

# Female Incontinence: *Common, Challenging, and Often Treatable*



Sarah McAchran  
May 21, 2016

# Objectives

- Urinary Incontinence in Women
  - Definitions & Prevalence
- Stress Incontinence
  - Etiology
  - Diagnosis
  - Treatment options
- Urge Incontinence (Overactive Bladder)
  - Etiology
  - Diagnosis
  - Treatment options



# Background

- What is it?
- Who has it?
- Why learn about it?



# What is Urinary Incontinence?

- **INVOLUNTARY** loss or leakage of urine
- **STRESS INCONTINENCE**
  - Related to activity
- **OVERACTIVE BLADDER**
  - *Urgency*—Sudden compelling desire to void that is difficult to defer
  - *Frequency*—Urinating greater than 8 times/ 24 hours
  - *Nocturia*—Waking up at night to urinate; more than twice is abnormal



# Bladder Control

*18 million women in the U.S. have  
urinary incontinence*



- Wu, Jennifer et al. Forecasting the Prevalence of Pelvic Floor Disorders. *Obstet and Gynecol*, 114 (6), December 2009.



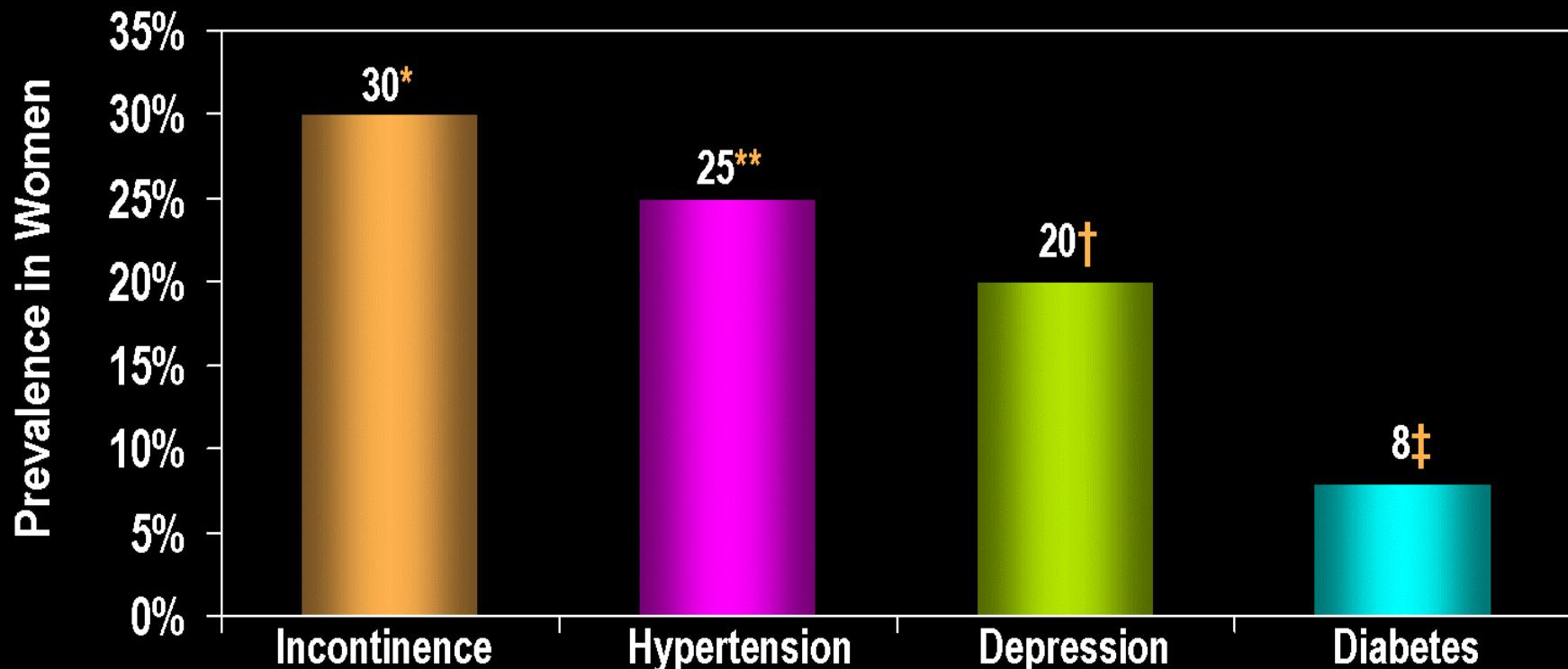
# Pop Quiz

Rank these common diseases from most to least common:

- A. High Blood Pressure, Depression, Incontinence
- B. Incontinence, High Blood Pressure, Depression
- C. Depression, Diabetes, Incontinence



# Urinary Incontinence Is More Prevalent Than Other Chronic Diseases in Women

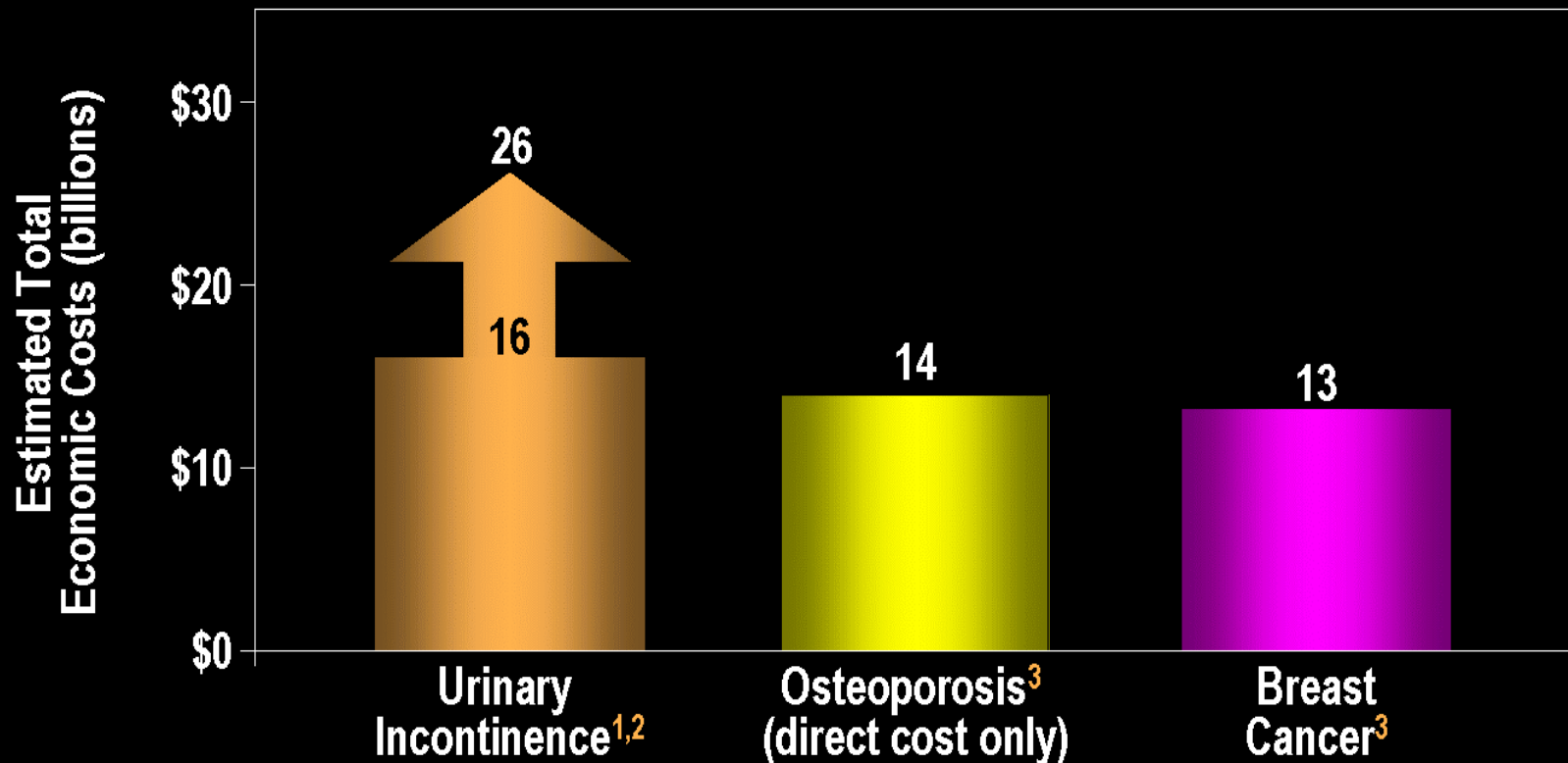


\*AHCPR. Rockville, Maryland: US Dept of Health and Human Services; 1996. 96-0682. \*\*AHA. 2001.

†American Family Physician. 2001. ‡NIDDK. 2001.

To Navigate: Use "Page Down" to move forward, "Page Up" to move backward and "Esc" to exit.

# Urinary Incontinence Expenditures Are Greater Than Other Women's Health Conditions



1. Wilson L, et al. *Obstet Gynecol.* 2001;98(3):398-406.

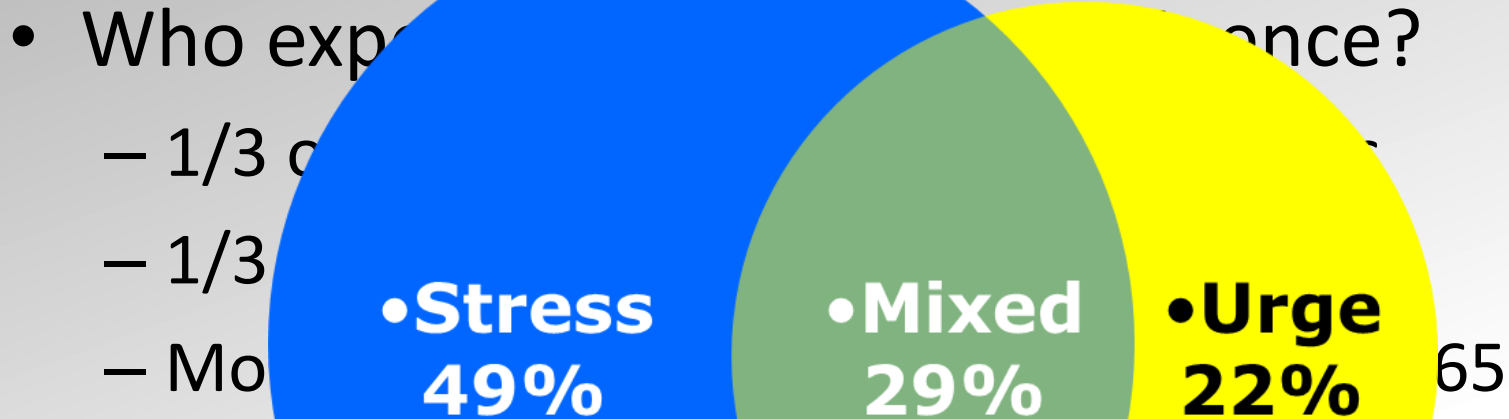
2. Wagner TH, Hu TW. *Urology.* 1998;51(3):355-361.

