Percorsi Simpesv
Prevenzione, diagnosi e cura
dell’incontinenza urinaria

PDTA pazienti incontinenti,
gestione di 2° livello:
- terapia farmacologica
- terapia chirurgica

Prof. Enrico Finazzi Agrò
Dept. of Experimental Medicine and Surgery
Tor Vergata University
Unit of Functional Urology
Tor Vergata University Hospital
Rome, ITALY
Initial Management of Urinary Incontinence in Women

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

**CLINICAL ASSESSMENT**

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

**MANAGEMENT**
- Life style interventions.
- Pelvic floor muscle training for SUI or OAB
- Bladder retraining for OAB
- Duloxetine* (SUI) or antimuscarinic (OAB ± urgency incontinence)

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

**SPECIALIZED MANAGEMENT**
- If other abnormality found e.g.
  - Significant post void residual
  - Significant pelvic organ prolapse
  - Pelvic mass

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

- Education
- Timed voiding
- Pelvic floor exercises
- Delayed voiding
- Diet
Bladder Training

• Modify bladder function

• Methods
  – bladder diary
  – gradually increase void interval
  – teach coping strategies

• Strengthen pelvic floor muscles and improving bladder stability
Management of Overactive Bladder

• Behavioral therapies\(^1\)
• Pharmacologic therapy
• Combined pharmacologic and behavioral therapy provides improved outcomes\(^2,3\)

Drugs used in the treatment of OAB

There are a number of pharmacological mechanisms that in theory could reduce overactive detrusor muscle activity.

- Antimuscarinic drugs
- Drugs acting on membrane channels
- Drugs with mixed actions
- Antidepressants
- Alpha-adrenoreceptor antagonists
- Beta-adrenoreceptor antagonists
- PDE-5 inhibitors (for male LUTS/OAB)
- Toxins
- Hormones

....However

EAU Guidelines, 2009
To date, the only approved treatments with Grade A recommendation based on level 1 evidence are anticholinergic drugs (specifically antimuscarinic).

EAU Guidelines, 2009; Incontinence, 2009

<table>
<thead>
<tr>
<th>Drugs</th>
<th>LE</th>
<th>GR</th>
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<tbody>
<tr>
<td><strong>Antimuscarinic drugs</strong></td>
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<tr>
<td>Tolterodine</td>
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<td>Trospium</td>
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<td>A</td>
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<tr>
<td>Solifenacin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Fesoterodine</td>
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<td>A</td>
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<tr>
<td>• Propantheline</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>• Atropine, hyoscyamine</td>
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<td>C</td>
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<td><strong>Drugs with mixed actions</strong></td>
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</tr>
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<td>• Oxybutynin</td>
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<td>A</td>
</tr>
<tr>
<td>• Propiverine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>• Dicyclomine</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>• Flavoxate</td>
<td>2</td>
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</table>
Antimuscarinic drugs on the market

- **Oxybutynin** (IR 7.5-10mg/day, IR 15 mg/day, TDS 3.9-4 mg/day)
- **Tolterodine** (IR 2mg/day, IR 4 mg/day, ER 4mg/day)
- **Propiverine**, (IR 30mg/die, IR 45 mg/die, ER 20mg/die, ER 30 mg/die)
- **Trospium**, (40mg/die)
- **Solifenacin** (5mg/day, 10 mg/day)
- **Darifenacin** (7.15 mg/day, 15 mg/day)
- **Fesoterodine** (4 mg/day, 8 mg/day)

Rationale for Use of Antimuscarinics in OAB

Effects on afferent activity (myocyte + urothelium)

"Therapeutic window" for OAB

Effects on voiding contraction

Concentration of antimuscarinic
The concerns that anticholinergics might be associated with impaired voiding and AUR do not appear to be supported by the evidence from the studies assessed. Anticholinergics are associated with a small rise in PVR, but not an increased rate of AUR.
Other drug classes to treat OAB?

- “Despite intensive research, few new therapeutic principles have emerged and been demonstrated to have sufficient efficacy and adverse effect profiles to be accepted for approval and clinical use”¹

- Research indicated that stimulation of $\beta_3$-receptors leads to bladder relaxation

- Discovery of $\beta_3$-adrenoceptors, predominately present on the bladder wall → development of $\beta_3$-adrenoceptor agonist


First FDA-approved antimuscarinic agent²
1975

FDA-approval $\beta_3$-agonist³
2012
Effects of NE and Ach on Bladder activity

Effector mechanisms involving NE and Ach on bladder activity are illustrated. Membrane receptors include β3, M2, and M3. NE activates β3, leading to cAMP production and relaxation through AC. Ach activates M2, promoting contraction through IP3 and Ca2+. M3 receptors also contribute to contraction. Membr. Cell. indicates the membrane cell structure. Chapple CR. *Urology*. 2000;55:33-46.
Binding affinity ($K_i$) of mirabegron for human ARs

