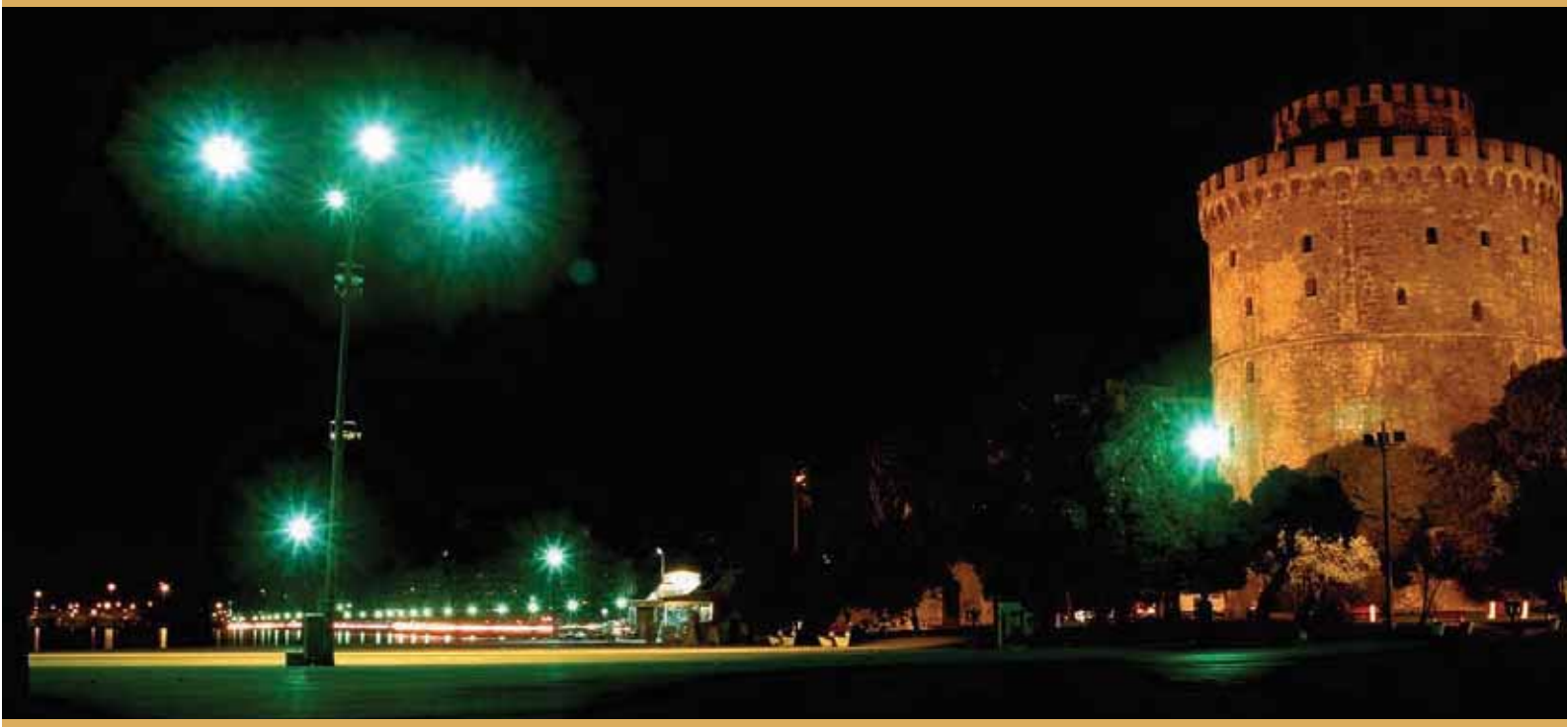
INTERNATIONAL CONTINENCE SOCIETY

EDUCATIONAL COURSE

MAY 11-12, 2007, THESSALONIKI, GREECE



PROGRAMME



www.icsoffice.org

ICS Educational Courses are heavily subsidised by the ICS and are aimed at those unable to attend our Annual Meetings due to lack of funding



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GREETINGS

Welcome to Thessaloniki!

In extending the scientific role of the International Continence Society all over the world, welcome to Thessaloniki!

For 35 years the ICS has held an internationally recognised multi-disciplinary annual meeting of the highest scientific quality and in recent years there have been pre-meeting workshops and ICS educational courses. Now the ICS Education Committee have created the stand alone ICS educational course outside of the annual meeting with the aims of discussion and exchanging experiences with colleagues of different countries.

These non-profit making courses are intended to appeal to younger doctors, nurses, physiotherapists and scientists who may find it difficult and too expensive to attend the annual ICS meeting but are keen to understand the important aspects of the ICS and to interact with other ICS members and listen and learn from relevant topics.

We have designed this course to bring together international speakers of different disciplines to share their experiences with all the delegates adding to the value and effectiveness of the event. There are many topics that are being covered by the course and we hope that you will receive an overview of incontinence issues.

Besides the course enjoy what Thessaloniki has to offer. Thessaloniki is divided into an old and new town. The old town is home to Byzantine churches and buildings and the port area is lined with numerous shops, cafés, and ouzeries. Join us on Friday evening at the welcome reception and mingle with colleagues, speakers and the exhibitors with a cocktail and food.

We hope that the Educational Course fulfils your expectations and in return all we ask is that you complete your evaluation form so that we learn from our experiences to make better Educational Courses in the future.



Linda Cardozo
Education Committee Chairperson



Stavros Charalambous
Course Coordinator



SPONSORS & EXHIBITORS

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UCB

ICS HISTORY AND COMMITTEES

Visit our website: www.icsoffice.org

The International Continence Society was founded in 1971 by Eric Glen under the name of the "Continent Club" and held its first annual meeting the same year in Exeter where 60 participants attended. We have more than 2000 members on our books from over 70 countries 1,800 delegates attended the 37th Annual Meeting of ICS in Christchurch, New Zealand at the end of 2006.

The ICS aims to provide education and advancement of sciences concerned with urinary tract and pelvic dysfunction including urology, neurourology, gynaecology and urodynamics. The Society also promotes research into the causes, remedies and relief of incontinence and provides access to the results of that research via website, email, post, telephone, paper publication, newsletters and presentations, annual congresses and courses.

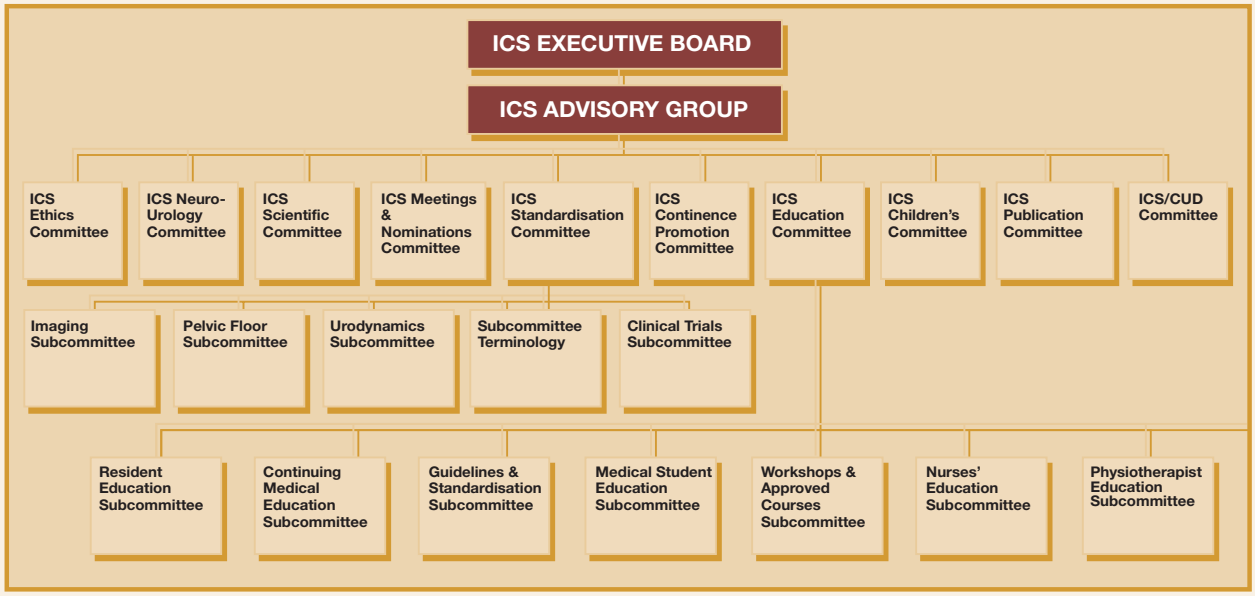
Our Annual Meeting is hosted by a different member each year, selected by members ballot four years in advance.

- 2005 Montreal, Canada
  Chair, **Jacques Corcos**
- 2006 Christchurch, New Zealand
  Chair, **Ted Arnold**
- 2007 Rotterdam, The Netherlands
  Chair, **Ruud Bosch**
- 2008 Cairo, Egypt
  Chair, **Sherif Mourad**

Our membership subscription remains at £50 per annum and includes:

- Six bi-monthly copies of the Journal Neurourology and Urodynamics
- 40% reduction in registration to our Annual Meeting
- The ICS members' book and certificate
- Two bi-annual ICS newsletters
- Access to other members worldwide
- Information and education via our website, office, courses and meetings.
- Free membership to the EU-ACME programme for continuing professional development

Today, the society employs three fulltime staff at its head office in Bristol, UK and has an Executive Board comprising four voluntary directors. There is also an Advisory Group and many committees dedicated to various tasks ensuring the Society's charitable objectives are maintained (see chart below).



ICS EDUCATION COMMITTEE

Walter Artibani
Carlos Levi D'Ancona
Michael Halaska
Hashim Hashim
John P.F.A. Heesakkers
Vikram Khullar
Helmut Madersbacher
Flavio Trigo Rocha
Linda Cardozo
Roger Roman Dmochowski
Menahem Neuman
Steven Peter Petrou
Peter K. Sand
Ajay Singla
Marijke C. Ph.Slieker ten Hove
Amanda Wells
Jean-Jacques Wyndaele

ICS THESSALONIKI EDUCATIONAL COURSE HONORARY COMMITTEE

Dimitris Kantzavelos
George Barbalia
Vasilios Rombis
Demitrios Radopoulos
Stavros Touloupides
Charalambos Theodorou



MEET THE SPEAKERS



Ray Addison



Apostolos Apostolides



Stavos Athanasiou



Anastasios Athanasopoulos



George Barbalias



Linda Cardozo



Stavros Charalambous



George Dimitriadis



Ioannidis Evangelos



Dimitris Kantzavelos



Kostas Konstantinidis



Eleni Kostantinidou

MEET THE SPEAKERS (CONT.)



Helmut Madersbacher



Iraklis Mitsogiannis



Menahem Neuman



Athanasios Papathanasiou



Anastasios Ptochos



Demitrios Radopoulos



Christina-Anastasia Rapidi



Dudley Robinson



Vasilios Rombis



Giorgos Salpingidis



Peter Sand



Ajay Singla



Frank Sofras



Theoharis Tantanasis



Charalambos Theodorou



Stavros Touloupides



John Tzafettas



Adrian Wagg



Jean-Jacques Wyndaele

GENERAL INFORMATION

Venue

Makedonia Palace Hotel
2 M. Alexandrou Ave
GR 54 640, Thessaloniki
Greece
Tel: +30 2310 897 197
Fax: +30 2310 897 211

The Makedonia Palace is a 5 star hotel located by the sea, within walking distance from Thessaloniki's business and shopping district.