3. NIH. Electronic citation; 2000.

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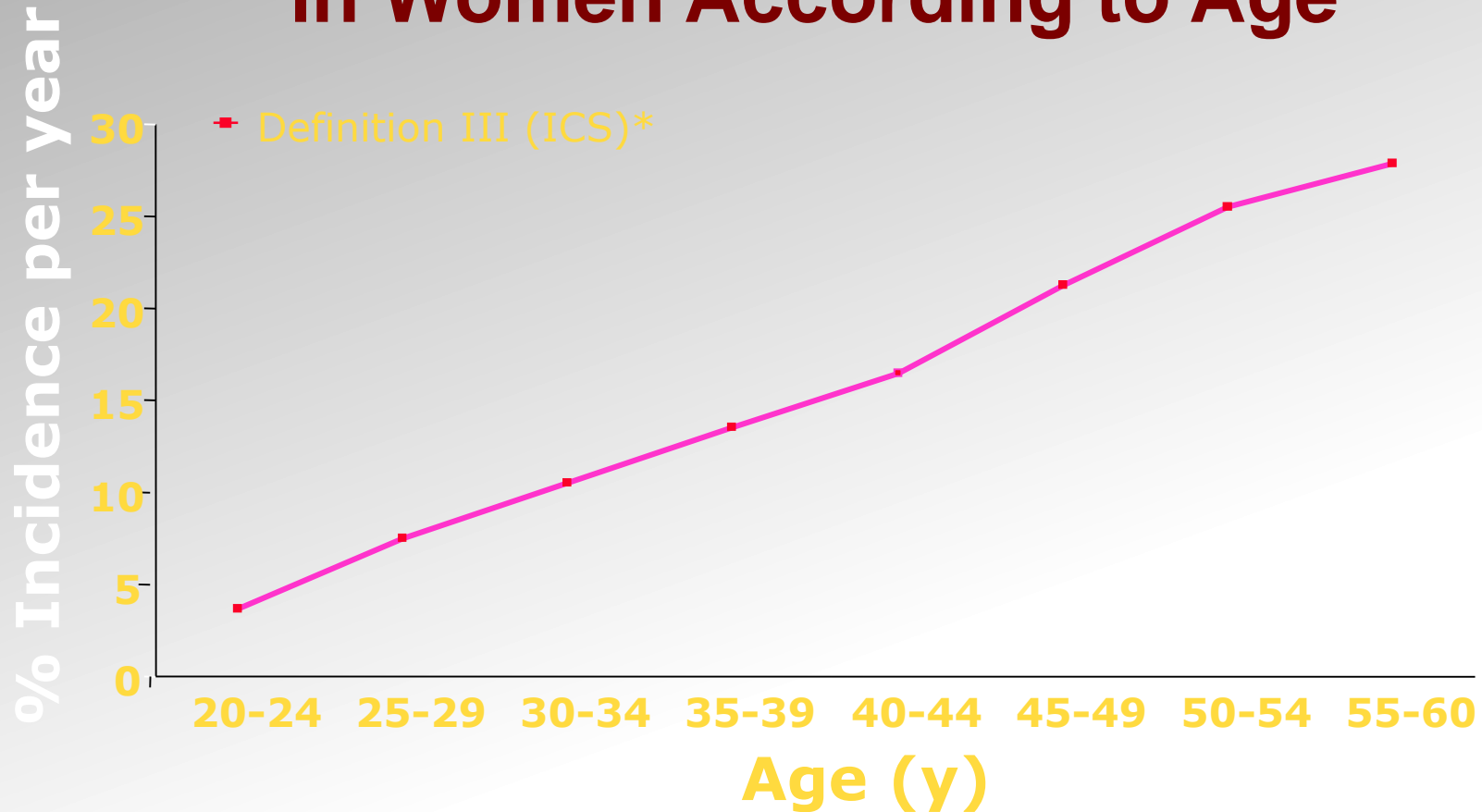
# Urinary Incontinence— Prevalence



Hunsakaar, Arnold, Burgio, et al. 2000  
Gorina, Schappert, Bercovitz, et al. 2014



# Cumulative Incidence of Incontinence in Women According to Age



*\*Per International Continence Society; requires objective demonstrability and presence of hygienic or social problem for uncontrolled loss of urine to be acknowledged as UI.*



# Under-Reported

- Most patients do not mention the problem to their doctor, some wait up to 3 years
  - Self-manage
  - 59% of patients do not seek help because they believe no effective treatment is available
  - 73% of patients who seek treatment are currently not on medication
- Most patients do not mention the problem to their friends
- Most people think incontinence is part of normal aging



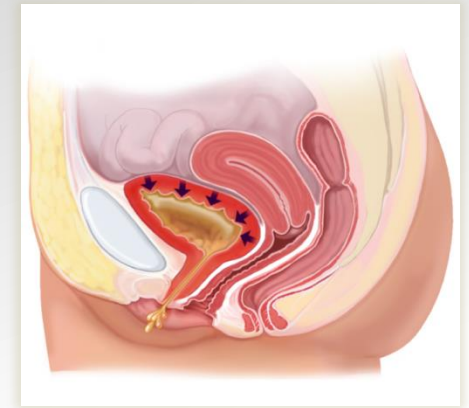
# Misconceptions

- “Part of normal aging or everyday life”
- “Not severe or frequent enough to treat”
- “No effective treatments exist”
- “Treatment would not help”
- “Too embarrassing to discuss”
- “I am the only one”
- “Mother/family had it”



# Types of Urinary Incontinence

- **Stress incontinence:**
  - Urine leaks with activities (coughing, sneezing, laughing, lifting, exercising).
- **Urge incontinence/overactive bladder (OAB):**
  - “Have to go **now**” sensation (urgency).
  - “Have to go **now**” with leakage (urge incontinence).
  - “Have to go **often**” (frequency).
  - Going often during the night (nocturia).
- **Other types:**
  - Mixed incontinence (stress and urge).
  - Continuous (unpredictable) incontinence.



▪ National Institute of Diabetes and Digestive and Kidney Diseases. Urinary Incontinence in Women, [kidney.niddk.nih.gov/KUDiseases/pubs/uiwomen](http://kidney.niddk.nih.gov/KUDiseases/pubs/uiwomen).



# STRESS URINARY INCONTINENCE



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# Stress Urinary Incontinence



Laughing shouldn't make you feel uncomfortable... but it can



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# Stress Urinary Incontinence

- 1 in 3 women will experience stress urinary incontinence (SUI) in their lifetime.
- It occurs when activity such as laughing or coughing or bending causes urine to leak out.
- The amount of urine that is lost can be a few drops to tablespoons or more.





# Resting



# Coughing



# SUI Risk Factors

- Caucasian or Hispanic race
- Overweight or Obesity
- Smoking
- Chronic coughing (asthma, GERD)
- Pregnancy and childbirth
- Nerve injuries to the lower back
- Pelvic Surgery



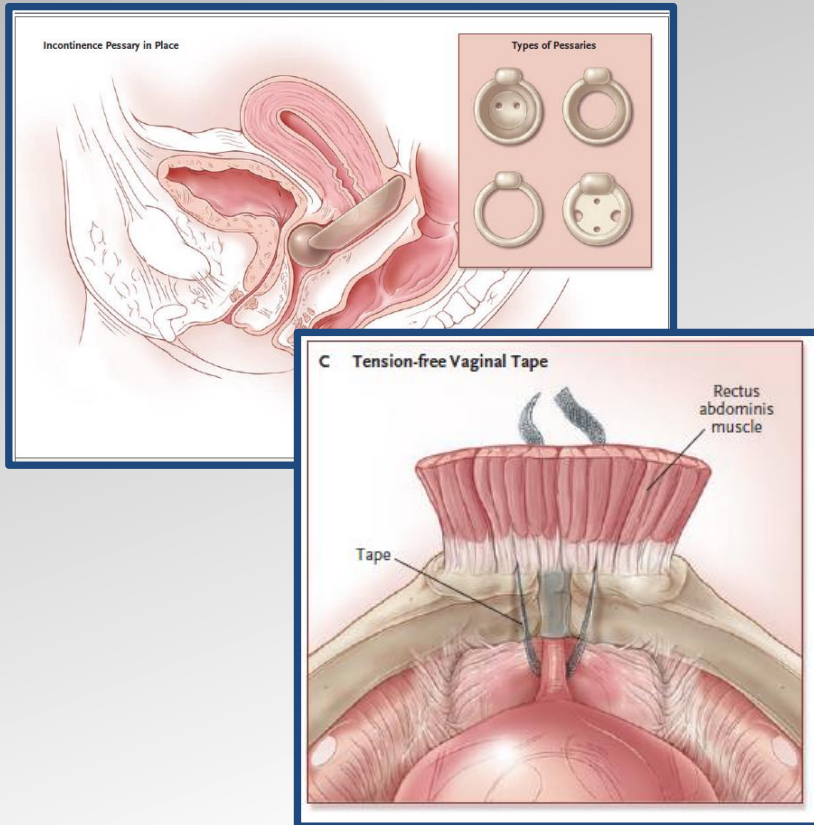
# Incontinence Diagnosis

- Review your medical history
  - Incontinence questionnaires
  - Bladder diary
- Physical examination
  - Pelvic exam
  - Cough Stress Test
- Urinalysis to rule out infection
- Urodynamics
- Cystoscopy



# Treatments—Stress Incontinence

## Goal: Improve Quality of Life



- Physical therapy:
  - Exercises to help strengthen and control the pelvic floor muscles.
  - Biofeedback.
- Pessary:
  - Treats incontinence and prolapse.
  - Different shapes and sizes.
  - Sized to fit each patient.
- Surgery:
  - Bulking agents
  - Retropubic Urethropexy
  - Fascial slings
  - Mesh slings

- Food and Drug Administration. Information for Patients for POP, [www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh).
- American Urological Foundation. A monograph from the AUA Foundation: Stress Urinary Incontinence. [http://www.urologyhealth.org/resourcecenter/bladder/bladderBrochures/SUI\\_Monograph.pdf](http://www.urologyhealth.org/resourcecenter/bladder/bladderBrochures/SUI_Monograph.pdf), 2011.