<table>
<thead>
<tr>
<th>Receptor subtype</th>
<th>Mirabegron $K_i$, nmol/L*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_1$-AR</td>
<td>4,200 ± 900</td>
</tr>
<tr>
<td>$\beta_2$-AR</td>
<td>1,300 ± 300</td>
</tr>
<tr>
<td>$\beta_3$-AR</td>
<td>40 ± 20.2</td>
</tr>
</tbody>
</table>

Lower $K_i$ values represent higher affinity

* Determined in *in vitro* receptor binding studies using Chinese hamster ovary cells expressing human $\beta$-AR subtypes; values are means of three replicates (± standard error)
End-point co-primario: numero medio di minzioni per 24 h

All p values <0.05 for Mirabegron 50 and 100 mg vs placebo

Women presenting with UI
EAU guidelines 2016

Discuss management

Individualised behavioural and physical therapies including pelvic floor muscle training

Stress incontinence
Advise on bowels, drugs, co-morbidity, fluid intake
Advise on weight loss
Offer pads or other containment device if needed
Consider topical vaginal oestrogen for post-menopausal women
Offer desmopressin for short term symptom relief
Offer timed or prompted voiding in elderly/care-dependent people

Mixed incontinence

Urgency incontinence

Failure of conservative or drug therapy – discuss surgical options

Anti-muscarinics
A
or mirabegron
B
No response
Consider P-PTNS
B
You should be able to have mirabegron if drugs called ‘antimuscarinics’ do not work, if they are not suitable for you, or their side effects are unacceptable.
Beta3Agonista

- Funziona meglio in pazienti non responder a antimuscarinici?
Prima o seconda linea di terapia?
Mean number of UI episodes/24 h

Khullar V et al. BMC Urology 2013, 13:45
Prima o seconda linea di terapia?
Mean number of micturitions/24 h

Khullar V et al. BMC Urology 2013, 13:45
Seconda linea di trattamento?
Beta3Agonista

Funziona in pazienti non responder a antimuscarinici?
Effect of mirabegron on patients with refractory OAB and on the waiting list for onabotulinumtoxinA (onabotA)


- Single-centre study (mean FU 55d)
- N=36 pts with refractory OAB and proven DO
  - 6 males, 30 females (mean age 60 yr) – 86% have UUI
  - on the waiting list for first/repeat onabotA therapy
  - received mirabegron 50 mg od
- Response rate of mirabegron: 67% (24/36 pts)
  - ICIQ-SF score: 13.36 → 9.41 (P=0.005)
  - 16/24 pts (67%) wanted to be removed from the waiting list, after 2 wk
- 13 of 36 pts (36%) with ≥1 prior onabotA treatment:
  - 7 wanted to be removed from waiting list, after 2 wk
- AEs:
  - palpitations (2), vomiting (1), rashes (1), lethargy (1), yellow urine (1)

Patients with refractory OAB seem to respond well to mirabegron. About one third are willing to be removed from the waiting list for onabotA injections

ICIQ-SF: Incontinence Questionnaire-Short Form
Platinum Priority – Voiding Dysfunction

Editorial by XXX on pp. x–y of this issue

Efficacy and Safety of Mirabegron Add-on Therapy to Solifenacin in Incontinent Overactive Bladder Patients with an Inadequate Response to Initial 4-Week Solifenacin Monotherapy: A Randomised Double-blind Multicentre Phase 3B Study (BESIDE)

Marcus J. Drake, Christopher Chapple, Ahmet A. Esen, Stavros Athanasiou, Javier Cambronero, David Mitcheson, Sender Herschorn, Tahir Saleem, Moses Huang, Emad Siddiqui, Matthias Stölzel, Claire Herholdt, Scott MacDiarmid, on behalf of the BESIDE study investigators
◆ Combination > Solifenacin 5 mg
◆ Combination <> Solifenacin 10 mg (with less side effects)
Funziona in pazienti non responder a antimuscarinici?

Sì...

