mechanism [12] although no proof of that exists as yet. Presumably, this same condition makes up a proportion of the women with unexplained urinary retention.

Though the mechanism of action of SNM remains indeterminate, there are various theories based on careful observations. Two components have been identified (i) activation of efferent fibres to the urethral sphincter with negative feedback to the bladder (pro-continence reflex) and (ii) activation of sacral spinal afferents resulting in inhibitory reflex efferent activity to the bladder. Reflex pathways at the spinal cord and supra spinal levels are thought to be modulated to achieve these effects [13, 14]. The prolonged beneficial effects of the stimulator, after it is switched off, support this observation. In urinary retention, SNM is

postulated to interfere with the inhibitory afferent activity arising from the urinary sphincter and thus restoring the sensation of bladder filling and the ability to void [4].
At a central level, decreases in regional cerebral blood flow measured by PET scanning was demonstrated in the cingulate gyrus, orbitofrontal cortex, midbrain and adjacent midline thalamus in chronically implanted patients with urge incontinence [13]. SNM appears to restore activity associated with brainstem auto regulation and attenuation of cingulate activity [14, 15], critical to bladder function.

Historically, the management of urinary incontinence and retention, with SNM has classically been with successful pre-test stage using percutaneous nerve evaluation before permanent implantation. Success rates with this method have been reported at 40 – 50% [8, 16] for the PNE and approximately 60% voided to completion with formal implant and a further 14% reported significant improvement at 18 months our results show that a two third of patients continue to void without catheterization at a mean follow up of 5 years [17] and 78% at a mean follow-up of 10 years [18]. The relatively low success rate of the PNE and single stage implant has led to the development of the staged implant, whereby the permanent 'tined' lead is inserted and a prolonged external stimulation period is assessed [19], if successful then the permanent IPG is implanted. Early reported results with this technique show 80% success rates [19, 20]. A pilot prospective randomised controlled trial comparing the 1-stage to the 2-staged shows a higher success rate for the staged operation. [21]. Results from our department are in line with these reports.

Our Department has previously reported on the traditional implantation technique that was used first at our unit using a one-stage procedure [3], preceded by a PNE. This took place until August 2004, until the author took over the programme for the hospital. The PNE was a way of evaluating the success of the final implant without the cost and trauma of the final implant and surgery respectively. The testing wire would remain in place for up to 7 days and

if patients reported at least a 50% improvement in their symptoms and their bladder diary confirmed this, they would go on to have a permanent lead and stimulator.

The disadvantage of the PNE was the rather variable success rate of 24-75% [8, 19, 21-26]. Although these patients were labelled as non-responders, the real reason for a proportion was dislodgement of the testing wire from the original optimum position close to the sacral branches of the pelvic plexus or pudendal nerve. Sacral radiographs often demonstrated that the wire had moved or was out of the foramen completely.

In previous reports of this technique there were several drawbacks noted, as up to 40% of patients who responded to the temporary PNE, did not void on insertion of the permanent electrode. A possible reason for this is that the site of permanent electrode implantation may have differed from that of the “successful“ PNE electrode [27]. Conversely the PNE temporary electrode may not be optimally placed leading to failure and patients not proceeding to permanent implantation [23]. In 1997, Janknegt et al., suggested the implantation of the permanent standard electrode in patients with a strong suggestive history, in whom the PNE failed [23]. In 2000 the two-stage percutaneous minimally invasive technique came into its own with the emergence of the self-securing tined electrode [8, 23]. This has a longer “test phase” to evaluate the procedure. Early data suggested that this has a higher success rate than the one-stage procedure of up to 80% [20, 21] and this has been our adopted method since 2004.

Using a percutaneous technique, fluoroscopic guidance, and local or general anaesthesia a permanent electrode is implanted as the first stage, and connected to a temporary external battery. If the first stage fails, the electrode can be removed. It is the authors’ belief that the two-stage technique overcomes problems with PNE lead migration. It helps clinicians decide which patients should go on to have a permanent battery. The average battery life with

Interstim® and Interstim II® is around 8 and 5 years, respectively, but this varies with the settings used [28].

SNM is not without its complications and need for revision surgery. Therefore, it is important that patients are counselled regarding failure of the procedure (25%), the significant revision rate (30-50%), and the risk of box site pain, sciatica and nerve injury (very low). At 10 year follow-up at the National Hospital for Neurology and Neurosurgery, 78% of the patients who previously had significant impairment or inability to void, were able to void [10, 18]. Despite proven efficacy the procedure is not without a significant complication rate both at our and other centres using the same technique [3, 29]. This includes lead migration, pain at the Implantable Pulse Generator (IPG) site, leg pain, infection and failure of the device over time. This finding is confirmed by other studies which reported an incidence of 11% in lead migration [15] and 20% in lead breakages[27, 28]. Siegel et al. summarised their adverse events in the 219 patients who underwent implantation of the Interstim® IPG and the most common complaint was pain at the IPG site in 15.3% of patients [26]. The surgical revision rate was 33%. Everaert et al. reported a 34% device related pain rate, with a 23% surgical revision rate [30]. Grunewald et al. reported a revision rate of 30% over 4 years. Lead migration was noted as 5.4% and IPG site pain as 8.1% [31]. Recently authors have reported much higher long term revision rates with 54% [3], 48.3% [28] and 43.9% [32] excluding normal battery changes. Similar results were obtained in a worldwide SNM clinical study in voiding dysfunction, carried out by Van Kerrebrock (2007) and colleagues [33].

The most important determinant of success, in women with chronic urinary retention or other pelvic floor symptoms (including pelvic pain syndromes, sexual dysfunction and bowel dysfunction) is the careful selection of the patient. This includes a urological and gynaecological history, pelvic examination to rule out surgical correctable causes and urine assessment to rule out infection and haematuria. We advocate the use of frequency-volume charts, urodynamic evaluation where indicated, post void residuals if they are able to void at

all and quality of life questionnaires to qualify the degree of improvement before and after the procedure.

In the last decade there has been a plethora of innovative neuromodulation devices for treatment of lower urinary tract symptoms and pelvic floor dysfunction, though sacral neuromodulation remains the most widely used form of peripheral neuromodulation. In this workshop, a review of the role of pudendal neuromodulation, percutaneous tibial nerve stimulation and sacral dermal neuromodulation devices will also be considered. Their place in an algorithm of bladder and pelvic floor management will be devised.

**Take Home Message**

-Neurological basis of bladder and pelvic floor dysfunction is essential to all practitioners

-In neurological patients, practitioners should investigate all aspects of bladder and pelvic floor dysfunction

-Different therapeutic options should be made available and discussed with all patients

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## Notes

Record your notes from the workshop here