# Weight Loss

- Being overweight or obese leads to more chronic pressure on the pelvic floor
- *5-10% reduction in total body weight results in 50-70% reduction in SUI in women*
- This doesn't mean that everyone has to reach their ideal weight, but maintaining a healthy weight can be preventative

Subak et al, NEJM, 2009: 360:481-90

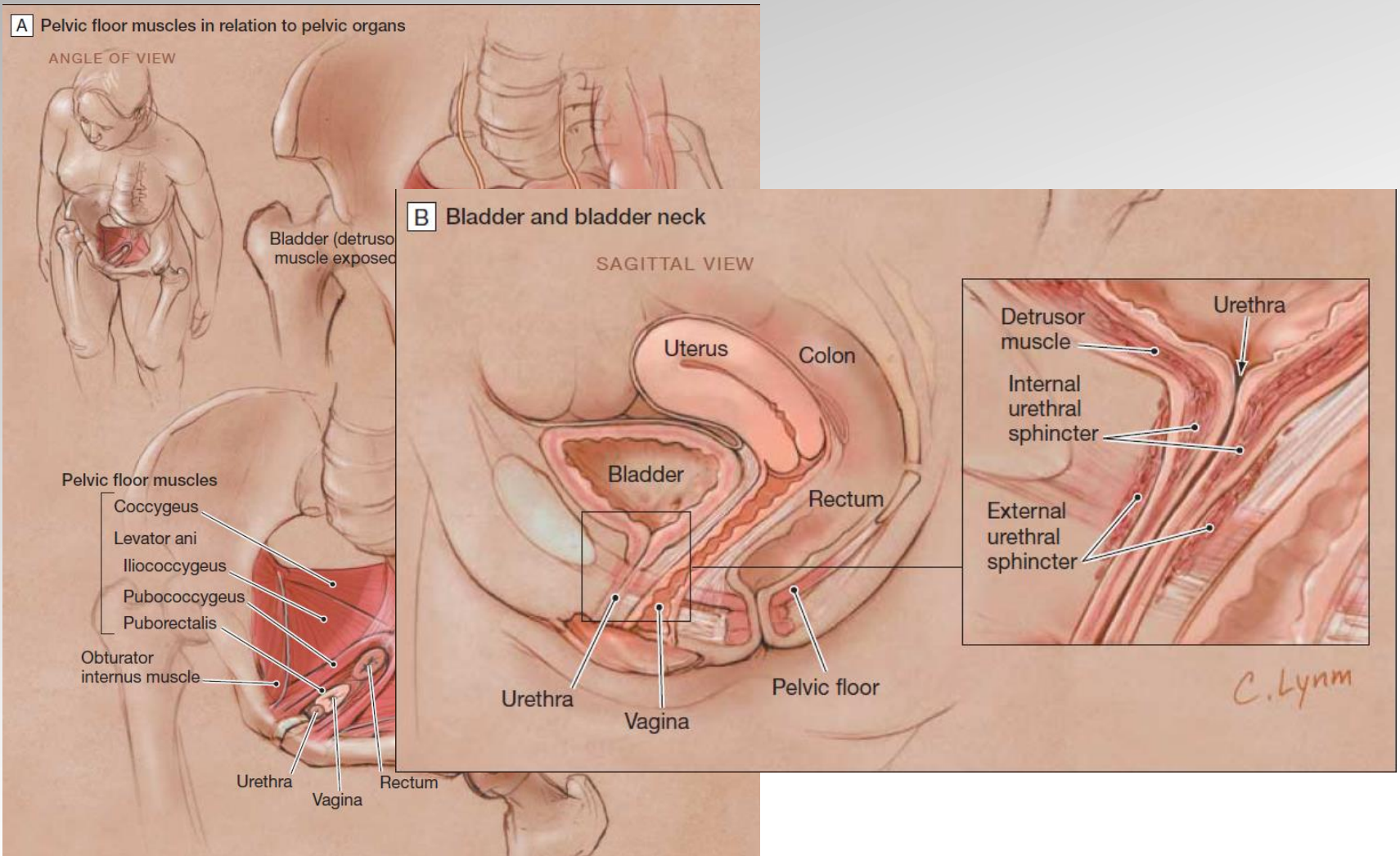


# Smoking Cessation

- Smoking cigarettes increases the likelihood that a woman will develop a chronic cough
- The chronic cough leads to increased pressure on the pelvic floor and increases a woman's risk of developing:
  - *STRESS URINARY INCONTINENCE*
  - *URGE URINARY INCONTINENCE*
  - *PELVIC ORGAN PROLAPSE*



# Pelvic Floor Physical Therapy



# Pelvic Floor Physical Therapy

- Consider working with a specialty-trained Pelvic Floor Physical Therapist
- In appropriately selected women, Pelvic Floor PT **reduced SUI by 33%**



## *Pelvic Floor Muscle Re-education* 277

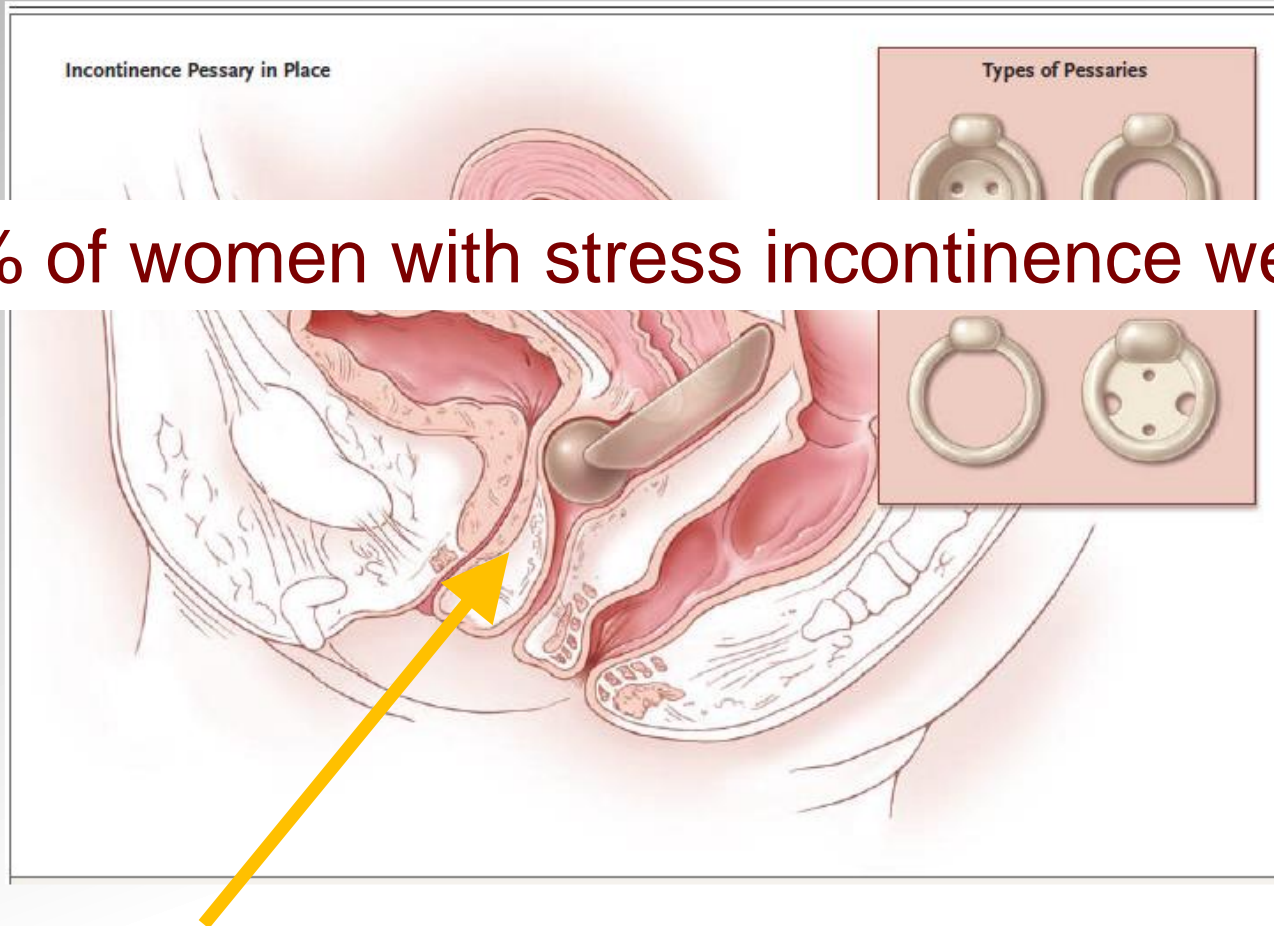
- |   |  |
|---|--|
| 0 | unable to isolate, or no perceived tightening                  |
| 1 | light contraction; unable to retain examiner's finger          |
| 2 | light contraction; unable to sustain tightening for 1 second   |
| 3 | moderate contraction; able to sustain tightening for 3 seconds |
| 4 | strong contraction; able to sustain tightening for 5 seconds   |

*FIG. 1.* Pelvic floor muscle contraction scale.