E anche in combinazione!
### Drugs with strong anticholinergic properties

<table>
<thead>
<tr>
<th>Antihistamines</th>
<th>Antiparkinson agents</th>
<th>Skeletal muscle relaxants</th>
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<tr>
<td>Brompheniramine</td>
<td>Carboxamine</td>
<td>Benzpropine</td>
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<td>Clemastine</td>
<td>Carisoprodol</td>
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<td>Cyproheptadine</td>
<td>Dimenhydrinate</td>
<td>Cyclobenzaprine</td>
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<td>Diphenhydramine</td>
<td>Hydroxyzine</td>
<td>Orphenadrine</td>
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<td>Meclizine</td>
<td>Tizanidine</td>
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<td>Benztropine</td>
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<tr>
<td>Trihexyphenidyl</td>
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<td>Carisoprodol</td>
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<td>Cyclobenzaprine</td>
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<td>Orphenadrine</td>
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<td>Tizanidine</td>
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<table>
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<th>Antidepressants</th>
<th>Antipsychotics</th>
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<td>Amitriptyline</td>
<td>Chlorpromazine</td>
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<td>Clomipramine</td>
<td>Fluphenazine</td>
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<td>Doxepin</td>
<td>Olanzapine</td>
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<td>Nortriptyline</td>
<td>Pimozide</td>
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<td>Protriptyline</td>
<td>Promethazine</td>
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<td>Trimipramine</td>
<td>Thiothixene</td>
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<td>Trifluoperazine</td>
<td>Thioridazine</td>
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<td>Clozapine</td>
<td>Trifluoperazine</td>
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<td>Loxapine</td>
<td></td>
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<td>Perphenazine</td>
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<td>Prochlorperazine</td>
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<table>
<thead>
<tr>
<th>Antimuscarinics (urinary incontinence)</th>
<th>Antispasmodics</th>
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<tbody>
<tr>
<td>Darifenacin</td>
<td>Atropine products</td>
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<tr>
<td>Flavoxate</td>
<td>Belladonna alkaloids</td>
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<td>Solifenacin</td>
<td>Dicyclomine</td>
</tr>
<tr>
<td>Trospium</td>
<td>Homatropine</td>
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<td></td>
<td>Hyoscyamine products</td>
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<tr>
<td></td>
<td>Propantheline</td>
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<tr>
<td></td>
<td>Scopolamine</td>
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The efficacy and tolerability of the β3-adrenoceptor agonist mirabegron for the treatment of symptoms of overactive bladder in older patients

Adrian Wagg1, Linda Cardozo2, Victor W. Nitti3, David Castro-Diaz4, Stephen Auerbach5, Mary Beth Blauwet6, Emad Siddiqui7

1Department of Geriatric Medicine, University of Alberta, Alberta, Canada
2Department of Urogynaecology, Kings College London, London, UK
3Department of Urology, NYU Langone Medical Center, New York City, NY, USA
4Department of Urology, University Hospital of the Canary Islands, Santa Cruz de Tenerife, Tenerife, Spain
5Department of Urology, Hoag Memorial Presbyterian Hospital, Newport Beach, Long Beach, CA, USA
6Department of Biostatistics, Astellas Pharma Global Development, Inc., Northbrook, IL, USA
7Astellas Pharma Europe Ltd, Chertsey, Surrey, UK and Department of Urology, Ealing Hospital, London, UK

Address correspondence to: A. Wagg. Tel: +1 780 492 5338; Fax: +1 780 492 2784. Email: adrian.wagg@ualberta.ca
Persistence with antimuscarinic agents is poor

- 12-month UK study on prescription data

% of patients remaining on AM therapy over a period of 12 months

![Graph showing percentage of patients remaining on antimuscarinic therapy over 12 months.](Image)

- Solifenacin (N=1,381)
- Tolterodine ER (N=1,758)
- Tolterodine IR (N=482)
- Oxybutynin ER (N=590)
- Oxybutynin IR (N=1371)
- Propiverine (N=97)
- Trospigum (N=352)
- Darifenacin (N=23)
- Flavoxate (N=89)

ER: extended release; IR: immediate release

Wagg A et al. BJU Int 2012;110:1767-74
Persistence with mirabegron vs antimuscarinics in OAB

- Analysis of prescription data from a UK longitudinal database: pts starting a new course of OAB therapy (2012-2013) and followed for 12 mo
  - N=10,238 pts receiving antimuscarinics; N=141 pts receiving mirabegron
- Treatment cessation = discontinuation of treatment >1.5 times the expected duration of the previous prescription, including switching to other drug
- Mirabegron had a higher persistence than antimuscarinics at 12 mo:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Persistence at 12 mo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirabegron</td>
<td>48%</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>35%</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>30%</td>
</tr>
<tr>
<td>Trospium</td>
<td>29%</td>
</tr>
<tr>
<td>Oxybutinin ER</td>
<td>28%</td>
</tr>
<tr>
<td>Tolterodine IR</td>
<td>25%</td>
</tr>
<tr>
<td>Tolterodine ER</td>
<td>24%</td>
</tr>
<tr>
<td>Oxybutinin IR</td>
<td>22%</td>
</tr>
</tbody>
</table>