Language

Lectures and presentations will be given in English.

CME Accreditation

EU-ACME – This Educational Course is accredited within the EU-ACME programme by the European Board of Urology Accreditation Committee with 10 credits. These credits are stated on your certificate of attendance. In order to receive your certificate of attendance please complete your evaluation form and hand in at the registration desk at the end of the course. If you are a member of the EU-ACME programme then please present your membership card for scanning at the EU-ACME desk to automatically receive your credits.

Registration and Hospitality Desk

The Registration and Information Desk will operate at the following times:

Friday May 11, 2007	09:00 – 18:00
Saturday, May 12, 2007	08:00 – 18:00

Welcome Reception

At the end of sessions on Friday, May 11, 2007



INTERNATIONAL CONTINENCE SOCIETY

EDUCATIONAL COURSE

PROGRAMME



PROGRAMME

FRIDAY, MAY 11, 2007

09:00 – 12:00	Registration
12:00	Buffet Lunch
13:00	Welcome & Introduction **Stavros Charalambous**
13:10	Welcome from: **Dimitris Kantzavelos**, President Hellenic Urological Association **Charalambos Theodorou**, President of UNUFU **Vasilios Rombis**, Head of the Urology Clinic, Thessaloniki
13:15	Aims and Objectives of this Educational Course **Linda Cardozo**
13:25	ICS Standardisation and Terminology Chair: **Vasilios Rombis** **Linda Cardozo**
14:00	Good Urodynamic Practice **Peter Sand**
14:50	Question and Answers
15:00	Coffee Break
15:30	ICI Algorithms Chair: **Linda Cardozo**
15:40	Women **Linda Cardozo**
15:55	Men **Helmut Madesbacher**
16:10	Elderly **Adrian Wagg**
16:25	Neurogenic **Jean-Jacques Wyndaele**
16:40	Questions and Answers
16:45	Conservative and Pharmacological Treatment of BPH Chair: **Frank Sofras**
16:55	LUTS, BPH, BPHO **Anastasios Athanasopoulos**
17:10	A-Reductase **Iraklis Mitsogiannis**
17:25	A-Blockers **Anastasios Ptochos**
17:40	TUNA **Giorgos Salpingidis**
17:55	Questions & Answers
18:00	Short presentation by **Stavros Charalambous** followed by Welcome Reception



SATURDAY, MAY 12, 2007

09:00 My Tape is Best for SUI
Chair: **Demitrios Radopoulos**

- 09:00 How and Why Tapes Work
  Dudley Robinson
- 09:15 TVT/TOT TVT Secure
  Menahem Neuman
- 09:30 T.O.T
  Ajay Singla
- 09:45 Remeex System
  Peter Sand
- 10:00 Questions & Answers

10:15 Coffee Break

10:45 Physiotherapy Session
Chair: **Stavros Touloupides**

- 10:45 Pelvic Floor Muscles Training
  Eleni Kostantinidou

11:15 Continence Care and Nursing
Ray Addison

11:45 How to Deal with Mixed Incontinence
Chair: **Ioannidis Evangelos**

- 11:45 **Apostolos Apostolides**

12:00 Buffet Lunch

13:00 Surgery for Prolapse and Incontinence
Chair: **John Tzafettas**

- 13:00 Surgical Correction of Stress Urinary Incontinence Associated with Pelvic Organ Prolapse
  Theoharis Tantanasis
- 13:15 Does Preoperative Urodynamics change the management of prolapse
  Georgios Dimitriadis
- 13:30 Mesh or not to mesh
  Stavros Athanasiou
- 13:45 "My mesh is the best"
  TVM Prolift
  Theoharis Tantanasis
- 14:00 Laser Vaginal Rejuvenation: Vaginoplasty – Labiaplasty
  Kostas Konstantinidis

14:15 Neurourology
Chair: **Ajay Singla**

- 14:15 Neurourology Update
  Jean-Jacques Wyndaele
- 14:30 Neurostimulation Neuromodulation
  Apostolos Apostolides

PROGRAMME (CONT.)

14:45 Intermittent Clean Catheterisation
Stavros Charalambous

15:00 Physical Medicine and Rehabilitation
Chair: **Athanasios Papathanasiou**

15:00 Neurogenic bladder in spinal cord lesions. Why long term follow up is needed
Christina-Anastasia Rapidi

15:30 Coffee Break

16:00 Urodynamics should be carried out prior to all surgery for SUI?
Chair: **Charalambos Theodorou**

For…
Georgios Dimitriadis

Against….
Stavros Athanasiou

16:30 Overactive Bladder Syndrome – Introduction
Chair: **George Barbalias**

My drug is the best for Overactive Bladder Syndrome

16:40 Tolterodine
Anastasios Athanasopoulos

16:50 Oxybutin
Peter Sand

17:00 Solifenacin
Dudley Robinson

17:10 Darifenacin
Adrian Wagg

17:20 Transdermal Oxybutin Patch
Linda Cardozo

17:30 Propiverine
Helmut Madersbacher

17:40 Placebo
Iraklis Mitsogiannis

17:50 Questions & Answers

18:00 Closing Words
Stavros Charalambous

INTERNATIONAL CONTINENCE SOCIETY

EDUCATIONAL COURSE

COURSE MATERIAL



LUTS, BPH, BPHO

Anastasios Athanasopoulos

Benign prostatic hyperplasia (BPH) is histologically a common condition among elderly men, occurring in up to 70% of the older than 60 years. Symptomatic BPH is thought to be mainly due to bladder outlet obstruction (BOO) and is frequently accompanied by lower urinary tract symptoms (LUTS). Urine storage symptoms are mainly attributed to OAB, which occurs in 40%-60% of patients with BOO. LUTS, especially storage/filling, such as daytime frequency, nocturia and urgency are bothersome, interfere with daily life activities and have a negative impact on quality of life (QoL).

Medical treatment of LUTS suggestive of BOO is nowadays the initial choice, and the a1-adrenoceptor antagonists remain the most widely used pharmacological agents directed towards relief of bladder outflow resistance. At present, four a1-adrenoreceptor antagonists have been introduced for BOO treatment globally; Terazosin, Doxazosin, Alfuzosin and Tamsulosin. Alpha blockade relieves bladder obstruction while it may control voiding function acting additionally on other sites such as bladder wall and spinal cord. These findings suggest that alpha blockade may exert a positive role in OAB. Contraction of the bladder involves stimulation of the muscarinic receptors on the detrusor muscle by acetylcholine. Anticholinergic (antimuscarinic) drugs are the treatment of choice for OAB. At present, there are in the market globally six widely accepted for their efficacy anticholinergic agents; Oxybutinin, Tolterodine, Trospium, Propiverine,Solifenacin and Darifenacin.

When OAB is associated with BOO, skepticism towards combined treatment is based on the theoretical danger of impairment of obstructive symptoms and possible acute urinary retention (AUR). However, anticholinergic at clinically recommended doses have little effect on voiding pressures and may act mainly during the bladder storage phase (suppressing detrusor overactivity), during which there is normally no parasympathetic outflow from the spinal cord . Anticholinergic drugs reduce bladder tone during storage, and increase cystometric bladder capacity and do not affect voiding pressures according to the existing trials. Moreover the data currently available do not support the view that antimuscarincs have a significant effect upon bladder contractility in patients with idiopathic detrusor overactivity, but suggest that the benefits seen in these patients are due to improvements in sensory variables.

Keeping in mind the prevalence and severity of symptoms due to OAB, it would be logical for one to expect that a combination of an a1-blocker with an anticholinergic would significantly alleviate LUTS and improve patient QoL .So far, there are in the international literature five trials, presentations in congresses and reviews and met-analyses that support the efficacy and safety of combination treatment of an a-blocker plus an anticholinergic for the treatment of BOO with concomitant OAB. The concerns for possible negative influence on residual urinary volume, and AUR proved non-realistic. Overall, the combination of these agents is safe and well tolerated. The co-administration of an a1-blocker with an anticholinergic agent seems to extend the ability for effective management of LUTS due to BPH and OAB. The combination of an a1-blocker with an anticholinergic for the treatment of BOO and concomitant OAB is promising. As LUTS are mainly a matter of QoL, any treatment that can improve this issue must be further evaluated in studies with long-term follow up and larger series of patients.



ABSTRACT 5α REDUCTASE INHIBITORS

Iraklis Mitsogiannis

Benign Prostate Hyperplasia (BPH) is a common problem in the ageing male population and its clinical manifestation as lower urinary tract symptoms (LUTS) may substantially affect patients' quality of life. In the past, surgery and watchful waiting were the only management options for LUTS suggestive of BPH, however there has been a great decline in surgery over the last 10 years and medical therapy is currently the most commonly used treatment for BPH.

5α reductase inhibitors (finasteride and dutasteride) act by blocking the enzyme 5α reductase, which is responsible for converting testosterone to dihydrotestosterone (DHT), a more potent androgen. DHT is the primary androgen involved in both normal and abnormal prostate growth. 5α reductase has two isoforms and finasteride competitively inhibits type 2 isoenzyme, thereby suppressing DHT by about 65-70% in the serum and by 85-90% in the prostate. Dutasteride is a dual 5α reductase inhibitor and suppresses serum DHT by about 90%.

Accumulated evidence has demonstrated a clear role for both 5α reductase inhibitors in the treatment of BPH. Finasteride reduces prostate volume by about 25-30% thereby reversing the progression of BPH. It also improves symptom scores and urinary flow rates and significantly reduces the risk of acute urinary retention (AUR) and the need for surgical treatment of BPH. Patients with large (>40 ml) prostate glands, who also are at increased risk of developing AUR, are most likely to benefit from finasteride therapy. In contrast to the α-blockers which act rapidly, the efficacy of finasteride reaches a maximum after 6 months but seems to be maintained in the long term. Similar results have been obtained with dutasteride.

5α reductase inhibitors have been shown to halve serum PSA levels and therefore the nominal PSA values in men on therapy should be doubled for the usefulness of PSA as a tumour marker to be preserved.

Side effects of 5α reductase inhibitors are mainly related to sexual function and include decreased libido, decreased ejaculate and erectile dysfunction. Gynaecomastia is also more frequent than placebo. The pathophysiology of sexual dysfunction is not entirely clear, but might be related to the reduction of DHT. Side effects tend to improve over time.

The combination of 5α reductase inhibitors with α_1 adrenoceptor antagonists seems logical, given the multifactorial causes of BPH; nevertheless no clinical benefit of the combination was initially proved in four direct comparative studies, probably because of the small-size prostate glands included and the short duration of the trials. More recently, the MTOPS study showed that, at a mean follow-up of 4.5 years, the combination therapy is better than either drug alone in preventing disease progression, relieving symptomatology, improving flow rates and decreasing the risk of AUR.

Finasteride has been found effective in controlling BPH-related bleeding and also in reducing perioperative bleeding at TURP, when given as a pre-treatment. The latter however still remains to be confirmed.

In conclusion, 5α reductase inhibitors are effective and safe drugs for the treatment of BPH, as they can alter the natural history of the disease and provide long-term symptom control.