# Devices-Pessary

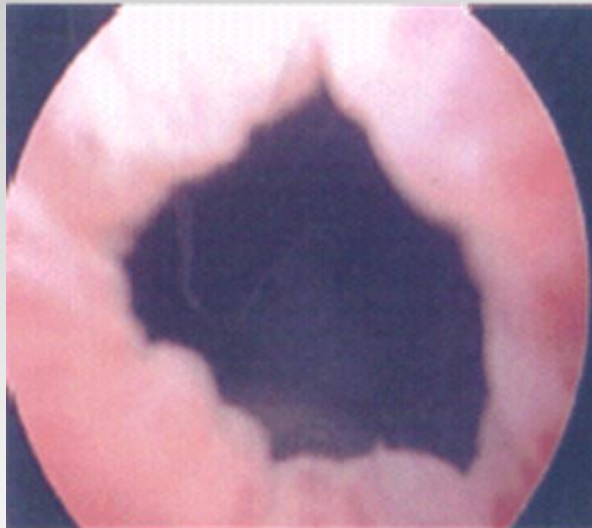


Knob sits under urethra to increase urethral support



# Urethral Bulking Agents

- Urethral bulking agent
  - A synthetic material is injected into the layers of the urethra to “bulk” it up and create outlet resistance



Bladder neck Incompetence



Bladder neck after  
Macroplastique injection

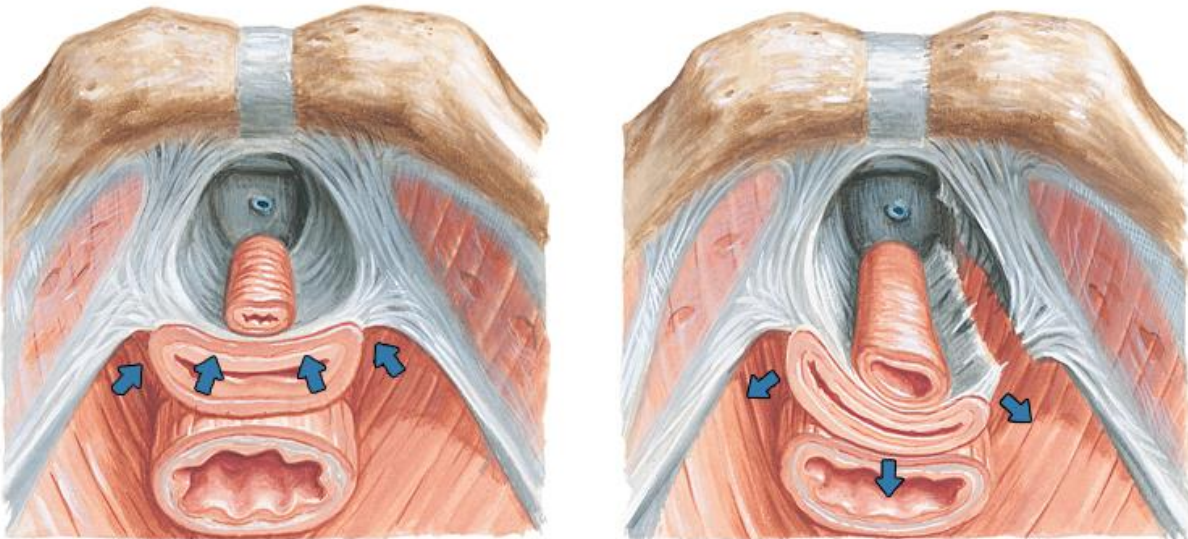


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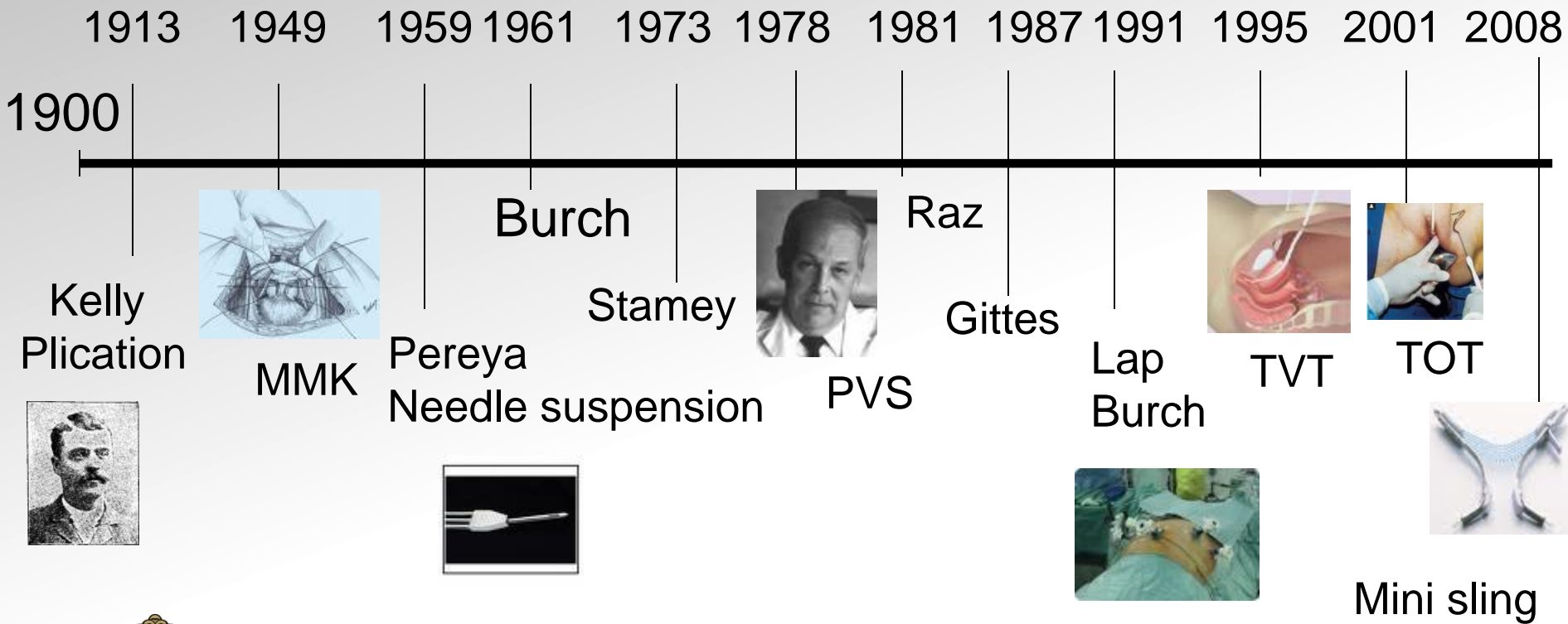
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JOHN A. CRAIG, MD  
C. Machado, M.D.  
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# History of Surgery for Stress Urinary Incontinence



# Theories & Treatments on Urinary Incontinence

Theory	Treatment
Hypermobility of the Bladder Neck and Proximal Urethra	Retropubic urethropexy (Burch or MMK) Pubovaginal Sling
Intrinsic Sphincteric Deficiency	Pubovaginal Sling
Loss of mid-urethral integrity	Midurethral slings (MUS)



# RETROPUBIC URETHROPEXY

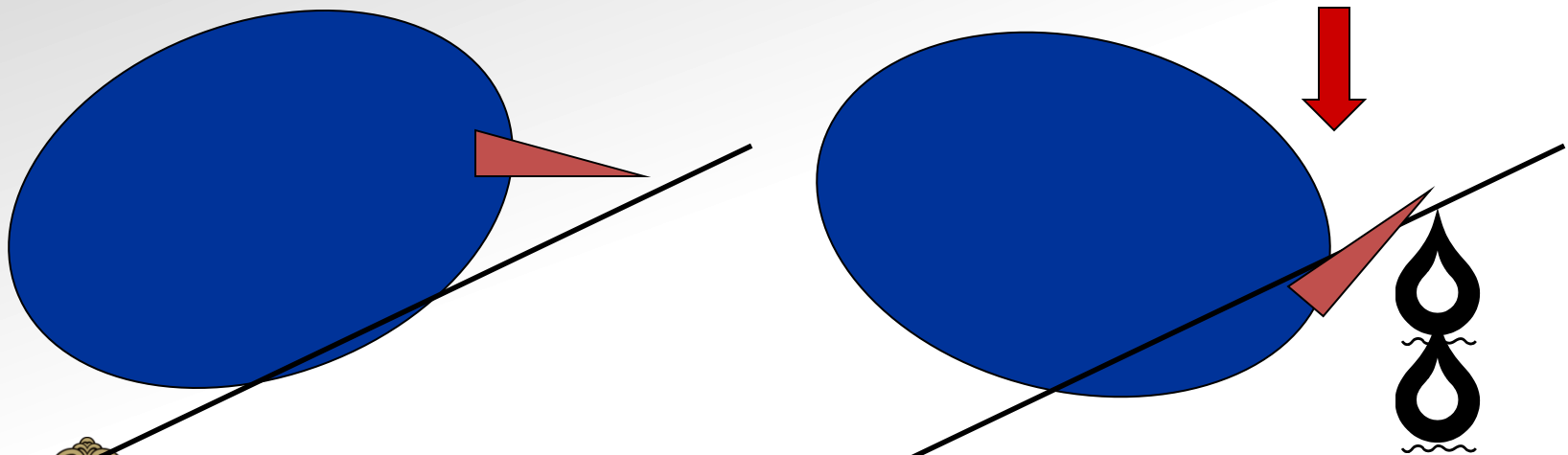


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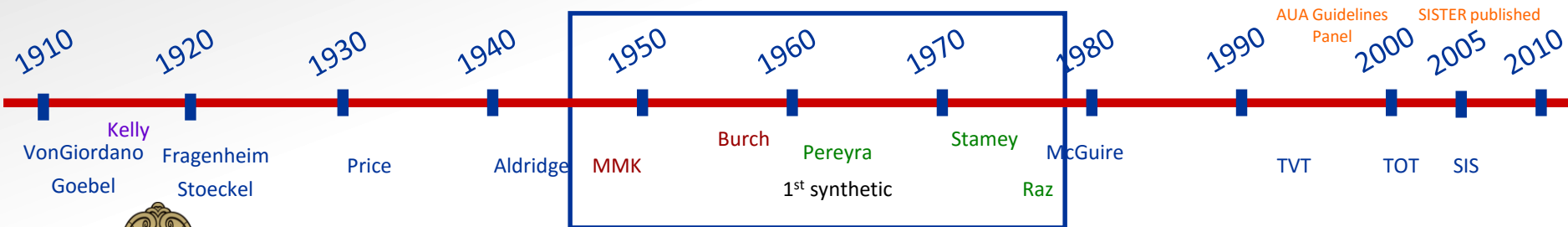
# Pressure Transmission

- Urethral compression when intrapelvic
- With descent, proximal urethra not compressible