Mirabegron seems to have a higher persistence rate at 12 mo than antimuscarinics in pts starting a new course of OAB treatment.
Out of pocket...
FARMACI PER L'INCONTINENZA URINARIA

SOTTOGRUPPO «FARMACI» DEL GRUPPO DI LAVORO SUI PROBLEMI LEGATI ALL'INCONTINENZA URINARIA E FECALE (D.M. DEL 2 OTTOBRE 2015)
Specialized Management of Urinary Incontinence in Women

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

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

**URODYNAMIC STRESS INCONTINENCE (USI)**
(Treat. most bothersome symptom first)

**MIXED INCONTINENCE (USI/DOI)**

**DETRUSOR OVERACTIVITY INCONTINENCE (DOI)**

**INCONTINENCE associated with poor bladder emptying**
- Bladder outlet obstruction
- Underactive detrusor

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

**DIAGNOSIS**
- Consider:
  - Urethrocystoscopy
  - Further imaging
  - Urodynamics

**TREATMENT**
- If initial therapy fails:
  - Stress incontinence surgery
  - Bulking agents
  - Tapes and slings
  - Colposuspension

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

- Correct anatomic bladder outlet obstruction (e.g. genito-urinary prolapse)
- Intermittent catheterization

- Correct anomaly
- Treat pathology

**Lower urinary tract anomaly / pathology**
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- Incontinence with mixed symptoms
- Incontinence with urgency / frequency

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- Intermittent catheterization

- Correct anomaly
- Treat pathology
Neuromodulazione sacrale

SISTEMA InterStim®
Procedure chirurgiche: neuromodulazione sacrale

• Neuromodulazione sacrale
  – Il meccanismo d’azione rimane dibattuto¹
  – Almeno due meccanismi potenziali:¹
    – Attivazione delle fibre efferenti che arrivano allo sfintere uretrale striato che di riflesso causa il rilassamento del detrusore (secondo Tanagho & Schmidt 1988²)
    – Attivazione delle fibre afferenti che causa l’inibizione a livello spinale o sopraspinale (secondo Fowler et al 2000²)

¹ Groen J, Bosch JLHR. BJU Int 2001;87:723–31
Eight reports of randomised studies that evaluated implants which provided continuous stimulation were included.

It seems clear that continuous stimulation offers benefits for carefully selected people with overactive bladder syndrome and for those with urinary retention.
### Table 5. Short-term results of treatment with SNM or with placebo among patients with OAB

<table>
<thead>
<tr>
<th>First author</th>
<th>Follow-up, months</th>
<th>General improvement, %</th>
<th>Voids/day, %</th>
<th>Voided vol., %</th>
<th>IE/day, %</th>
<th>Proportion of group with 100% continence, %</th>
<th>Pads/day, %</th>
<th>MCC, %</th>
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<tr>
<td>Weil [36]</td>
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<td>−56</td>
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<td>van Voskuilen [45]</td>
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<td>−65</td>
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<td>Hijaz [41]</td>
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<td>75</td>
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</tbody>
</table>
Percutaneous Tibial Nerve Stimulation (PTNS)

- Neuromodulation technique of the lower urinary tract obtained with electrical stimulation of the posterior tibial nerve
PTNS: procedura

- Trattamento ambulatoriale
- Una seduta di stimolazione a settimana
- 30 minuti
- Periodo di valutazione: 12 settimane
Percutaneous Tibial Nerve Stimulation Effects on Detrusor Overactivity Incontinence are Not Due to a Placebo Effect: A Randomized, Double-Blind, Placebo Controlled Trial

Enrico Finazzi-Agrò,*,† Filomena Petta, Francesco Sciobica, Patrizio Pasqualetti, Stefania Musco and Pierluigi Bove

From the Department of Surgery/Urology, Tor Vergata University (EFA, FP, FS, PB), SeSMIT, Service for Medical Statistics and Information Technology, AFeR, Fatebenefratelli Hospital, Isola Tiberina (PP) and Fondazione S. Lucia (SM), Rome, Italy

North Carolina (SAM)
Offer, if available, PTNS as an option for improvement of urgency urinary incontinence in women, but not men, who have not benefited from antimuscarinic medication.
Tossina botulinica di tipo A: una grande proteina tridimensionale

<table>
<thead>
<tr>
<th>Composto</th>
<th>MW</th>
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<tbody>
<tr>
<td>Aspirina (acido acetilsalicilico)</td>
<td>180 Da³</td>
</tr>
<tr>
<td>Uraplex® (cloruro di trospio)</td>
<td>430 Da³</td>
</tr>
<tr>
<td>Omnic® (tamsulosina)</td>
<td>445 Da³</td>
</tr>
<tr>
<td>Viagra® (citrato di sildenafil)</td>
<td>667 Da³</td>
</tr>
<tr>
<td>Complesso BOTOX® (tossina botulinica di tipo A)</td>
<td>~900,000 Da⁴</td>
</tr>
</tbody>
</table>

BoNT-A, Tossina botulinica di tipo A; MW, peso molecolare.