α-BLOCKERS

Anastasios Ptochos

α-blockers were first introduced into clinical practice for the treatment of LUTS secondary to BPH in 1978. The initial non-selective α-blockers were replaced over the last 10 years by a variety of α_1 -selective α-blockers (terazosin, doxazosin, alfuzosin, tamsulosin etc.). They reduce the dynamic element of prostatic obstruction by antagonizing the adrenergic receptors responsible for smooth muscle tone within the prostate and bladder neck. Newer α-blockers have the advantage of being long-acting and are taken orally once daily.

Symptoms can improve within 48 hours, although an I-PSS assessment requires at least one month of therapy. In general, overall symptoms improve by 30-40% and flow rates by 16-25%, compared with placebo. Long-term efficacy and the effect on natural history of BPH are still unclear. Treatment should be discontinued, if a patient does not experience an improvement in symptoms after an 8-week trial. One-third of men will not experience significant symptom reduction.

The most common side effects with α-blockers therapy are headaches, dizziness, postural hypotension, asthenia, drowsiness, nasal congestion and ejaculatory disorders. In general, the rate of side effects in studies looking at tamsulosin and alfuzosin are equivalent to placebo.

Patients may choose to stop taking medication for several reasons, mainly because of the occurrence of adverse side effects and lack of efficacy. In general, the symptom status of men did not predict whether they are likely to stop therapy. Studies have shown that drop-outs occurred at the same rate, irrespective of whether symptoms were moderate or severe.

Early trials comparing α-blockers to placebo showed an increased likelihood of a successful trial, without catheter, following an episode of acute urinary retention. As a result, many urologists have adopted this practice. The effect seems to be independent of the type of α-blocker studied. However, most men being on an α-blocker without catheter after an acute episode of urinary retention, experience re-retention within the first two months.

The combination of a 5α-reductase inhibitor (finasteride, dutasteride) with an α-blocker in the treatment of LUTS due to BPH was examined in many clinical trials. Almost all have shown that the combination was beneficial. This combination therapy was superior to either drug alone in reducing I-PSS, in increasing median maximal flow rates and in reducing the likelihood of acute urinary retention and surgery. It is reasonable that the 5α-reductase inhibitor needs time to reveal its beneficial therapeutic capacity. The cost of combination therapy remains a problem.

Additionally, a combination treatment of α-blockers and antibiotics seems to have a higher curative rate than antibiotics alone in inflammatory chronic pelvic pain syndrome (CPPS) type IIIA+B of NIDDK/NIH classification. This treatment option is favored by many urologists.

Broadly speaking, α-blocker therapy can result in a rapid improvement in symptoms of clinical BPH and all α_1-selective α-blockers have a similar efficacy. Although the side-effect profiles for some drugs are reported to be more favorable, supportive data are weak. However, pharmaceutical industry focuses on this issue in an effort to increase the efficacy and reduce the side effects of existing products (XL or OD formulation of alfuzosin, OCAS formulation of tamsulosin etc.) or to create novel ones (e.g. silodosin). The results remain to be seen in clinical practice.



TUNA®

Giorgos Salpiggides

Benign Prostatic Hyperplasia (BPH) is the most common benign neoplasm affecting aging males. The incidence of histologically identification of BPH for 60 year old males is more than 50% and riches 90% at age 85 years. There is not any doubt that transurethral resection of the prostate (TURP) is the "gold standard" for BPH treatment. But new medications and minimally invasive modalities offer a greater range of challenging choices to the urologist and patient. It is well known that only 20-30% of BPH patients have the certain indication for surgery. Thus the vast majority of BPH men are open to an other alternative treatment. The points that urologist have to considerate in selecting the appropriate treatment are: the age of man, the his medical history, the quality of live, the sexual activity, the financials – insurance and his preference for treatment.

For men who are unwilling to remain on medication, in whom medical therapy has failed or are unsuitable candidates for surgery several minimally invasive therapies have been developed in the last 12 years among these Transurethral Needle Ablation (TUNAR) is an out patient procedure. TUNA® uses low radiofrequency energy (300-3,000 MHz) to heat prostate tissue. With TUNA treatment the inner region of the prostate is selectively ablated with temperatures approaching 90-100 oC while the urethra is preserved. The TUNA® catheter consists of a 18 F plastic specialized cystoscope connected to a radiofrequency generator. Two flexible needles, which can be deployed at an acute angle of 40o to each other and at 90o to the catheter emerge at his tip. The low radiofrequency energy and finally the heat produces necrotic lesions inside the prostate adenoma.

The TUNA® procedure is performed under topical urethral anesthesia with Xylocaine® gel and pethidine administration, with the patient in cystoscopy position. The needles are deployed at the 8 and 10 positions in the right lobe and at 2 and 4 positions in the left lobe. The depth of the needle insertion is determined by measurement of the transverse section of the prostate using transrectal ultrasound. The initial puncture is made 1cm from the bladder neck and last 1 cm proximal to the verumontanum. The number of pair lesions is one per 15g of prostate tissue.

TUNA® is a well tolerated and effective modality of treatment for symptomatic BPH. This technique although does not reach the level of the efficacy and long lasting success as TURP seems to be superior to TURP in terms of morbidity, anaesthesia, blood transfusion, catheter and hospitalization.

HOW AND WHY TAPES WORK

Dudley Robinson

The bladder neck and proximal urethra are normally situated in an intra-abdominal position above the pelvic floor and are supported by the pubourethral ligaments. Damage to either the pelvic floor musculature (levator ani) or pubourethral ligaments may result in descent of the proximal urethra such that it is no longer an intra-abdominal organ and this results in leakage of urine during stress.

Continence is maintained by the presence of the bladder neck above the pelvic floor and thus cough pressure is equally transmitted to the proximal urethra maintaining closure pressure. However, when the support is defective cough pressure results in the descent of the bladder neck through the urogenital diaphragm resulting in the loss of urethral closure pressure.[1]

The traditional approach to continence surgery has consequently to re-position the bladder neck above the urogenital diaphragm resulting in the widespread use of the retropubic suspension procedures such as the Burch colposuspension and Marshall-Marchetti-Krantz procedures.

More recently the 'mid-urethral theory' or 'integral theory' has been described by Petros and Ulmsten[2]. This concept is based on earlier studies suggesting that the distal and mid-urethra play an important role in the continence mechanism[3] and that the maximal urethral closure pressure is at the mid urethral point[4] (Westbury et al, 1982). This theory proposes that damage to the pubourethral ligaments supporting the urethra, impaired support of the anterior vaginal wall to the mid urethra, and weakened function of part of the pubococcygeal muscles which insert adjacent to the urethra are responsible for causing stress incontinence.

This more recent theory regarding the pathogenesis of stress urinary incontinence has led to the development of both the retropubic and trans-obturator mid-urethral tapes and these have now largely replaced the use of retropubic suspension procedures in the surgical management of women with stress urinary incontinence. The purpose of this lecture is to review the traditional approach to continence surgery in addition to examining the concept of the integral theory of incontinence and its clinical application with regard to the mid urethra.

References

1 Enhorning GE. A concept of urinary incontinence. Urol Int 1976; 31: 3-5.

2 Petros P, Ulmsten U. An integral theory of female urinary incontinence. Experimental and clinical considerations. Acta Obstet Gynaecol Scand 1990; 153 (Suppl): 7-31.

3 Ingelman-Sundberg A. Urinary incontinence in women, excluding fistulas. Acta Obstet Gynaecol Scand 1953; 31: 266-295.

4 Westbury M, Asmussen M, Ulmsten U. Location of maximal intraurethral pressure related to urogenital diaphragm in the female subject as studied by simultaneous urethra-cystometry and voiding urethrocystography. Am J Obstet Gynaecol 1982; 144: 408-412.



TVT, TVT-OBTURATOR AND TVT SECUR: NOVEL ANTI-INCONTINENCE PROCEDURES

Menahem Neuman

The Tension-free Vaginal Tape (TVT) procedure is a well-established surgical procedure for the treatment of female stress urinary incontinence. The operation, described by Ulmsten in 1996, which is based on a mid-urethral Prolene tape support, is accepted worldwide as an easy-to-learn, effective and safe surgical technique. Common complications in previously performed surgeries for the treatment of stress urinary incontinence, such as intra-operative blood loss, pelvic and abdominal organ injury, post-operative de novo detrusor instability, dyspareunia and urethral erosion, are rare in the TVT era. Prospective randomized multi-center studies, comparing TVT to the former gold standard Burch colposuspension, demonstrated similar therapeutic impact for both. However, TVT was associated with a higher intra-operative complication rate while colposuspension was associated with a higher post-operative complication rate and a longer recovery period. Some typical TVT operative complications of concern to the operating surgeons include: bladder penetration, urinary outlet obstruction, potential bowel penetration, intra-operative bleeding and post-operative infections. Against this background, and knowing that surgical procedures are more likely to cure stress urinary incontinence rather than non-surgical procedures, de Leval adopted the TVT-Obturator procedure to avoid the aforementioned complications. His novel type of surgery enables mid urethral support for the treatment of female urinary stress incontinence, while not encroaching on the bladder, the femoral blood vessels, or the bowel. This is achieved by exploiting the Obturator fossa as a route for the Prolene tape, replacing the retropubic space. The reported data regarding efficacy of the TVT-Obturator in terms of cure as well as intra-operative and early post-operative complication rates is encouraging Bladder penetration, previously reported in relation to “outside-in” trans-Obturator designed mid urethral tape procedures, has not been described in association with an “inside-out” trans-Obturator procedure. Though bladder perforation could not be ruled out as diagnostic cystoscopy is not routinely performed, the absence of any indicative signs provides additional support to the idea that the TVT-Obturator does not cause bladder penetration. Therapeutic failure, intra-operative bleeding, post-operative infection and voiding difficulties also seem to occur less with the TVT-Obturator than previously reported for TVT. However, the TVT-Obturator is not free of operative complications: thigh-pain is reported to interfere with patient satisfaction, operative infections and post-operative bladder outlet obstruction still occurs as well as occasional operative hemorrhage. The TVT-SECUR was designed to minimize the operative procedure as much as possible in order to reduce those undesired complications. This new device is composed of an 8 cm long laser cut polypropylene mesh and is introduced to the internal Obturator muscle (Hammock position) by a metallic inserter, while no exit skin cuts are needed. This approach imitates the sub-mid-urethral support provided with the TVT-Obturator, yet imitating the TVT is possible as well, by introducing the TVT-SECUR arms retropubically rather than to the Obturator area. The “U” position approach necessitates urethral catheterization as well as diagnostic cystoscopy for recognition of possible bladder penetration.

In summary, the TVT-SECUR procedure appears to be potentially easier to perform and relatively trouble-free for both surgeons and patients and might not require urethral catheterization or diagnostic cystoscopy during surgery. Paying respect to procedural specific surgical steps might shorten the TVT-SECUR learning curve. The novel TVT-SECUR’s actual place among TVT and TVT-related procedures can only be determined with randomized prospective longitudinal comparisons.

TRANS-OBTURATOR TAPE – A NEW MINIMALLY INVASIVE PROCEDURE FOR SUI IN WOMEN

Ajay K Singla

Introduction:
There has been an evolution in the surgical management of stress urinary incontinence (SUI) in women. Various new minimally invasive procedures for SUI have been introduced. These have replaced open bladder suspension procedures. These procedures can be categorized into two groups: Non-adjustable and Adjustable.

Minimally Invasive Procedures

- Non-adjustable
  - Trans Obturator Tape (T.O.T)
  - Percutaneous Vaginal Tape (PVT)
  - Tension free vaginal Tape (TVT)
  - Pre-Pubic Vaginal Tape
- Adjustable
  - ACT
  - Remeex

TOT is becoming increasingly more popular among these tension free tapes. The main difference being sub-urethral placement of the tape below the pelvic diagram without the need for perforation of endopelvic fascia.