# Restore Position

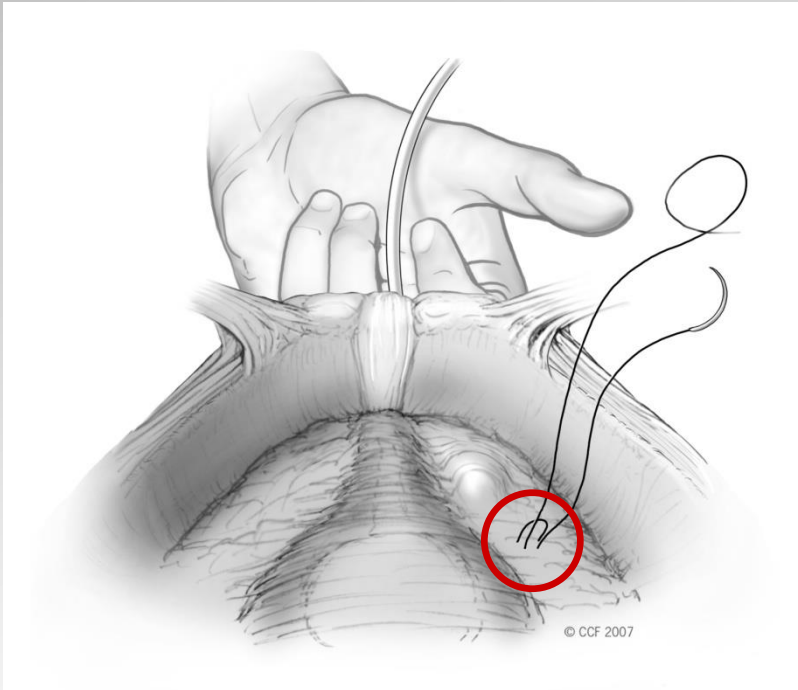
- Retropubic Urethropexy
- Needle suspensions
- Restore bladder neck / proximal urethra to a high retropubic position



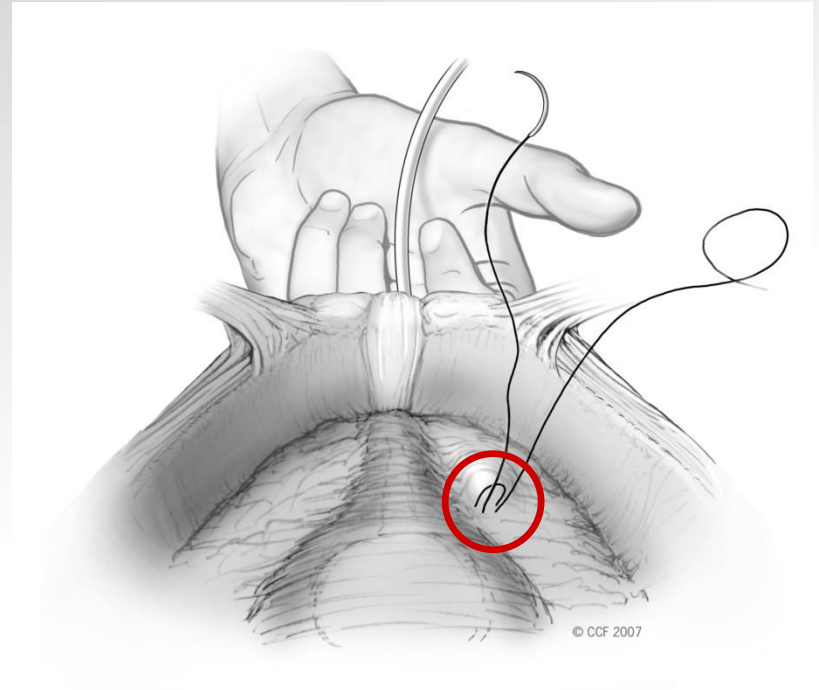


# Retropubic Urethropexy

## BURCH



## MMK



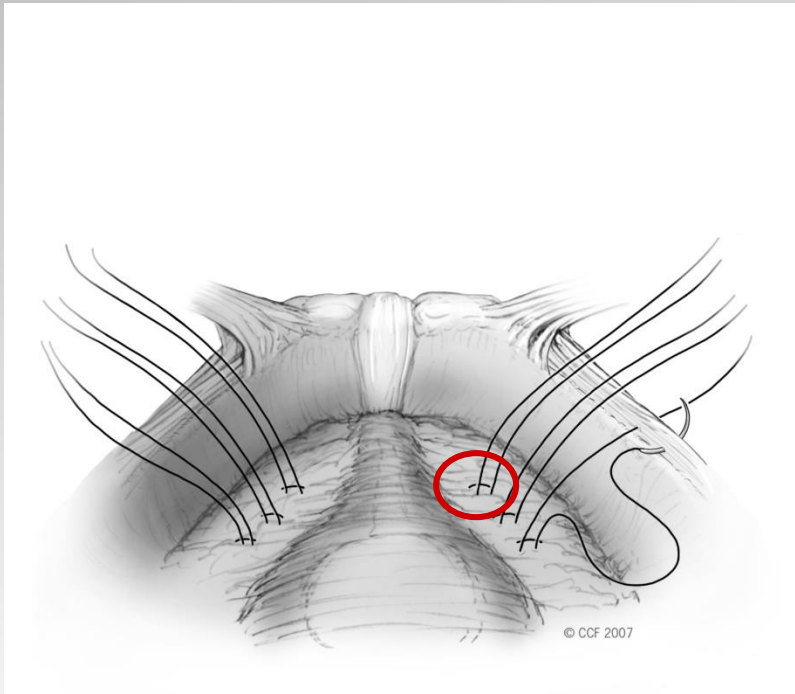
Vaginal finger aids in exposure of peri-urethral fascia & vaginal wall