L’inibizione dell’interazione tra le vescicole sinaptiche e le membrane del terminale nervoso è fondamentale per l’azione motoria e sensoriale di **BOTOX®**

1. La tossina botulinica si lega al recettore
2. Endocitosi della tossina botulinica
3. La catena leggera rompe alcune proteine **SNARE** specifiche
4. Non si forma il complesso **SNARE**
Linee guida che consigliano le iniezioni di tossina botulinica per l’incontinenza neurogena (Grado A)

<table>
<thead>
<tr>
<th>Linee guida</th>
<th>Livello d’evidenza/Grado di raccomandazione</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICI guidelines 2013 (tossina botulinica [neurogena], iniettata nel detrusore)(^1)</td>
<td>1A</td>
</tr>
<tr>
<td>EAU guidelines 2009 (disfunzione neurogena del basso tratto urinario)(^2)</td>
<td>1 A</td>
</tr>
<tr>
<td>EAU guidelines 2011 (disfunzione neurogena del basso tratto urinario)(^3)</td>
<td>A</td>
</tr>
<tr>
<td>EAU guidelines 2011 (incontinenza urinaria)(^3)</td>
<td>2 A (neurogena)</td>
</tr>
</tbody>
</table>

EAU, European Association of Urology; ICI, International Continence Society.
EMBARK: due studi pivotali di fase III\textsuperscript{1,2}

**OnabotulinumtoxinA 100 U**
- Pre-screening/randomizzazione

**Placebo**
- Pre-screening/randomizzazione

**Studi**
- **Studio (N=577)\textsuperscript{1}**
- **Studio (N=548)\textsuperscript{2}**

**End point primario**
- Primo momento in cui si può trattare nuovamente

**Settimane**
- -3 0 2* 6* 12* 18 24

**Uscita dallo studio**
- Se non è stato effettuato un nuovo trattamento

**Estensione a lungo termine:**
- Studio 096

**Fino a altri 3 anni aggiuntivi**

---

*Periodo di confronto placebo-controllo.

1. Nitti et al. _JUrol_ 2013
2. Chapple et al. _EurUrol_ 2013
Diminuzione significativa degli episodi d’incontinenza urinaria giornaliera rispetto al placebo

Alla 12^ settimana, OnabotulinumtoxinA consentiva di ottenere il 51% di riduzione degli episodi di UI rispetto al basale contro il 18% col placebo (P<0.001)

Variazione media rispetto al basale (episodi/giorno)

<table>
<thead>
<tr>
<th>Settimana 2</th>
<th>Settimana 6</th>
<th>Settimana 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2.85**</td>
<td>-3.11**</td>
<td>-2.80**</td>
</tr>
<tr>
<td>-1.22</td>
<td>-0.95</td>
<td></td>
</tr>
</tbody>
</table>

Valori al basale
Placebo: 5.39/giorno
OnabotulinumtoxinA100 U: 5.49/giorno

**p<0.001 vs. placebo.
UI, incontinenza urinaria.

1. Adattato da Nitti et al_JUrol_2013
2. Chapple, EurUrol 2013
Miglioramenti clinicamente significativi in tutti i domini della I-QOL.

Variazione rispetto al basale dei punteggi della I-QOL alla 12^ settimana.

<table>
<thead>
<tr>
<th>Domini</th>
<th>Variazione media rispetto al basale</th>
<th>Placebo</th>
<th>Onab-A 100 U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comportamento evitante e limitativo</td>
<td>6,6</td>
<td>23,7</td>
<td>**</td>
</tr>
<tr>
<td>Impatto psicosociale</td>
<td>6,3</td>
<td>20,5</td>
<td>**</td>
</tr>
<tr>
<td>Imbarazzo sociale</td>
<td>6,8</td>
<td>23,8</td>
<td>**</td>
</tr>
<tr>
<td>Punteggio totale</td>
<td>6,6</td>
<td>22,8</td>
<td>**</td>
</tr>
</tbody>
</table>

**p<0.0001 vs. placebo.

I-QOL, Questionario sulla qualità della vita specifico per l'incontinenza..

Adattato da Nitti W et Al 2012 J of Urology
La maggioranza dei pazienti non aveva bisogno del CIC

*Pazienti che hanno avuto bisogno del CIC in qualsiasi momento durante il 1° ciclo di trattamento. CIC, cateterismo intermittente pulito.