Technique:

- Exaggerated lithotomy position
- Mid-urethral incision
- Lateral dissection to the level of ischio-pubic ramus
- No perforation of endopelvic fascia
- Feel the inner aspect of ischiopubic ramus with your index finger
- Put an index finger in the vaginal incision and a thumb on the inner surface of the thigh, lateral to the labia majora
- Locate the ischiopubic ramus
- Press the two fingers together (Pinch Maneuver)
- Feel the path around the ischio-pubic ramus
- Skin Puncture
- Passing of Introducer at the level of clitoris 1 cm below the adductor longus tendon
- Thread the end of the tape into the eye of the introducer
- Cystoscopy?
- Sling Adjustment. To avoid over tension of the sling, there should be visible space between the urethra and sling/tape. The space can be insured by using a clamp placed between the urethra and tape.
- Vaginal incision is closed interruptedly with 2-0 polyglactin 910 (Vicryl, Ethicon, Inc, Somerville, NJ) suture.
- Skin adhesive (derma bond) is applied to the puncture sites

Results:

One Large European series by Dr. Delorme A total of 567 patients underwent TOT with follow up of 3months to 5 years. A total of 3 injuries (2 bladder, 1 urethra because the finger was outside the vaginal incision) were encountered. Only 5 patients experienced obturator pain during one week to one month after surgery. A total of 89% patients were cured, 11% improved or not cured, and 3% developed de novo urgency. Patients with no cure either had too loose tape or intrinsic sphincter deficiency.

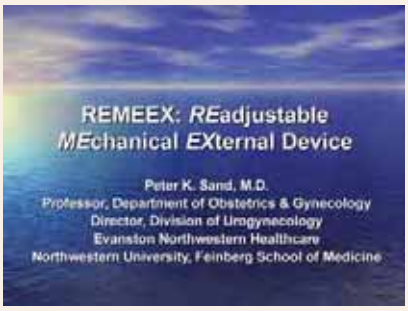
Another European Multicentric Prospective Study by R de Tayrac, MD
A total of 368 patients with SUI underwent prospective open observational study with TOT outside-in (Delorme's technique) from the period of July 2004 to February 2006. The mean age in years was 57.6 (range 30-85). A total of 153 (41.6%) patients had pure SUI and 137 (37.2%) had mixed incontinence. One-year cure rate was 91.4%, Intra-operative complications were 6.8%, Post-operative voiding difficulties being 4.6%.

Conclusion:

T.O.T., a novel approach for SUI in women is safe and effective procedure. Five years data has shown promising results with a low morbidity. It has a low learning curve. The long term results are needed to establish the durability of this procedure.

REMEEX SYSTEM

Peter Sand



















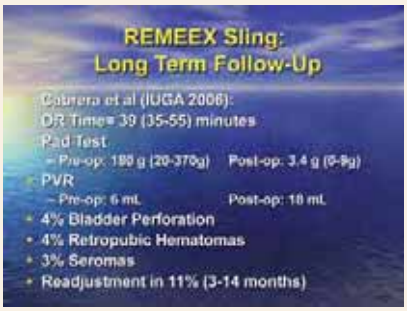


REMEEX SYSTEM (CONT.)



















PELVIC FLOOR MUSCLE- TRAINING

Eleni Kostantinidou

The role of the pelvic floor is integral in the anatomical support of the pelvic organs, preservation of continence and also normal sexual function. Physiotherapy and especially pelvic floor muscle training (PFMT) are recommended by several consensus statements as first line treatment for women with stress urinary incontinence. It is also used in the treatment of women with mixed incontinence, and, less commonly, urge incontinence. Many studies have already demonstrated the effectiveness of PFM exercises, with subjective cure/improvement rates varying in the range of 56-75%.

Kegel was the first to describe the use of pelvic floor muscle training as a treatment for female stress urinary incontinence. The PFMs are skeletal muscles consisting by 33% of fast-twitch fibres and 67% slow-twitch fibres. The normal function of these muscles is to squeeze around the vaginal, urethral and anal openings and to lift inwards in a cranial direction.

The rationale for PFM training is based on 2 concepts: (1) improvement of urethral resistance and pelvic visceral support, including urethral support, by increasing the strength of the voluntary PFMs and (2) voluntary contraction of the PFMs before increase in intra-abdominal pressure. The improvement of pelvic floor support will prevent descent of the bladder neck and urethra and close the urethra during abrupt increase in intra-abdominal pressure by PFM contraction. An increase in intra-abdominal pressure results in unconscious activation of the PFMs. Patients can learn to contract these muscles before activities that increase intra-abdominal pressure (e.g.cough). However, it is impossible for the patients to contract their PFMs for a long time.

The pelvic floor comprises several muscles including the anal sphincter, the ischiocavernosus, the bulbospongiosus, the transverse perineal muscle, the striated urogenital sphincter and the levator ani (puborectalis, pubococcygeus and iliococcygeus muscles). The contraction of these muscles is not visible but PFMs are possibly contracted synergistically with the abdominal, hip adductor and gluteal muscles. Activation of the local stabilising muscles of the lumbo-pelvic region, such as the transversus abdominis, psoas and lumbar multifidus, facilitates activation of the PFMs.

The first step of PFMT includes vaginal examination that will determine correct muscle action of the PFMs. The PERFECT Scheme was developed to assess PFM contractility and enable the planning of patient-specific muscle training regimens. Moreover the digital assessment contributes to achieve sensory awareness of the pelvic floor muscles. The training includes functional pelvic floor exercises in order to increase awareness, muscular strength, endurance and to restore coordination. Training programs differ in type of exercise, frequency, duration and intensity. No program can be successful in a patient who is unable to identify the PFM properly. Adjuncts, such as biofeedback or electrical stimulation, are also commonly used with PFMT. Biofeedback measures the response from a single PFM contraction and helps patients to control and enhance the strength of the contractions. Electrical stimulation can be used for partial paralysed muscles or for stimulation of muscle activity when the patients are not able to contract.

CONTINENCE CARE AND NURSING

Ray Addison

My presentation will consider a broad perspective of continence care nursing and the development and role of the specialist nurse. The third International Consultation on incontinence in 2005 highlighted organisations in 31 countries with three core roles – educate professionals, educate public and promote continence. Nursing is in the front line to facilitate this and reflects the worldwide movement in continence care.

Nursing encompasses the care of patients with urinary incontinence, voiding problems, urinary infection, night time bladder problems, faecal incontinence and constipation. Nurses at all levels of practice provided aspects of this care from the unqualified healthcare assistant to Consultants and Professors of Nursing. Nursing offers versatility with a wide collection of competencies at many levels from essential to advanced. This is delivered in many care settings including the community, hospital and private sectors with key links to pressure ulcer, infection and falls prevention.

Established specialist nursing roles in continence care are found in Australia, Canada, New Zealand, Ireland, Singapore and the UK. Specialist roles in continence care are developing in Taiwan, Malaysia, Hong Kong, Japan, Brazil, Netherlands and Scandinavia. They are in an embryonic phase in Greece, Spain and Italy. A higher nursing status can be found in Australia and the UK where nurse consultants have been established with academic supportive frameworks. The specialist nursing role has four aspects : clinical caseload, education and training at all levels both formal and informal, Audit and research (leading on conservative treatment), and managing a service and resources. Key nursing developments and milestones include being multi skilled, Consultant status, the nurse led clinic, prescribing and ability to diagnose.

Nursing has adopted a culture of integration providing a seamless care pathway which can be simple to complex. Multidisciplinary team working is valued by nursing with the nurse, therapist and Doctor at the core. Nursing is a vital part of care package being able to cross boundaries and specialities.

Accepting the nurse to assess and triage patients is key to the success of nursing. Assessment includes symptom reviews using questionnaires, screening, risk identification, use of charts baseline observations and examination. Where indicated, nurses order & undertake diagnostics, make a diagnosis, refer and consult, prescribe, treat, follow up/review and discharge. Common interventions initiated and delivered by nurses in continence care include life style advice, bladder retraining, medication, pelvic rehabilitation, biofeedback, fluid advice, catheter care (including intermittent) and neuromuscular stimulation

Barriers to the development of the nursing role in continence care in certain countries can be financial, professional, educational and political. Clinical challenges facing nurses in certain countries include the development of multi resistant infection, access to diagnostics and equipment, positive attitude shift towards continence care and gaining competence within this specialised field. A UK model will be presented. Worldwide challenges facing continence care nursing will be highlighted. ICS membership benefits for nurses will be presented.



HOW TO DEAL WITH MIXED INCONTINENCE

Apostolos Apostolides

Mixed urinary incontinence (MUI) is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing. It is the second more prevalent type of incontinence, representing 30-45% of all incontinent women at various age groups, although differences exist between questionnaire-based surveys and physician-operated urodynamic studies. A recent epidemiological study in the USA general population showed a low prevalence of 2.7%. The prevalence increases with age. Severe, bothersome incontinence was found to be more common in patients with MUI compared to those with stress or urge only incontinence. Increased Body Mass Index was associated with a higher risk for MUI than for stress or urge only incontinence in all ages above 25 years.

Diagnosis of MUI is a symptomatic one, and the role of urodynamics in evaluating patients with mixed incontinence remains controversial. Accurate history and clinical examination supplemented by a bladder diary are the proposed diagnostic tools.

The mechanisms involved in MUI have yet to be determined. A recent study suggested a pathogenic mechanism associated with a neuromuscular disorder of the urethra in both stress and urge incontinence. This included an overactive opening mechanism with a urethral pressure fall instead of a pressure increase on provocation during the filling phase of the bladder, and during bladder emptying a more efficient opening of the bladder outlet than in normal women. In addition, animal experiments have shown that activation of urethral afferents by urethral perfusion can modulate the micturition reflex. Thus in the presence of stress incontinence leakage of small amounts of urine into the proximal urethra could activate the micturition reflex or deteriorate existing detrusor overactivity.

Such observations became the rationale for the surgical treatment of MUI, as correction of stress incontinence could also result in cure of MUI. Retrospective studies of TVT surgery, sling procedures and Burch colposuspension for MUI reported variable cure rates of the urge component (between 69% and 93%) after successful operation for the stress component. High pressure detrusor overactivity was found to be associated with poorer outcomes.

However, surgical management has been proposed as second line treatment following application of conservative therapies, such as bladder training, pelvic floor exercise, biofeedback, and electrical stimulation. These however are known to offer moderate success in women with mixed incontinence. Pharmacological treatment of MUI also gave encouraging results, but there are only few randomized, placebo-controlled trials. In a recent trial, solifenacin restored continence in 49% of patients with MUI as opposed to 33% of placebo effect. Combination studies of pharmacological treatment of both the stress and urge components of MUI are missing.