Proximal suture is placed slightly proximal to the bladder neck

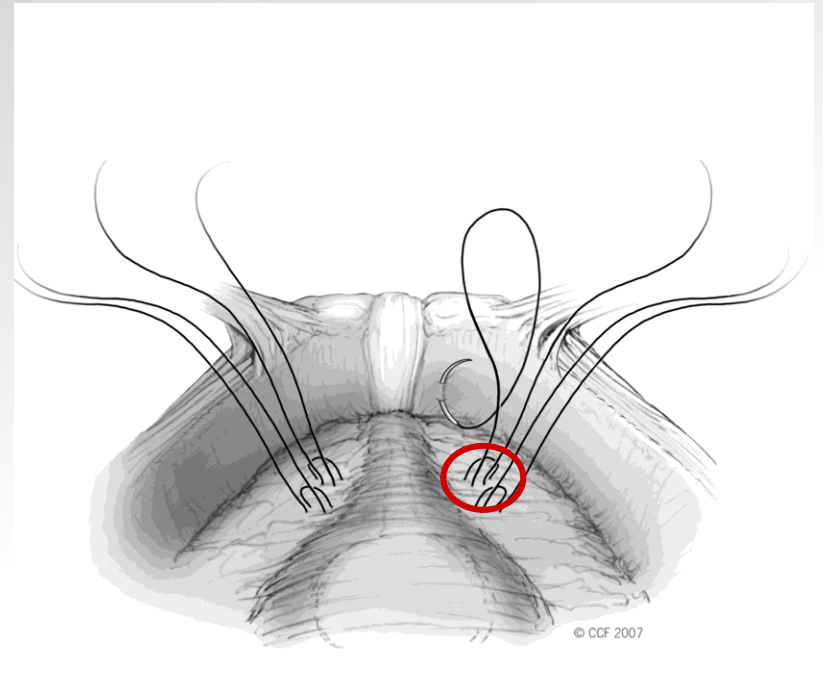


# Retropubic Urethropexy

## BURCH



## MMK

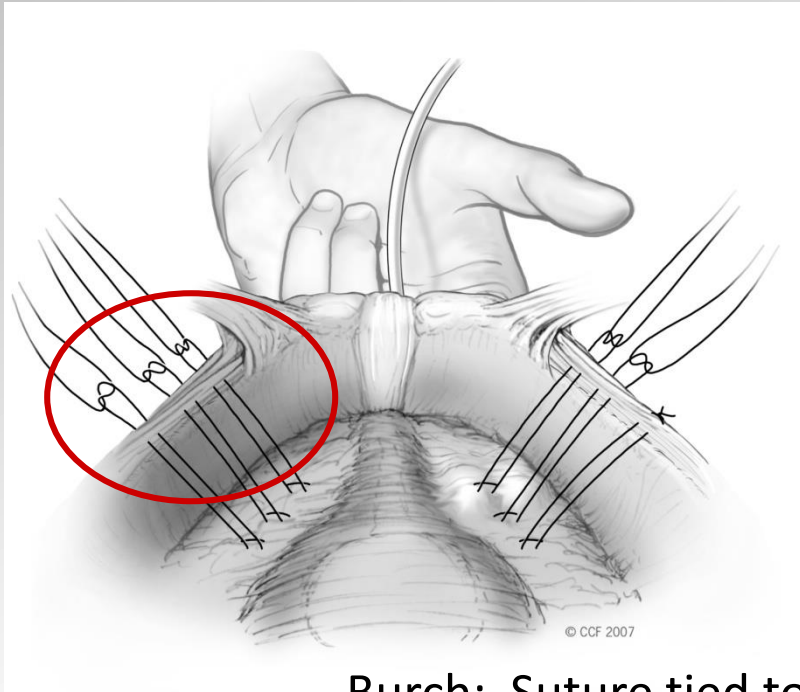


Distal suture is placed 2cm lateral to the proximal 1/3 of the urethra

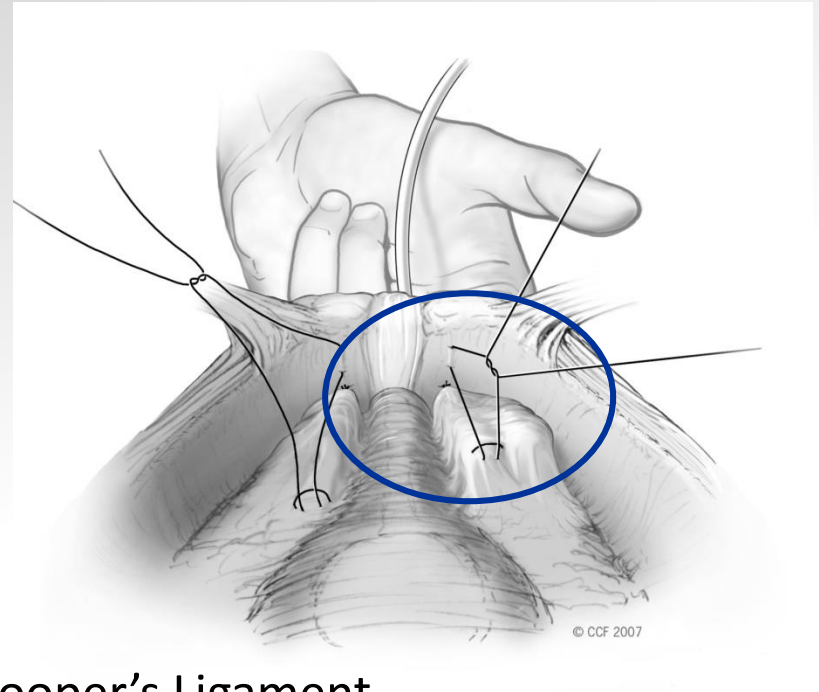


# Retropubic Urethropexy

BURCH



MMK



Burch: Suture tied to Cooper's Ligament

MMK: Suture tied periosteum of pubic symphysis

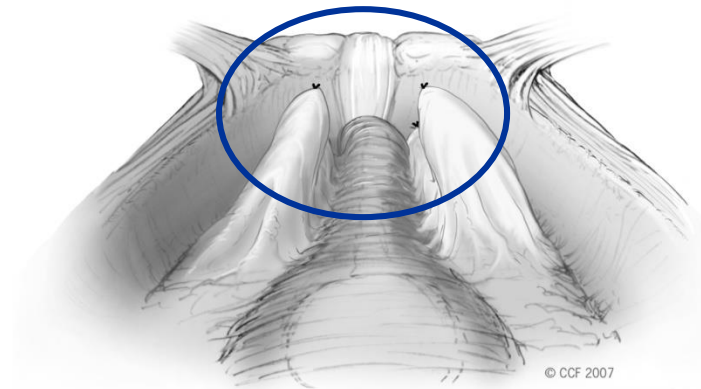
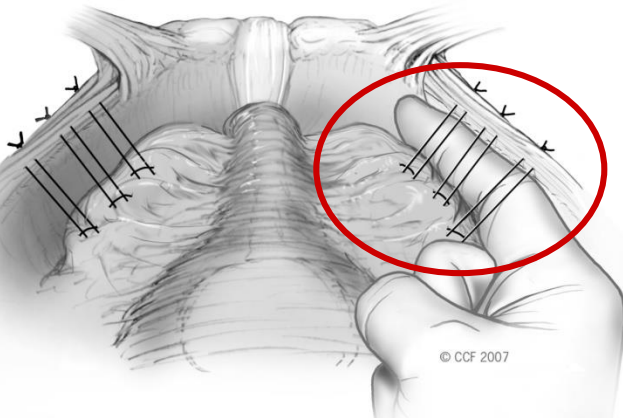


# Retropubic Urethropexy

## BURCH

## MMK

Suture placement is most likely to injure the obturator n. or entrap the ilioinguinal n.



Burch: The goal **is not** direct tissue apposition

MMK: Direct tissue apposition

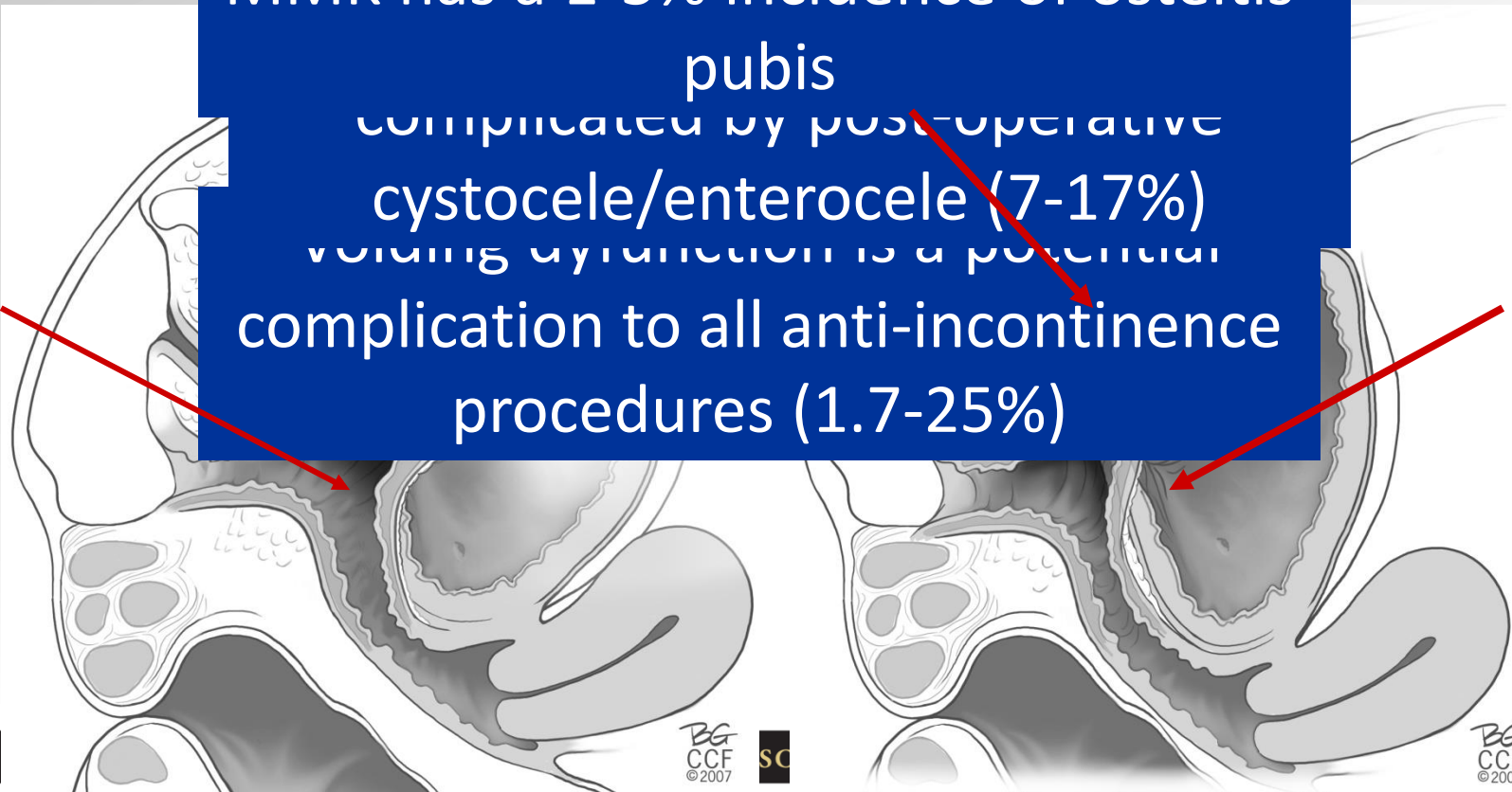


# Retropubic Urethropexy

BURCH

MMK

MMK has a 1-5% incidence of osteitis pubis complicated by postoperative cystocele/enterocele (7-17%) voiding dysfunction is a potential complication to all anti-incontinence procedures (1.7-25%)



# Burch Long Term Results

- N = 44 93% responded
- Follow up – average 8 ½ years
- 78% cured of SUI
- 12% significantly improved