CIC = 6.5% (36/552 pazienti)*

% dei pazienti
- Non ha iniziato il CIC
- Ha usato il CIC ≤6 settimane
- Ha usato il CIC >6 e ≤12 settimane
- Ha usato il CIC >12 e ≤18 settimane
- Ha usato il CIC >18 e ≤24 settimane
- Ha usato il CIC >24 settimane

Le percentuali del CIC sono basse e principalmente transitorie

Nitti W et al 2012 J of Urology
Chapple C, et al, European Urology, 201
Il tempo medio per la richiesta di un nuovo trattamento da parte del paziente è ~6 mesi

Il tempo medio della durata della risposta dopo inoculo di OnabotulinumtoxinA in base alla richiesta del paziente di un nuovo trattamento, era di 166 giorni (~24 settimane)

Gestione dell’incontinenza urinaria: Linee guida EAU 2013\(^1\)

<table>
<thead>
<tr>
<th>Tossina botulinica di tipo A (intravescicale; 100–300 U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proporre iniezioni intravescicali di tossina botulinica di tipo A ai pazienti affetti da incontinenza urinaria refrattari alla terapia antimuscarinica (A*)</td>
</tr>
<tr>
<td>Avvertire i pazienti della durata limitata della risposta, del possibile prolungato bisogno di autocateterismo (verificare che siano disposti e capaci di farlo), e del rischio di infezioni delle vie urinarie (A*)</td>
</tr>
<tr>
<td>Inoltre, i pazienti devono essere informati dello stato di autorizzazione della tossina botulinica di tipo A, e che gli effetti negativi a lungo termine, anche se improbabili, rimangono incerti (A*)</td>
</tr>
</tbody>
</table>


* Raccomandazione EAU di Grado A: In base a studi clinici di buona qualità e la consistenza riguardo le raccomandazioni specifiche e che includono almeno uno studio clinico randomizzato

EAU, European Association of Urology.

ILEOCYSTOPLASTY
Specialized Management of Urinary Incontinence in Women

**History/Symptom Assessment**
- Incontinence on physical activity
- Incontinence with mixed symptoms
- Incontinence with urgency/frequency
- Assess for pelvic organ mobility/prolapse
- Consider imaging of the UT/pelvic floor
- Urodynamics (see notes)

**Clinical Assessment**

**Urodynamic Stress Incontinence (USI)**
- Treat most bothersome symptom first

**Mixed Incontinence (USI/DOI)**

**Detrusor Overactivity Incontinence (DOI)**
- Bladder outlet obstruction
- Underactive detrusor

**Incontinence associated with poor bladder emptying**
- Consider:
  - Urethrocystoscopy
  - Further imaging
  - Urodynamics

**Diagnosis**

**Treatment**
- If initial therapy fails:
  - Stress incontinence surgery
  - Bulking agents
  - Tapes and slings
  - Colposuspension

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

- Correct anatomic bladder outlet obstruction (e.g., genito-urinary prolapse)
- Intermittent catheterization

- Correct anomaly
  - Treat pathology

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

Lower urinary tract anomaly/pathology
WHAT CAN WE DO IN WOMEN?
Low-tension Mid-Urethral Sling

Tension free intravaginal slingplasty

Ulmsten & Petros 1995
TVT

at rest

at stress
Low-tension Mid-Urethral Sling

TOT - TRANSOBTURATOR TAPE

- Tape runs through both obturator foramina
- Cystoscopy not necessary (bladder perforation unlikely)

Delorme 2001
Single-incision mini-sling (SIMS) vs standard midurethral slings (SMUS) for female SUI

- Systematic review and meta-analysis of n=25 RCTs including N=3,114 women with SUI (literature search until March 2013)
- SIMS:
  - Mini-Arc: n=6 studies; N=566 women
  - Ajust: n=3 studies; N=350 women
  - Ophira: n=1 study; N=130 women
  - Contasure: n=1 study; N=257 women
  - TFS: n=1 study; N=80 women
  - Solyx: n=1 study; N=30 women
  - TVT-Secur: n=12 studies; N=1,606 women
- No significant differences between SIMS and SMUS (when excluding TVT-Secur) in patient-reported cure rate and objective cure rate at 12-24 mo FU

<table>
<thead>
<tr>
<th>RR (95% CI; P value)</th>
<th>SIMS vs SMUS</th>
<th>SIMS excl. TVT-Secur vs SMUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient reported cure rate</td>
<td>0.90 (0.85-0.95; P=0.0003)</td>
<td>0.96 (0.88-1.03; P=0.26)</td>
</tr>
<tr>
<td>Objective cure rate</td>
<td>0.90 (0.84-0.95; P=0.0003)</td>
<td>0.97 (0.92-1.02; P=0.26)</td>
</tr>
</tbody>
</table>