SURGICAL CORRECTION OF STRESS URINARY INCONTINENCE ASSOCIATED WITH PELVIC ORGAN PROLAPSE

Theoharis Tantanasis

Woman with severe genitourinary prolapse may also have clinical stress incontinence, but, more often, they are subjectively continent because of urethral kinking or compression.
According to the literature 36% to 80% of women with advanced vaginal prolapse are at risk for development of stress incontincence after reconstructive surgery.
Considerable controversy exists regarding the wisdom of performing a concomitant anti-incontinence procedure in women with severe prolapse in whom stress incontinces is not demonstrated preoperatively. Some surgeons routinely perform an anti-incontinence procedure during prolapse repair. On the contrary, others believe that this approach exposes many women to unnecessary morbidity due to overcorrection and development of voiding dysfunction.
A plethora of surgical procedures have been devised for treatment of overt stress incontinence but no single technique has met with widespread acceptance.
Several previously published studies have indicated various incontinence rates after different prophylactic anti-incontinence procedures but data on long term follow up in these series are sparse. The traditional management of overt stress incontinence is based on urethral mobility, intrinsic sphincter function and surgeon experience with the procedures.
Preoperative urodynamic evaluation with and without prolapse reduction is essential for making the correct diagnosis of masked stress incontinence in women with urogenital prolapse. The decision to perform a concomitant prophylactic anti- incontinence procedure should be tailored to individual urodynamic findings.

DOES PREOPERATIVE URODYNAMICS CHANGE THE MANAGEMENT OF PROLAPSE?

Georgios Dimitriadis

It is not at all uncommon for women with severe prolapse to have bladder outlet obstruction, detrusor instability, and latent stress incontinence that is demonstrable only with reduction of the prolapse. A 3-day voiding diary, including the time, amount voided and time and amount of fluid consumed, indicates functional bladder capacity.

Uroflow examination determines the average and maximum flow rates, and the shape of the curve can help to identify Valsalva induced voiding (shown by multiple peaks and troughs).

Multichannel urodynamics or videourodynamics with prolapse reduced can be important when incontinence procedures or prolapse surgery has failed. Videourodynamic assessment should be used selectively. Otherwise, simple multichannel urodynamics should suffice for most patients. However, videourodynamics may provide some physiological and anatomical information that may be useful in indicated patients with multiple prior operations for prolapse or incontinence. Whether such studies are necessary to evaluate the ability of prolapse to produce bladder outlet obstruction during urodynamic assessment is really physician dependent. However, it is emphasized that urodynamic assessment in patients with prolapse reduction is useful in assessing potential occult SI and DO. Fluoroscopy during videourodynamics can augment the surgeon assessment with regard to prolapse. To determine vault prolapse prior to placement of the urodynamic bladder and rectal catheters a ring forceps with sponge can be dipped into contrast medium and the vault can be outlined with dye and removed. While the patient is performing the Valsalva maneuver a lateral view of the pelvis can determine vault prolapse with the patient sitting or standing. If an enterocele is in question after videourodynamics is completed, a defecography study can be performed with the patient sitting or standing. Examinations with the patient standing are indicated when the patient history and symptoms imply prolapse that was not documented during physical examination. The standing position may hopefully increase the effects of gravity on prolapse and enhance prolapse recognition.

Urethral pressure profile and Valsalva leak point pressure measurements are controversial. Results differ significantly depending on the type of measuring device and patient position, while urethral pressure profiles have been poorly reproducible. Moreover, urethral pressure profile measurements do not consistently differentiate between continent and incontinent women and do not always correlate with the severity of incontinence. It has recently been suggested that “urethral pressure profilometry is not a useful diagnostic test for stress urinary incontinence in women”.

Newer techniques may improve the clinical value of these measurements. Ambulatory recording of urethral and bladder pressure, which proved helpful in patients with mixed urge and stress incontinence, have recently been proposed. Computer assisted virtual profilometry, in which the measurement catheter is stopped at intervals during withdrawal while the patient coughs may also prove useful in the near future. Selection of concomitant stress incontinence procedure is an area of great debate. Thus far it appears that, as with non-prolapse indications, sling operations fair best, with good continence rates and relatively low de-novo detrusor instability rates.

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"MY MESH IS THE BEST" TVM PROLIFT

Theoharis Tantanasis

Vaginal reconstructive surgery for pelvic organ prolapse is one of the most challenging aspects of surgical gynecology. There are several site specific defects in support which have to be carefully addressed to ensure an optimal outcome.

Particularly, anterior vaginal prolapse may re-occur after standard anterior colporrhaphy in up to 40% of patients. In a recent study conducted in the 2nd Dept. OBGYN of the Aristotle University, Thessaloniki/Greece, 22 patients underwent pelvic reconstructive surgery including anterior – posterior colporrhaphy with or without vaginal hysterectomy. Mean follow up was up to 22 months. Concomitant to the anterior colporrhaphy sutures we performed placement of TVT or TVT-O not underneath the midurethra but underneath the bladder base as an additional reinforcement.

To date the anatomical correction of the anterior vaginal compartment is satisfactory. Further follow up and larger study sample are needed in order to draw definite conclusions.

Since beginning of 2006 we started using the Prolift Kit instead, to date we have evidence available regarding 38 patients. There were two mesh erosions, one case of inner thigh pain.

Summing up, pelvic floor reconstruction using polypropylene implants is a treatment option especially for the surgical correction of the recurrent vaginal prolapse.

The prolift mesh consists of a specially tailored "H" shaped polypropylene mesh with arms. The arms are passed laterally through a special technique, thus providing support to the organs, i.e. the bladder, laying upon the central part of the mesh.

While evidence is being accumulated, there is lack of sufficient data from prospective randomized trials and lack of standardized techniques to draw any definite conclusions.

Recently published data are encouraging; they indicate that patient satisfaction is high and complications rates are relatively low.

Yet, more data concerning the aforementioned issues are needed. This will be the aim of further clinical studies to analyse the long term results and to provide useful clinical information concerning the applicability of polypropylene implants and their definite role in treating pelvic floor insufficiency.

LASER VAGINAL REJUVENATION (LVR©):A NEW APPROACH TO VAGINAL SURGERY: THE GREEK EXPERIENCE OF THE FIRST 12 PATIENTS

E.C.Bellonias MD,S. Chandakas MD MBA PhD,K.Kostantinidis

Sexual wellbeing is important to a happy, well balanced life. In addition to physical pleasure, sex strengthens emotional bonds between partners, and adds excitement to life. Vaginal relaxation and affects greatly the sexual life of the woman. In the last two months we performed 12 cases of LVR© and DLV© (Designer Laser Vaginoplasty). Both LVR© and DLV© were combined with Aesthetic procedures in three of the cases. The women's age ranged between 32 and 51. The number of labors ranged between 1 and 4.The major complain was looseness of the vagina and the pelvic floor combined with very little sensation. All procedures were performed under general anesthetic on a outpatient basis, except the two combined cases of abdominoplasty where the patients stay in hospital overnight. The average operating time for the LVR© was 100 min. The overall complication rate 8,3% (1 case) and the rate of satisfaction 91,66%.Average blood loss for LVR© and DLV© less than 5 ml.

In conclusion we believe that there is strong evidence that LVR© is a quick and effective way to restore vaginal muscle tone, strength and control. On the other hand DLV© is the group of cosmetic laser procedures which repairs, enhances and beautifies the genitalia

NEUROUROLOGY UPDATE

Jean-Jacques Wyndaele

Neurophysiology

The innervation of the lower urinary tract combines activity of autonomic and somatic nerves. Its central control makes a "voluntary" working of a mostly "autonomic" system possible, adapted to daily living.. ***Overview of actual knowledge of the normal neurology of the lower urinary tract LUT***

The innervation of the lower urinary tract is manyfold.
Sympathetic, parasympathetic and somatic nerves are involved.
Neuropharmacological studies and studies on receptors and transmittors have given an incomplete but easy to use scheme for daily practice.
The innervation of the LUT counts sensory and motor nerves.
The sensory system is related mainly to free nerve endings in the bladder wall and to receptors which are linked to at least two types of nerve fibres: Adelta and several types of C, some of which are becoming active only when there is neuropathy.
Elbadawi and others have shown that a special distribution exists of neuroreceptors in the LUT.

receptor
location
neurotransmittor
function
function
alpha
Bladder neck
noradrenaline
Closing bladder neck
continence
beta
Bladder wall
noradrenaline
Relaxing bladder
Bladder filling low pressure
muscarinic
Bladder wall
acetylcholine
Contraction bladder
voiding

The higher neurologic system has several pathways in the spinal cord, the brainstem and the brain. There is increasing interest in the nonadrenergic-non cholinergic system and its transmitters as Substance P, CGRP, VIP, about the function of NO and about other receptor types as X2P or vanilloid receptors. A neurologic lesion as in the spinal cord can cause great disturbance in the LUT functions. The neurologic lesion can occur abrupt as with trauma or can develop more slowely as in medical causes

Diagnosis of neurologic LUt and acute treatment

The clinical history is an essential part in patients with neurologic LUT disease. In most patients this history is obvious : an accident has happened and lesions have been noted.
In the acute spinal patient the period of spinal shock has to dealt with with great attention: a proper bladder drainage has to installed and this will most probably be indwelling to cover the period of cardiovascular instability, changes in diuresis and bladder areflexia. Intermittent catheterization is best started as soon as possible. If longer indwelling catheter is needed a suprapubic tube would lower the risk of urthral problems especially in men. Two main goals during this period: AVOID OVERDISTENTION AND AVOID INFECTION OF THE URINARY TRACT.
It is without saying that a complete history taking is needed.
The clinical examination has a general and a specific part. The clinical neurologic examination has also an important role for the early approach of the urinary system.
The specific clinical neurological examinationrelated to the pelvic region is mandatory. Urodynamic testing is mandatory and should be done whenever available with urovideo. The evaluation of upper tract should be part of the management. Activity of the bladder neck has to be evaluated. Sensation can be present or absent and this information can be important for the treatment (Spinal Cord 2004; 42: 110-6). Clinical observation during hospitalization is important: incontinence, smelly urine, evacuation of



calculi, fever et al need to be reported. Bedside icewatertest has been moved towards urodynamic ice water test in patients with very long bladder areflexia.

Postshock treatment

Goals are to safeguard the kidneys and keep the patient alive plus to restore bladder function to permit a good quality life

- To empty the bladder regularly and completely
- To keep the intravesical pressure low during filling and micturition
- To avoid infection of the lower urinary tract
- To avoid other complications as lithiasis, reflux, kidney problems
- To keep the patient continent
- To achieve a state of "balanced" bladder which permits a good quality of life

To keep the pressure in the bladder low at all time has been shown to be one of the most important things to do.

The therapy can consist of several things

1. Reeducation
2. Physiotherapy
3. Drugs
4. Catheterization
5. External appliances
6. Surgery

Depending on the combined disorders of detrusor and sphincter the following very general guidelines can be put forward. One must however bear in mind that treatment of a patient with a neurologic bladder dysfunction is and has to be very individual thus adapted to the patient's possibilities and needs. Recent evaluation have shown that triggering and Valsalva voiding are often dangerous and that intermittent self catheterization should be preferred. Indwelling catheters to be used if no other way possible. Electrical stimulation in bladder and on involved nerves is under further development. Medication is mostly bladder relaxing. Newer approaches are intravesical injection of Botuline, Surgery aims at restoring low pressure bladder: bladder augmentation or detrusor myomectomy. Sacral neuromodulation –anterior rooth stimulation (Brindley) have indications.
For low pressure in the urethra sling or artificial sphincter can be used.

Conclusion
Treatment of patients with neurologic bladder has seen evolution through better knowledge and better understanding. Treatment must always be individual and aims at getting patient dry , with complete emptying of a low pressure bladder in a way that permits to avoid complications and allows a good prognosis.

Postscriptum:
The most recent literature shows the first results of restoring LUT function by nerve transplantation. This needs much more study but has in theory a possible real role in future treatment and recovery.