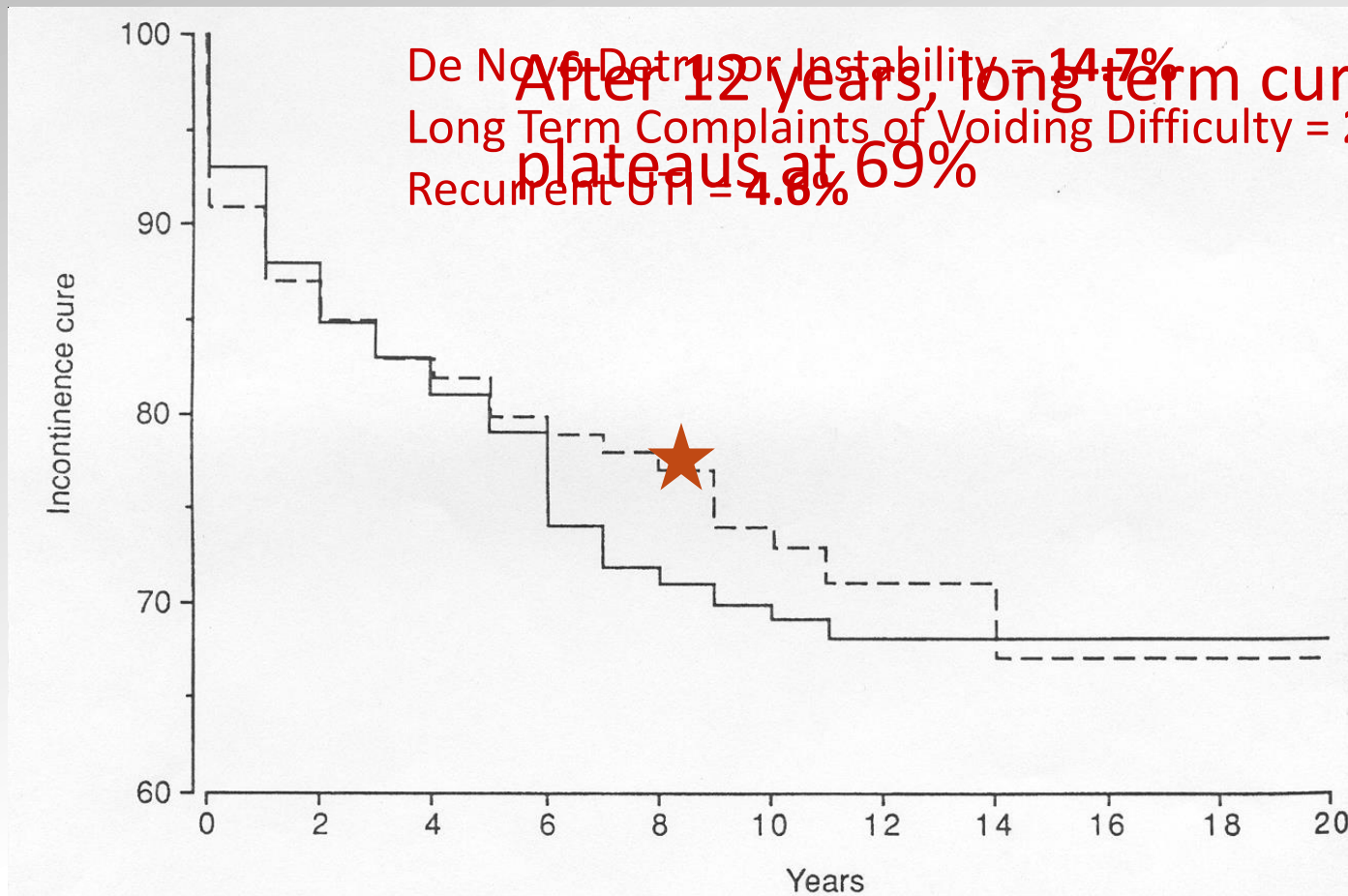
Valansky et al, Ceska Gynekol, 2002



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# Burch Long Term Results



# FASCIAL PUBOVAGINAL SLING

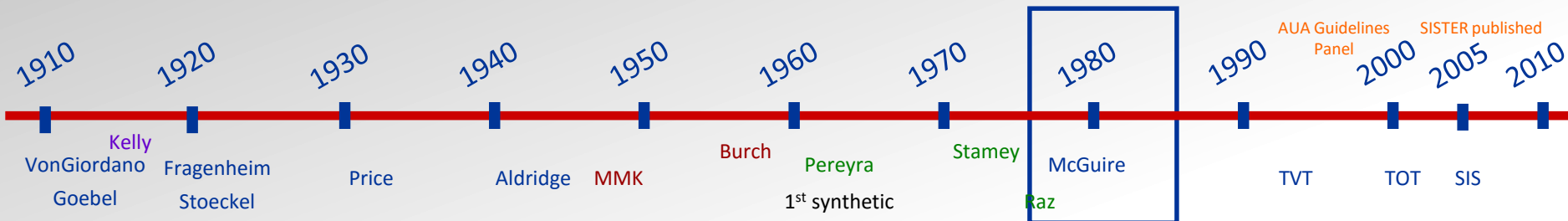


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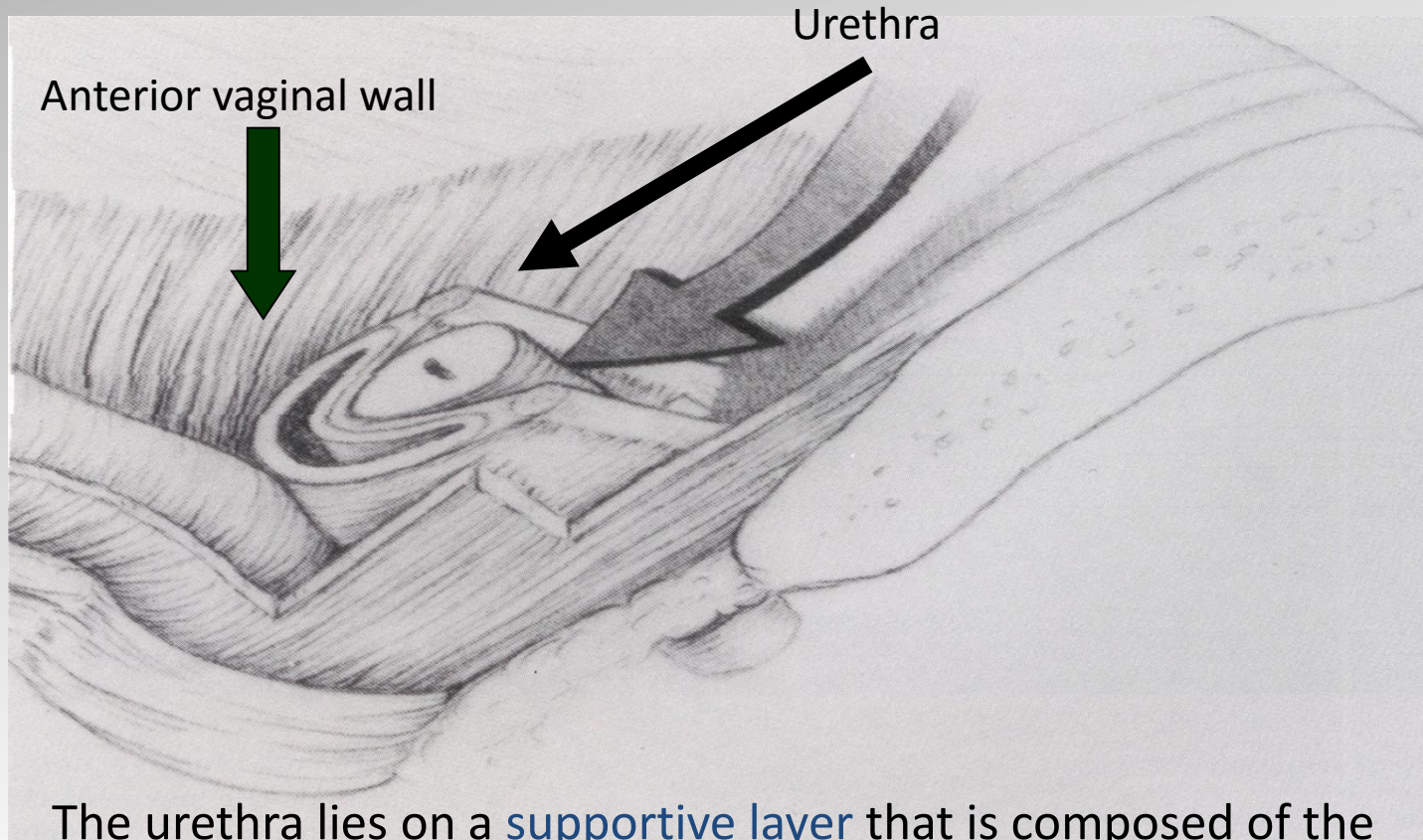
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# Revival of the Sling



# Hammock Hypothesis



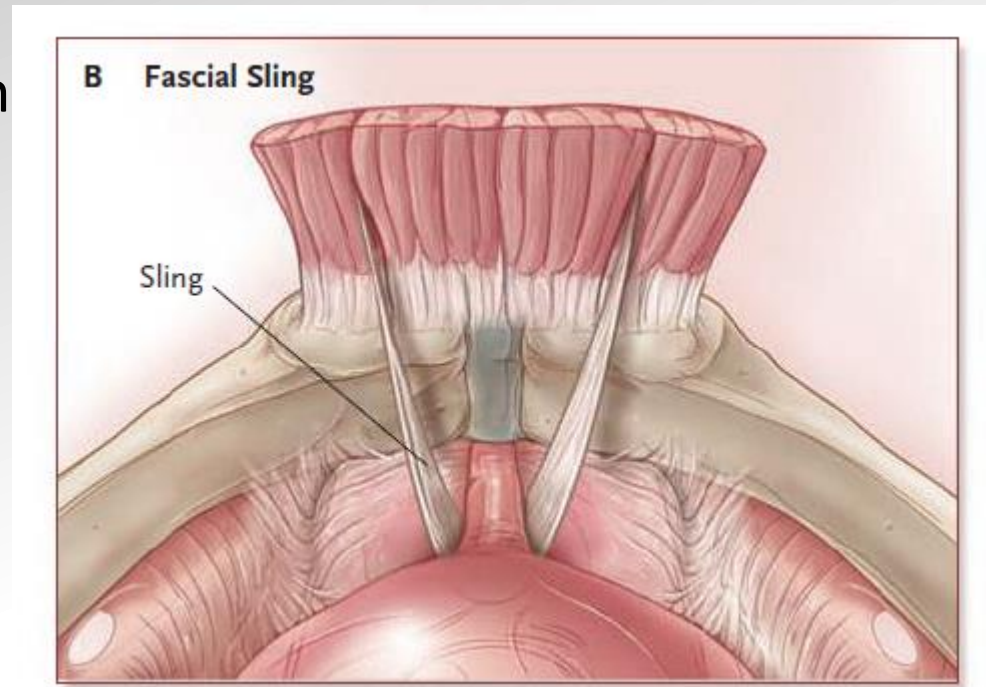
The urethra lies on a **supportive layer** that is composed of the endopelvic fascia and the anterior vaginal wall.

John DeLancey, 1994.

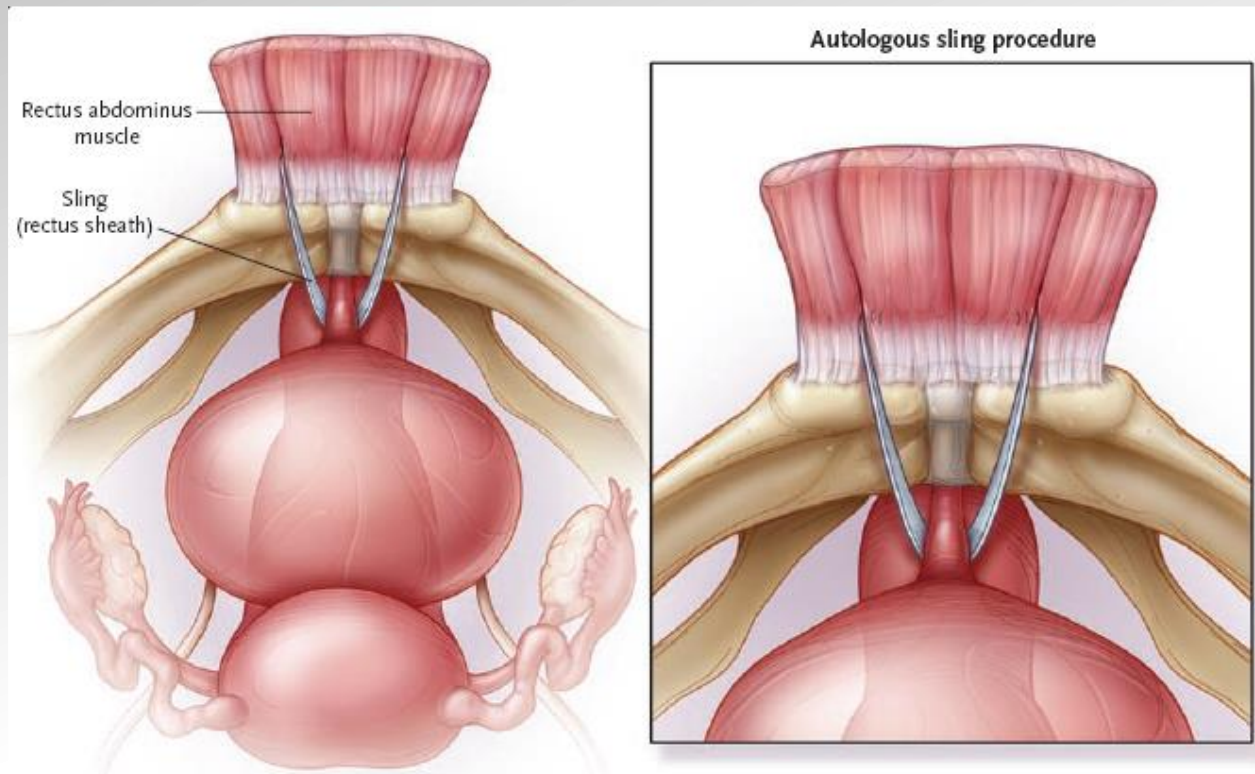


# Fascial Slings SUI (Pubovaginal Sling)

- Two incisions
  - Bikini line or outer thigh
  - Vaginal
- Overnight hospitalization
- Patients can resume normal, non-strenuous activities 6 weeks after the procedure.