RR: relative risk; CI: confidence interval
Single-incision mini-sling (SIMS) vs standard midurethral slings (SMUS) for female SUI

• SIMS vs SMUS
  – Better operative and peri-operative outcomes
  – Earlier return to normal activities and work

<table>
<thead>
<tr>
<th>SIMS vs SMUS</th>
<th>WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time</td>
<td>-2.04 min (-3.51 to -0.58 min)</td>
</tr>
<tr>
<td>Postoperative groin pain</td>
<td>-2.51 (-3.62 to -1.40)</td>
</tr>
</tbody>
</table>

WMD: weighted mean difference; CI: confidence interval

• No difference in lower urinary tract injuries, postoperative voiding difficulties, de-novo urgency/worsening of pre-existing urgency, QoL and sexual function

• Vaginal erosion and repeat continence surgery were significantly higher in the SIMS vs SMUS group but this was mainly due to significant difference in the TVT Secur group

SIMS, excluding TVT-Secur, seem to have a similar cure rate and better post-operative outcomes vs SMUS at 12-24 mo FU
<table>
<thead>
<tr>
<th>Recommendations for surgery for uncomplicated stress urinary incontinence in women</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer the mid-urethral sling to women with uncomplicated stress urinary incontinence as the preferred surgical intervention whenever available.</td>
<td>A</td>
</tr>
<tr>
<td>Warn women who are being offered a retropubic insertion of mid-urethral sling about the relatively higher risk of peri-operative complications compared to transobturator insertion.</td>
<td>A</td>
</tr>
<tr>
<td>Warn women who are being offered transobturator insertion of mid-urethral sling about the higher risk of pain and dyspareunia in the longer term.</td>
<td>A</td>
</tr>
<tr>
<td>Warn women who are being offered a single-incision sling that long-term efficacy remains uncertain.</td>
<td>A</td>
</tr>
<tr>
<td>Do a cystourethroscopy as part of the insertion of a mid-urethral sling.</td>
<td>C</td>
</tr>
<tr>
<td>Offer colposuspension (open or laparoscopic) or autologous fascial sling for women with stress urinary incontinence if mid-urethral sling cannot be considered.</td>
<td>A</td>
</tr>
<tr>
<td>Warn women undergoing autologous fascial sling that there is a high risk of voiding difficulty and the need to perform clean intermittent self-catheterisation; ensure they are willing and able to do so.</td>
<td>C</td>
</tr>
<tr>
<td>Inform older women with stress urinary incontinence about the increased risks associated with surgery, including the lower probability of success.</td>
<td>B</td>
</tr>
<tr>
<td>Inform women that any vaginal surgery may have an impact on sexual function.</td>
<td>B</td>
</tr>
<tr>
<td>Only offer new devices, for which there is no level 1 evidence base, as part of a structured research programme.</td>
<td>A*</td>
</tr>
<tr>
<td>Only offer adjustable mid-urethral sling as a primary surgical treatment for stress urinary incontinence as part of a structured research programme.</td>
<td>A*</td>
</tr>
<tr>
<td>Do not offer bulking agents to women who are seeking a permanent cure for stress urinary incontinence.</td>
<td>A*</td>
</tr>
</tbody>
</table>

* Recommendation based on expert opinion.
<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-urethral injection of bulking agent may provide short-term improvement in symptoms (3 months), but not cure, in women with SUI.</td>
<td>2a</td>
</tr>
<tr>
<td>Repeat injections to achieve therapeutic effect are often required.</td>
<td>2a</td>
</tr>
<tr>
<td>Bulking agents are less effective than colposuspension or autologous sling for cure of SUI.</td>
<td>2a</td>
</tr>
<tr>
<td>Adverse effect rates are lower compared to open surgery.</td>
<td>2a</td>
</tr>
<tr>
<td>There is no evidence that one type of bulking agent is better than another type.</td>
<td>1b</td>
</tr>
<tr>
<td>Transperineal route of injection may be associated with a higher risk of urinary retention compared to the transurethral route.</td>
<td>2b</td>
</tr>
</tbody>
</table>
## Acceptability of Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Yes (%)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic floor exercises for 6 months</td>
<td>60</td>
<td>26</td>
</tr>
<tr>
<td>Pelvic floor exercises for life</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>Regular drugs for life</td>
<td>14</td>
<td>69</td>
</tr>
<tr>
<td>Drugs to take as needed</td>
<td>51</td>
<td>32</td>
</tr>
<tr>
<td>Major operation (85% cure; 2% risk of catheterising)</td>
<td>23</td>
<td>57</td>
</tr>
<tr>
<td>Minor operation (85% cure; 2% risk of catheterising)</td>
<td>38</td>
<td>43</td>
</tr>
<tr>
<td>Clinic procedure (60% improvement; no long term risk)</td>
<td>57</td>
<td>24</td>
</tr>
<tr>
<td>Long term catheter</td>
<td>3</td>
<td>79</td>
</tr>
<tr>
<td>Learning to self catheterise</td>
<td>11</td>
<td>73</td>
</tr>
</tbody>
</table>