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NEUROUROLOGY UPDATE (CONT.)

Facts sheet neurologic bladder

- The innervation of the lower urinary tract (LUT) is both complicated and subtle. The system works in an interrelated action of autonomic and somatic nerves, with both afferent and efferent branches and under mostly indirect voluntary control which in itself is subject to several influences and regulating mechanisms. It does not surprise that LUT function gets disturbed in most of the neurologic pathologies and such with different prevalence and extent.
- The diagnosis of neurologic bladder comes from information gathered by clinical assessment including history, with symptoms and signs, physical examination with neurological tests, urine evaluation. However these do not permit a detailed individual diagnosis. Urodynamic investigation and preferably videourodynamic testing is strongly advocated. Evaluating sensation will add to the diagnosis.
  A combination of all tests offers the possibility of typing the neurologic dysfunction with specification of detrusor, bladder neck and striated sphincter activity and the relation between these. Important is the measuring of the intravesical pressure development during filling and voiding as one of the main goals of treatment will be to have a low pressure urine reservoir, continence and appropriate regular emptying to avoid upper urinary tract complications and urinary infection. The individual diagnosis will permit the choice of the most appropriate treatment.
- Conservative treatment can consist of behavioural therapy, catheterisation, intake of drugs, electro stimulation. Triggered voiding is to be used only in patients whose situation has proven to be urodynamically safe and stable and who can manage reflex incontinence. Bladder expression is basically dangerous and its indications are limited. Timed voiding, habit retraining, prompted voiding can be part of each individual rehabilitation. Clean intermittent catheterisation is safe and effective in the short-term and in the long-term and CIC is recommended as first choice of treatment for those with inability to empty the bladder adequately and safely, but proper education and teaching is necessary. Indwelling catheters transurethrally /suprapubically are no safe methods for long-term use. If indicated strict care can prevent some of the complications. External appliances can be needed for controlling urinary incontinence in neurologic patients. Bladder relaxing drugs are used frequently to create a low pressure reservoir and treat reflex incontinence. Botulinum toxin injections are a promising alternative. Electrical neuromodulation is not a first line treatment for neurologic bladder as yet but its role may grow in future. Intravesical electrical stimulation is the only available option to induce/improve bladder sensation and enhance micturition reflex in neurologic hyposensitive and hypocontractile detrusor.
- Surgical treatment can be indicated if conservative treatment fails. Sacral anterior root stimulation combined with posterior rhizotomy can restore bladder function in selected spinal cord injured patients with treatment refractory detrusor overactivity. Transurethral sphincterotomy is an option to adequately drain the bladder in spinal cord injured male patients. Injections of botulinum toxine in the sphincter can be an alternative. Enterocystoplasty has passed the test of time in achieving a low pressure reservoir but complications and reinterventions are not rare. Neurological decentralization has been most successful with sacral rhizotomy. Increasing urethral resistance in patients with good bladder capacity and compliance but stress incontinence is surgically mostly done with the implantation of an artificial urinary sphincter, though a sling procedure may be an alternative assuming that CIC can be done. Though less frequently used, after failure of other treatment options, continent or non continent urinary diversion can be needed. More results are awaited from research in bladder reinnervation techniques.



NEUROSTIMULATION NEUROMODULATION

Apostolos Apostolides

Neuromodulation is now being proposed as 2nd line treatment for LUTS refractory to conservative management. This is despite the lack of placebo-controlled trials due to the nature of the treatment, which allows only level 2-3 evidence to support its use in conditions such as intractable urinary incontinence, urgency-frequency syndrome and idiopathic, non-obstructive urinary retention.

Neuromodulation can be peripheral or central, short-term or chronic, surgical or pharmacological. Peripheral neuromodulation involves electrical stimulation of the perineum, anus, vagina or dorsal penile surface, aiming to stimulate the pudendal nerve in order to suppress the hypogastric/pelvic plexus. Alternatively it involves stimulation of the common peroniaio or the posterior tibial nerve, aiming to stimulate the sacral nerves. Central neuromodulation is surgical, the most widespread type being sacral nerve stimulation (SNS), which was first applied 25 years ago in the treatment of bladder dysfunction. SNS involves the stimulation of sacral nerves in order to modulate the neural reflexes that regulate the function of the bladder, urethral sphincter and pelvic floor muscles. SNS using the Interstim device (Medtronic, Minneapolis, USA) has been licensed for the treatment of urge incontinence, urgency-frequency syndrome and idiopathic, non-obstructive urinary retention that are refractory to conservative management. A 2-staged surgical technique is now applied: a stimulation lead is placed next to the dorsal root of S3 nerve for a period of 1-4 weeks (stage 1). If a more than 50% improvement in symptoms is achieved then the patient is offered permanent implantation of the stimulator in the soft tissue of the buttock (2nd stage).

Several studies to date support the efficacy of SNS, with more than 50% symptomatic improvement being reported in 51-100% of treated patients with urge incontinence, 55% in urgency-frequency syndrome and 70% in idiopathic urinary retention. However, SNS may be accompanied by several complications, the commonest being pain at the site of the implant or the electrode, migration of the lead and infections that may require re-operation in up to one third of the cases.
Sacral anterior root stimulation is the most common form of surgical neuromodulation in intractable neurogenic incontinence. It includes dissection of posterior sacral roots and implantation of an anterior sacral nerve stimulator. Complete continence rates between 65-91% have been reported and its efficacy is lasting in follow-ups of up to 7 years.

Pharmacological neuromodulation is achieved via intravesical application of the so-called neurotoxins, namely capsaicin and resiniferatoxin and, more recently, botulinum toxins. The former two act possibly via a reversible degeneration of sensory nerve fibres in the bladder wall when administered intravesically. Adversely, Botulinum toxin type A (BoNT/A) seems to reduce the levels of sensory receptors in intact nerve fibres. Small placebo-controlled trials support the efficacy of capsaicin and resiniferatoxin mainly in patients with neurogenic detrusor overactivity. However, clinical profile problems have been the main reason why these neurotoxins remain unlicensed and are only being used in specialised research centres. In contrast, intradetrusor or suburothelial injections of BoNT/A used over the past 9 years as an unlicensed treatment are gaining worldwide acceptance due to the minimally invasive nature of the procedure, the good safety profile, the high efficacy rates in both neurogenic and idiopathic detrusor overactivity (restoration of continence in up to 73% and 86% respectively), the reversible long-lasting effect (mean duration approximately 10 months) which is sustained with repeat treatment sessions. Large placebo-controlled trials are awaited before BoNT/A takes its place as an efficacious 2nd line treatment option for bladder storage symptoms that are refractory to conservative management.

CLEAN INTERMITTENT CATHETERISATION

Stavros Charalambous

The aims of the Urologist in the management of patients with neuropathic bladder dysfunction are to preserve renal function, achieve satisfactory bladder drainage and continence, minimize complications, such as infections and stones in the bladder or kidney, and maximize patient independence. Unfortunately, there is no perfect method to attain all of these goals.

The introduction of clean intermittent self-catheterization (CCIC) as a method of management for patients with impaired bladder emptying has been a major advance in clinical Urology. Intermittent catheterisation (IC) was introduced by Sir Ludwig Gutmann in Stoke Mandeville for bladder emptying during the spinal shock phase already in the late 50's and was popularized by Jack Lapides in 1972. He recommended the clean technique also for long-term bladder emptying Intermittent catheterization has been applied for many centuries for many indications.

However, the indications for the use of clean intermittent catheterization have certainly improved because of new insights that were shown to us by great men in the past.

Indications of intermittent clean self catheterization are: Neurogenic bladder and sphincter dysfunction, Detrusor areflexia, Detrusor-sphincter dyssynergia, Sensory hypotonic bladder, Spina bifida, Augmented bladder etc

Advantages of Clean Intermittent Catheterisation with hydrophilic catheters are: reduces friction, less risk of trauma, reduces the risk of infections, more comfortable for the patient, increased quality of life, no gel or lubricant needed, Easier handling

The frequency of catheterization needed can depend on many factors such as bladder volume, fluid intake, post-void residual and urodynamic parameters (bladder compliance, detrusor pressure). Usually it is recommended to catheterize 4_-6 times a day during the acute phase after spinal cord lesion. Some will need to keep this frequency if IC is the only way of bladder emptying

Complications from catheterisation are as follow:
Occasionally there may be trauma if sphincter is spastic or occurrence of stricture along with acontractile detrusor, or haematuria secondary to trauma or severe urethritis. Formation of false passage in rare occasions. One of the most frequent complications is infection of the urinary tract (UTI). Studies show that in patients with spinal cord injuries, the incidence of bacteria in the bladder is 1-3% per catheterization and 1-4 episodes of bacteriuria occur per 100 days of intermittent catheterization performed 4 times a day. In general, routine use of long-term suppressive therapy with antibiotics in patients with chronic clean intermittent catheterization is not recommended. In high-risk populations, such as patients with an internal prosthesis (eg, artificial heart valve, artificial hip) or patients who are immunosuppressed because of age or disease, determine whether to use antibiotic therapy for asymptomatic bacteriuria on individual merits.

Potential advantages of performing intermittent catheterization include patient autonomy, freedom from indwelling catheter and bags, and unimpeded sexual relations.

Studies have demonstrated that long-term use of intermittent catheterization appears to be preferable to indwelling catheterization (ie, urethral catheter, suprapubic tube) with respect to urinary tract infections and the development of stones within the bladder or kidneys.

Intermittent self catheterisation is a safe and valuable technique in people with significant post-void residuals owing to Neurogenic bladder.



NEUROGENIC BLADDER IN SPINAL CORD LESIONS. WHY LONG TERM FOLLOW UP IS NEEDED

Christina-Anastasia Rapidi

Patients with spinal cord lesion (SCL), either traumatic or non-traumatic, present neuropathic bladder dysfunction of mainly four types: detrusor and sphincter mechanism overactivity (type 1), detrusor and sphincter mechanism underactivity (type 2), detrusor underactivity and sphincter mechanism overactivity (type 3), and detrusor overactivity and sphincter mechanism underactivity (type 4).

The therapeutic approach depends on the detailed diagnosis of the specific type of neuropathic bladder dysfunction. In every type of dysfunction the optimal management must ensures the upper urinary tract (low/acceptable bladder pressure during storage and emptying) with socially accepted urine continence. Intermitted bladder catheterization (IC) with or without bladder relaxing drugs is nowadays the most usually recommended method in type 1, type 3 and sometimes in type 2. Incompetent sphincter mechanism or impaired hand function bring limitations to IC. Triggered/reflex voiding could be recommended in type 1 and bladder expression maneuvers in type 2 but in both cases very regular follow up is needed due to the high risk of upper urinary tract deterioration. Indwelling catheter should be avoided if possible.

In any case long term follow up is needed due to a number of reasons. Bladder and renal function must regularly be assessed and bladder management may need reevaluation. Long term follow up is crucial because:

- Early diagnosis is mandatory when primary goals of bladder management are not reached any more and treatment modification may be necessary in order to be preserved the safety parameters for the upper urinary tract.
- Complications interfere (recurrent urinary tract infections, stone formation, vesicoureteric reflux, deterioration of upper urinary tract, e.t.c.)
- There is a matter of age: As time passes a child becomes an adult with great changes in body and mind and an adult is no longer young; aging problems accumulate and a new therapeutic approach is needed.
- There is a matter of lesion type: As time passes incompleteness or progression of the lesion may alter the bladder dysfunction.
- New drugs and methods appear as therapeutic options promising better results and fewer side effects.
- Concerning bladder management reinforcement of patient's compliance is needed. A number of patients prefer to enroll some modifications in the recommended method of bladder management (i.e. clean intermitted catheterizations in combination with straining or reflex/triggering voiding) and that cannot assure the safety of upper urinary tract.

Questions to be answered:
Which are the optimal follow-up intervals?
Which cases need more often follow-up?
Clinical assessment, blood and urine analysis, urodynamics, ultrasound, radioisotope renal scanning, intravenous pyelography, retrograde cystography are necessary in every follow up session?

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TOLDERODINE

Anastasios Athanasopoulos

Tolderodine is a competitive, nonselective pure muscarinic receptor antagonist. This agent is the first that was developed specifically for the treatment of overactive bladder (OAB). Both the original substance and its primary metabolite have bladder over salivary gland selectivity. Tolderodine is available in immediate-release (IR) and extended-release (ER) formulation, which have been shown to be bioequivalent in their pharmacologic profile. It has been proven that the ER formulation has improved efficacy and tolerability compared with the IR formulation.

The efficacy of tolderodine has been evaluated by numerous clinical trials. Appel (1997) reported on a pooled analysis of 1120 patients that compared tolderodine with placebo significantly decreased the number of incontinent episodes (40-60%) and number of micturitions occurring in 24 hours(20%) and increased the volume voided per micturition. Similarly Cancellor and Freedman (2000) concluded that tolderodine IR reduced ugency incontinence (UI) , frequency and produced significant reduction in pad use compared with placebo. Furthermore, in a multicenter trial Van Kerrebroeck et al (2001) showed 71% reduction from baseline for UI episodes with tolderodine ER and 33% for placebo. Median reduction from baseline for severe UI was 68% for tolderodine ER and 30% for placebo (Landis et al, 2004, post hoc subgroup analysis).On the other hand, Siami et al (2002) assessed the speed of onset of therapeutic benefit with tolderodine in 1138 patients with OAB and concluded that median reduction in urgency episodes from baseline per 24h was 56%, 75% and 86% for week1, 4, 12 respectively. More recently Elinoff et al (2006) in IMPACT, a 12 week study of 863 patients, found regarding the most bothersome OAB symptom, that tolderodine ER reduced in median from baseline UI 80%, urgency 78%, nocturnal frequency 40% and daytime frequency 30%. In the same study Roberts et al (2006) analyzed the patients' subjective impression and concluded that, 75% of patients reported improvement in bladder condition, 86% in urgency, 79% in nocturnal frequency and 78% in daytime frequency. Regarding long term efficacy of tolderodine ER, Kreder et al (2006) found that it was sustained in 1 year with median reduction of UI from baseline per week as 83%. Dmochowski et al (2007) evaluated the efficacy of tolderodine ER in men and women with OAB in 1698 patients concluding that, for both genders tolderodine ER group achieved significantly greater reductions than placebo group in micturion frequency.

Regarding the safety and tolerability of tolderodine accumulated data of the last decade from the aforementioned studies and others concluded that this agent is associated with few adverse events and most of them are of mild or moderate severity. The most common side effect as in all antimuscarinics is dry mouth with a median presence in 23% but severe dry mouth is reported only in 2-3% of patients (Abrams et al (2001), Kreder et al (2002)) Other side effects reported in >3% of patients are constipation (6%), abdominal pain (4%), Dyspepsia (3%), Dry eyes (3%), Somnolence (3%) and Headache (6%). Nitti et al (2006) found a withdrawal rate occurred in 14,8% of patients given tolderodine ER and in 13,6% of patients given placebo. Main contraindication of tolderodine as of all antimuscarinics is narrow-angle glaucoma. As efficacy of older a newer anticholinergics on clinical base seems to be more or less the same, tolerability play a major role in the total profile of an anticholinergic .According to the existing data tolderodine is prevailing in this issue.

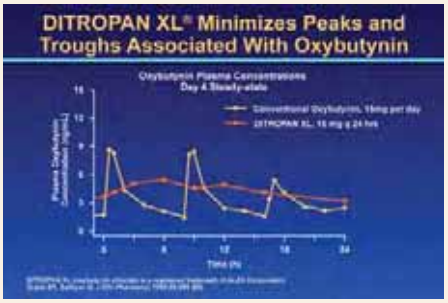


OXYBUTIN

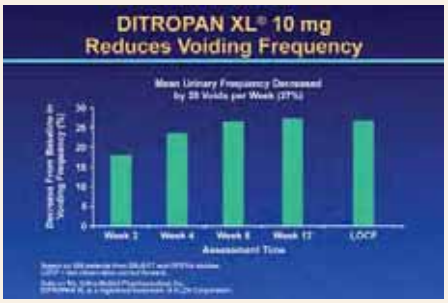
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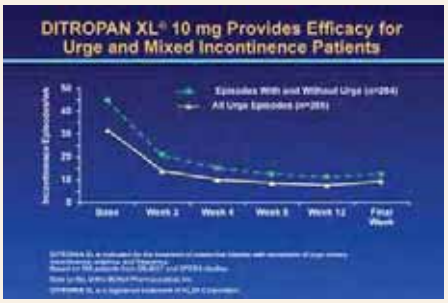


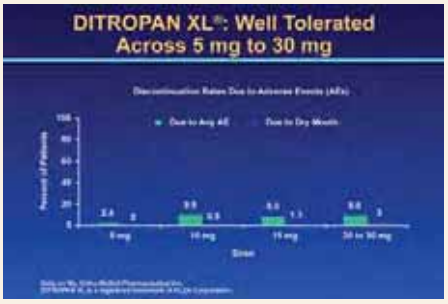


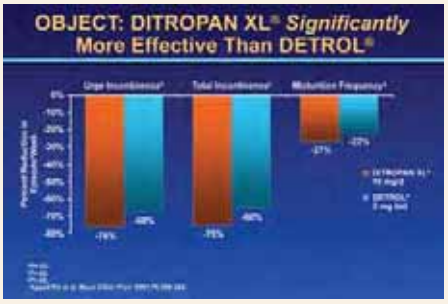




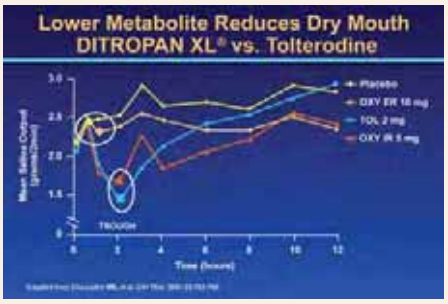


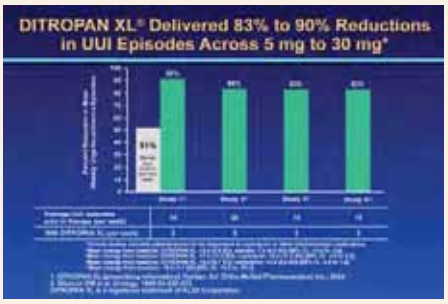


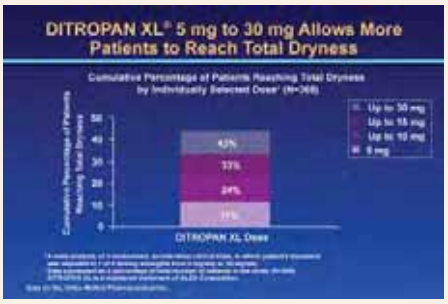


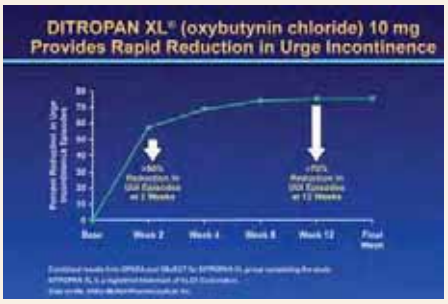


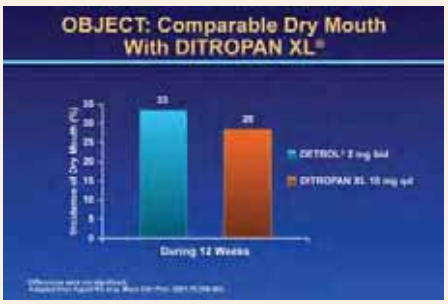
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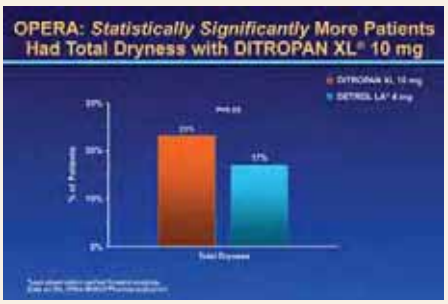


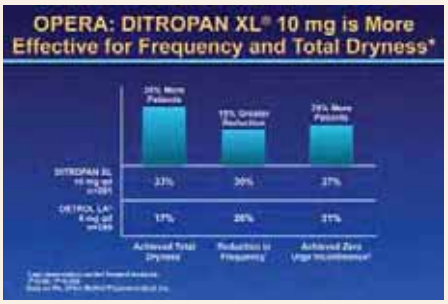


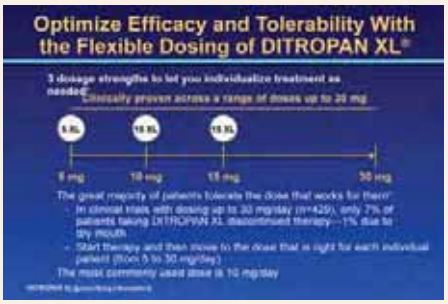














SOLIFENACIN

Dudley Robinson

Solifenacin is a potent M_3 receptor antagonist that has selectivity for the M_3 receptors over M_2 receptors and has much higher potency against M_3 receptors in smooth muscle than it does against M_3 receptors in salivary glands.

The clinical efficacy of solifenacin has assessed in a multi-centre, randomised, double-blind, parallel group, placebo controlled study of solifenacin 5mg and 10mg once daily in 857 patients with overactive bladder. There was a statistically significant reduction of the micturition frequency with both 5mg and 10mg doses when compared with placebo. In addition solifenacin was found to be superior to placebo with respect to the secondary efficacy variables of mean volume voided per micturition, episodes of urgency per 24 hrs, number of incontinence episodes and episodes of urge incontinence. The most frequently reported adverse events leading to discontinuation were dry mouth and constipation. Solifenacin has also been directly compared to tolterodine 2mg twice daily in a phase three randomised, double-blind, parallel group, placebo and active controlled multi-centre study of 1033 patients in Europe and South Africa[2]. There was a statistically significant reduction of micturition frequency with both solifenacin 5mg and 10 mg when compared with placebo, the former equating to a reduction of 2.2 micturitions/24 hrs and the latter 2.6. Tolterodine showed a smaller reduction of 1.9 micturitions. In addition solifenacin was statistically superior to placebo with respect to the secondary outcome variables. In those patients who were incontinent 37.3% of the placebo group were continent at the end of study compared to 51.1%, 50.6% and 48.4% in the 5mg, 10mg and tolterodine groups respectively.