Robinson et al, 2003
WHAT CAN WE DO IN MEN?
Agenda

• Male urinary stress incontinence
  – Bulking agents
  – Fixed male slings
  – Adjustable male slings
  – Compression devices in males
    • Circunferential (AUS)
    • Non Circunferential (Adjust. Balloons)
Agenda

• Male urinary stress incontinence
  – Bulking agents
  – Fixed male slings
  – Adjustable male slings
  – Compression devices in males
    • Circunferential (AUS)
    • Non Circunferential (Adjust. Balloons)
Bulking agents

- Few studies
- The only one included in a Cochrane Rev was on Macroplastique
  - Bulking agent vs. AUS:
    Continence rate 46% vs. 82%

**Evidence summary**

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no evidence that bulking agents cure post-prostatectomy incontinence.</td>
<td>2a</td>
</tr>
<tr>
<td>There is weak evidence that bulking agents can offer temporary, short-term,</td>
<td>3</td>
</tr>
<tr>
<td>improvement in QoL in men with post-prostatectomy incontinence.</td>
<td></td>
</tr>
<tr>
<td>There is no evidence that one bulking agent is superior to another.</td>
<td>3</td>
</tr>
</tbody>
</table>
Agenda

• Male urinary stress incontinence
  – Bulking agents
  – Fixed male slings
  – Adjustable male slings
  – Compression devices in males
    • Circumferential (AUS)
    • Non Circumferential (Adjust. Balloons)
Non adjustable Slings

InVance Bone Anchor

Advance Transobturator

I-STOP TOMS

VIRTUE Quadratic Sling
Fixed Male slings

Subjective cure rate: 50%; Improvement 30%; Failure: 20%

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is limited short-term evidence that fixed male slings cure or improve post-prostatectomy incontinence in patients with mild-to-moderate incontinence.</td>
<td>3</td>
</tr>
<tr>
<td>Men with severe incontinence, previous radiotherapy or urethral stricture surgery may have less benefit from fixed male slings.</td>
<td>3</td>
</tr>
<tr>
<td>There is no evidence that one type of male sling is better than another.</td>
<td>3</td>
</tr>
</tbody>
</table>
Success - 75.8% chance if preoperative pad weight < **496** gm
Odds of a successful surgery if pad wt < 496 gm are 7X greater than
odds of successful surgery if pad wt > 496 gm
Agenda

• Male urinary stress incontinence
  – Bulking agents
  – Fixed male slings
  – Adjustable male slings
  – Compression devices in males
    • Circunferential (AUS)
    • Non Circunferential (Adjust. Balloons)
### Evidence summary

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is limited evidence that adjustable male slings can cure or improve SUI in men.</td>
<td>3</td>
</tr>
<tr>
<td>There is limited evidence that early explantation rates are high.</td>
<td>3</td>
</tr>
<tr>
<td>There is no evidence that adjustability of the male sling offers additional benefit over other types of sling.</td>
<td>3</td>
</tr>
</tbody>
</table>
Agenda

- Male urinary stress incontinence
  - Bulking agents
  - Fixed male slings
  - Adjustable male slings
  - Compression devices in males
    - Circumferential (AUS)
    - Non Circumferential (Adjust. Balloons)
Adj. Ballons
Inflating the ballons...
Adj. Ballons

Improved pts: 65%

Very limited short-term evidence suggests that the non-circumferential compression device (ProACT®) is effective for treatment of post-prostatectomy SUI.

The non-circumferential compression device (ProACT®) is associated with a high failure and complication rate leading to frequent explantation.
Agenda

• Male urinary stress incontinence
  – Bulking agents
  – Fixed male slings
  – Adjustable male slings
  – Compression devices in males
    • Circunferential (AUS)
    • Non Circunferential (Adjust. Balloons)
AMS 800 (AMS)

- Fluid reservoir
- Urethral compression cuff
- Activation pump
- Control pump
- Pressure-regulating balloon
- Color-coded, kink-resistant tubing
- Surface treated, narrow-backed cuff

Enhances continence, simplifies tubing connections, reduces kinking, maintains continence, lengthens cuff wear, decreases surgical time.
AMS 800 (AMS)

- Two systematic reviews (poor quality studies)
- Continence rate: 80%
  - Lower in pts after RXT
  - More erosion if complete continence
- Effective as «salvage» treatment