In order to assess the long-term safety and efficacy of solifenacin (5mg and 10mg once daily) a multi-centre open label long term follow up study has recently been completed. This was essentially an extension of two previous double blind placebo controlled studies and 1637 patients elected to continue taking solifenacin 5mg or 10mg once daily[3]. Overall the efficacy of solifenacin was maintained in the extension study and the mean number of micturitions per 24 hours was reduced by 22.1% at the end of the study.

Most recently solifenacin 5mg and 10mg od have been compared with tolterodine ER 4mg od in the Solifenacin (flexible dosing) od and Tolterodine ER 4mg od as an Active comparator in a Randomised trial (STAR).[4] This was a prospective double-blind, double dummy, two-arm, parallel-group, 12-week study with the primary aim of demonstrating non-inferiority of solifenacin to tolterodine ER in 1200 patients. The outcome of the primary efficacy analysis was that solifenacin was non inferior to tolterodine ER with respect to change from baseline in the mean number of micturitions per 24 hrs (reduction of 2.45 micturitions/24hrs Vs 2.24 micturitions/24hrs; p=0.004). In addition solifenacin resulted in a statistically significant improvement in urgency (p=0.035), urge incontinence (p=0.001) and overall incontinence when compared with tolterodine ER. In addition 59% of solifenacin treated patients who were incontinent at baseline became continent by the study endpoint compared with 49% of those on tolterodine ER (p=0.006). The most commonly reported adverse events were dry mouth constipation and blurred vision and were mostly mild to moderate in severity.

The aim of this lecture is to give an overview of the role of solifenacin in the management of overactive bladder.

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OXYBUTYNIN PATCH

Linda Cardozo

Oral Oxybutynin has been used for many years in the treatment of overactive bladder syndrome (OAB). Its principal action is to block M3 muscarinic receptors, reducing detrusor contractility. However oxybutynin is also active against muscarinic receptors in the salivary glands, leading to an unacceptably high rate of dry mouth.

Problems with antimuscarinic side effects such as dry mouth, have led to the development of alternative agents and formulations. These include extended release oxybutynin, marketed as Ditropan or Lyrinel XL, and newer anticholinergics such as Darifenacin and solifenacin. All oral formulations of anticholinergics are subject to extensive hepatic and gastro-intestinal pre-systemic metabolism. Oxybutynin is rapidly metabolised to N-desethyloxybutynin.

This reduces bioavailability, and leads to troughs and peaks in drug concentration following administration.

Transdermal formulations of other drugs have been available for almost 25 years. They are popular with patients, and are used for a range of medications requiring continuous release, including oestradiol, fentanyl, and nicotine. This route of administration helps avoid first-pass metabolism, stabilising drug concentrations. The lower drug concentrations lead to a reduced rate of dose-related side effects, while maintaining therapeutic blood levels. The combination of fewer side effects and ease of administration increases patient compliance with therapy.

Oxybutynin is now available in a matrix-type transdermal patch, for twice weekly administration. It is marketed as Oxytrol or Kentera. The licensed dose is a 36mg patch, releasing an average of just 3.9mg oxybutynin/24 hours.

One Phase II study demonstrated that transdermal oxybutinin has equivalent efficacy, on both objective and subjective measures, to oral immediate release oxybutynin (max 20mg od). The incidence of anticholinergic side effects was much reduced, with 89% of patients reporting, "none", or "mild" effects only. A further Phase III study has shown that transdermal oxybutynin and extended release tolterodine (4mg od) are associated with equal improvement in incontinence episodes, urinary frequency, mean voided volumes, and incontinence specific quality of life scores, with statistically significant benefit compared with placebo. Although these trials are powered only to detect a difference in efficacy, the rate of anticholinergic side effects is no higher for transdermal oxybutynin compared with placebo.

In common with other transdermal systems there is an associated rate of erythema and pruritus (up to 14%). These separate adverse effects may limit compliance in some patients.

Transdermal oxybutynin is a novel treatment for OAB, with significant benefits compared with existing oral medications. It offers the efficacy of these established anticholinergics, with an unprecedented low rate of adverse anticholinergic effects. Were cost not an issue, the combination of efficacy and acceptability should make it an obvious choice as a first line treatment for OAB.



PROPIVERINE

Helmut Madersbacher

PROPIVERINE – WHAT ARE THE MARKETING MESSAGES?
Propiverine, in contrast to other drugs indicated for detrusor overactivity, comprises a dual mode of action with neurotropic and musculotropic properties (Madersbacher & Muertz, World Journal Urology, 2001). Efficacy has been proven in numerous studies conducted in Europe and Japan in Caucasian and Japanese / Korean patients covering a broad range of different indications: symptoms of the OAB, idiopathic and neurogenic detrusor overactivity in adults, idiopathic and neurogenic detrusor overactivity (myelomeningocele) in children. In elderly men with OAB and concomitant BPE/BPO propiverine and alpha-adrenoceptor antagonists were administered together (Lee et al., Journal Urology, 2005).

In OAB propiverine and tolterodine are equieffective as was shown in a head-to-head study in adults (Jünemann et al., European Urology, 2005). Furthermore, propiverine and tolterodine are equally tolerable. In long-term studies it was proven that adverse events decreased during the time-course following propiverine treatment (e.g. Madersbacher & Muertz, World Journal Urology 2001). In unobstructed and obstructed male patients with OAB and BPE/BPO no clinically relevant inc rease of post-void residual, no acute urinary retention was observed (Lee et al., Journal Urology, 2005).

PROPIVERINE - WHAT IS THE SCIENTIFIC BASIS FOR THESE MESSAGES?
A complex dual mode of action is based on the parent drug propiverine hydrochloride comprising antimuscarinic and calcium_+-modulating properties. Three major main metabolites were detected, the N-oxide is the main metabolite. In the experimental setting only the combination of atropine (antimuscarinic) and nifedipine (Calcium-channel blocker) achieved an extent of detrusor inhibition which was comparable to that of propiverine. In preclinical studies (in–vivo studies in the mini-pig) propiverine and tolterodine induced an equivalent decrease of salivation, thus suggesting comparable tolerability of both drugs also in humans (Scheepe et al., Aktuelle Urologie, 2000).

PROPIVERINE – WHAT IS THE DOCUMENTATION FOR THESE MESSAGES?
In regards to idiopathic detrusor overactivity Jünemann and coworkers (European Urology, 2005) showed in a head-to-head study that the increase in maximum cystometric bladder capacity following propiverine and tolterodine was comparable. Also in regards to tolerability there was no difference between these two drugs, as was evidenced with respect to the overall adverse event incidence rate and with respect to the incidence rate of dryness of the mouth.
In regards to CNS adverse events cognitive, mental and motor functions in elderly patients with various neurological diseases (multiple cerebral infarction, M. Parkinson, M. Alzheimer) were not negatively affected during a 8-week treatment with propiverine (Uchiyama et al., ICS 2005).

In regards to neurogenic detrusor overactivity in a placebo-controlled (Stöhrer et al., Spinal Cord 1999) as well as a comparator-controlled study (Stöhrer et al., European Urology, 2007) again the maximum cystometric bladder capacity increased, the maximum detrusor pressure amplitude during voiding decreased significantly following propiverine treatment.

In several studies in men with OAB and concomitant BPE/BPO alpha-adrenoceptor antagonist monotherapy was compared to the combined usage of an alpha-adrenoceptor antagonist and propiverine: this combination regimen achieved higher rates of improvement in OAB-symptoms. In only one out of four studies 2 out of 75 patients (Saito et al., Japanese Journal Urology Surgery 1999) experienced urinary retention.

Tolterodine, trospium, darifenacin and solifenacin are not registered for the use in children and only very few studies with these drugs are published. Additionally, oxybutynin has traditionally been used in children (Hehir & Fitzpatrick, European Urology 1985), however numerous reports evidenced an unfavourable adverse event profile. Propiverine, registered for the use in children in Germany and some other countries, exerts significantly less adverse events compared to oxybutynin according to a very broad paediatric data base (Marschall-Kehrel et al., Journal Urology 2004, Madersbacher et al., European Urology 2006, Alloussi et al., European Urology 2006). Therefore, propiverine proved to be significantly better tolerated compared to oxybutynin also in children suffering from idiopathic or neurogenic detrusor overactivity.

The advantages of a propiverine extended release formulation compared to the propiverine immediate release formulation have been shown, especially with respect to a further improved tolerability profile (Jünemann et al., Urologia Int 2006).

PROPIVERINE (CONT.)

WHY IS PROPIVERINE THE BEST DRUG FOR OAB?
Propiverine is unique in regards to its dual mode of action. Numerous placebo- and/or reference-controlled studies as well as open-label studies evidenced excellent results in the following patient populations: idiopathic detrusor overactivity and neurogenic detrusor overactivity, both in adults and in children. Especially for children a dose formulation containing 5 mg propiverine (Mictonetten®) has been designated. In men with OAB and concomitant BPE/BPO very promising results were achieved by combining alpha-adrenoceptor antagonists and propiverine.

In conclusion, propiverine comprises an excellent efficacy and tolerability profile, it is the market leader in Japan. However the marketing possibilities are according to a medium-sized family-owned company.

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PLACEBO

Iraklis Mitsogiannis

Overactive bladder (OAB) is a most distressing syndrome which affects a substantial number of patients worldwide. The standard therapy for OAB is the combination of behavioural and pharmacological treatments. Antimuscurinic agents are currently the pharmacological treatment of choice for patients with OAB, having proved to be efficacious and safe in randomised controlled trials. However, these trials consistently report high placebo responses as well and this has led some authors to dispute the true efficacy of the antimuscurinics. The so-called "placebo effect" is a widespread and universal, although poorly understood, phenomenon. It is generally reported to be much higher in disorders liable to subjective experience by the patients (e.g. pain, depression), than in those that measure objective parameters. Success rates yielded by placebo may, in some instances, reach those of the genuine drug.

Several clinical trials assessing antimuscurinics for the treatment of OAB have shown a surprisingly high placebo response when subjective parameters are evaluated. For instance, the reduction in the reported urge incontinence episodes by placebo ranges from 32-64%, which is slightly lower than that of the active drug (45-77%). However, when objective outcomes are measured, the difference in favour of the active drug is more prominent; placebo has been found to increase the mean voided volume per micturition only by 5-6%, whereas the active drug increases it by 10-22%. The high placebo response in all the subjective parameters of OAB may be explained by the fact that the patients, by completing frequency-volume charts, become aware of their voiding habits and probably try to modify them regardless of the medication taken. Furthermore, the information about the positive effects of the active drug, given before initiation of treatment, may modify the patients' response to it and consequently increase the placebo effect.

As previously mentioned, it is not clear how the placebo acts. Amongst several theories put forth to explain the mechanisms of placebo, the "conditioning theory" suggests that the placebo response represents a type of classical conditioning that is based on learning through association. The "expectancy theory" suggests that the placebo effect is related to patients' expectations of improvement, which are connected to the changes that take place. Expectation is a conscious process whereas conditioning is assumed not to involve cognition; however both are learned through patients' previous contact with the medical system.

The placebo effect may be influenced by several factors related not only to the disorder or the patient but also to the trial. Studies including a run-in period usually show less placebo responses during the following treatment. In addition, a decrease of the placebo effect over time has been observed. Consequently, inclusion of run-in periods and longer duration of the trial period, which for OAB is usually 12 weeks, should theoretically decrease the placebo effect.

In conclusion, there is a noticeable placebo response in patients with OAB, particularly when assessing subjective parameters. This may be diminished by inclusion of more objective parameters in the randomised controlled trials for OAB and by taking under consideration the factors which influence it.