# Current Fascial Sling



# Autologous Fascia – Complications

<u>Complication</u>	<u>Incidence</u>	<u>%</u>
Unexpected permanent urinary retention	4/251	2
De novo urge incontinence	7/251	3
Persistent urge incontinence	38/165	23
Bladder injury during surgery	2/251	0.6
Urethral injury	0/251	
Prolonged pain	1/251	0.3
Death	1/251	0.3

Chaikin & Blaivas, J Urol, 1998



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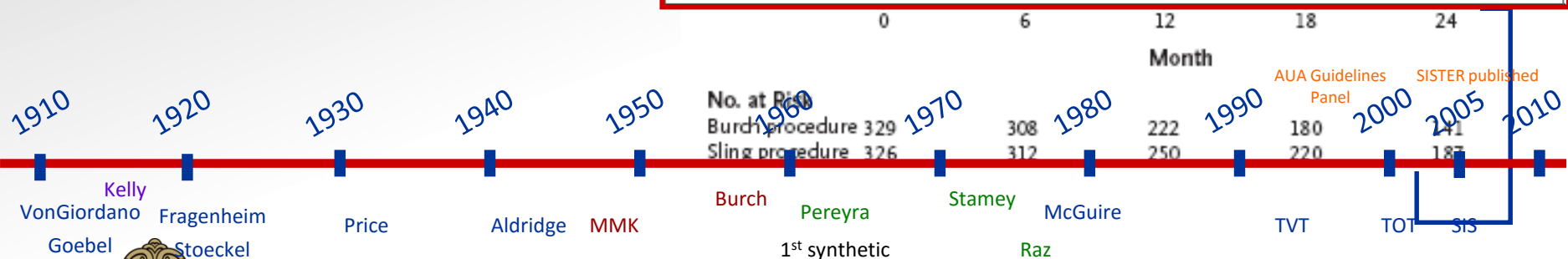
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# SIS

- Randomized: Burch Vs A
- N = 665, **79% completed**
- Results at 24 months
- SUI success:
  - Sling 66%
  - Burch 49%
- *Significantly more women with voiding dysfunction and UTIs*

**Table 2. Adverse Events.\***

Event	Burch Procedure (N=329)	Sling Procedure (N=326) no. (%)	P Value†
<b>Serious adverse events‡</b>			
Patients with event	32 (10)	42 (13)	0.20
Total events	39	47	
<b>Genitourinary</b>			
Ureteral injury	2	0	0.12
Ureterovaginal fistula	1	0	
Incidental vaginotomy	1	0	
Incidental cystotomy	10	2	
Erosion of suture into bladder	1	0	
Recurrent cystitis, leading to diagnostic cystoscopy	5	6	
Pyelonephritis	1	1	
Catheter complication	1	1	
Voiding dysfunction leading to surgical revision	0	20	
Pelvic pain	0	2	0.25
Bleeding	3	1	0.62
Wound complication requiring surgical intervention	13	11	0.83
Gastrointestinal	1	1	1.00
Respiratory distress requiring intubation	0	1	0.50
Laryngospasm requiring reintubation	0	1	0.50



# SISTer Trial

- Primary Outcome—Composite Measure of Overall Urinary Incontinence

- No self-reported symptoms of urinary incontinence
- <15 gram increase in pad weight in 24 hours
- No incontinence
- Negative cough stress test
- No retreatment

Overall Incontinence Success

Sling = 47%

Burch = 38%

- Secondary Outcome—Composite Measure of Overall Urinary Incontinence

- No self-reported symptoms of urinary incontinence
- Negative cough stress test with bladder filled to 300mL
- No retreatment for stress incontinence



# SISTer Trial

- Serious adverse events were not statistically different
- Surgical procedures to reduce voiding symptoms or improve retention were performed exclusively in the sling group
- Time to return to normal voiding was statistically significant

## Void with PVR < 100 mL

	Burch	Sling
At hospital discharge	58	44
At 6 weeks	97	86





# SISTer Trial--Conclusion

- “Our data show that the pubovaginal fascial sling has significantly higher efficacy than the Burch abdominal colposuspension at 24 months in women with predominant stress incontinence, *but* such success comes at the cost of more complications.
- Clinicians should discuss such trade-offs when making recommendations to patients regarding the optimal procedure and should emphasize that *complete resolution of incontinence symptoms after surgery is unlikely.*”

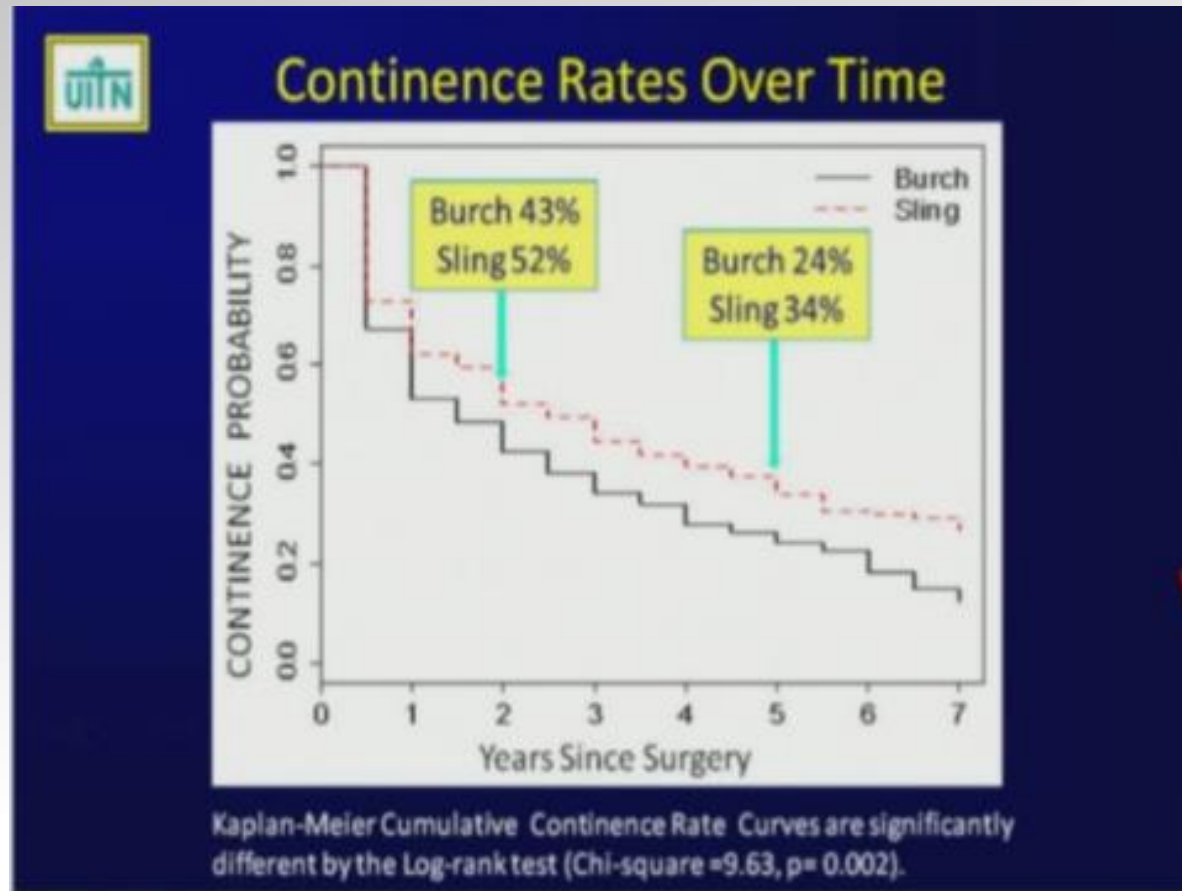
Albo et al, NEJM, 356;2143-55



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# Extended SISTER Trial (5 years)



# MESH MIDURETHRAL SLINGS



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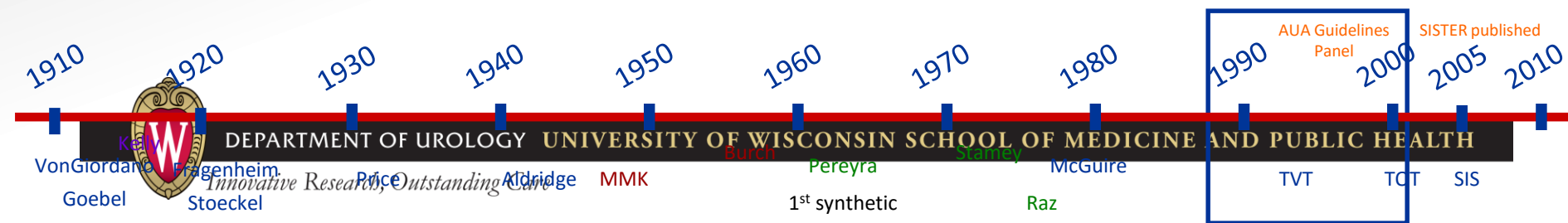
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# Integral Theory

Contenance dependent upon:

- Fixation of *midurethra* to pubic bone
- Physiologic backboard—midurethra should be supported but not elevated or obstructed
- Support of stretch receptors at proximal urethra

*Petros, Ulmsten: Acta Obstet Gynecol Scand Suppl 1990;153:7-31.*



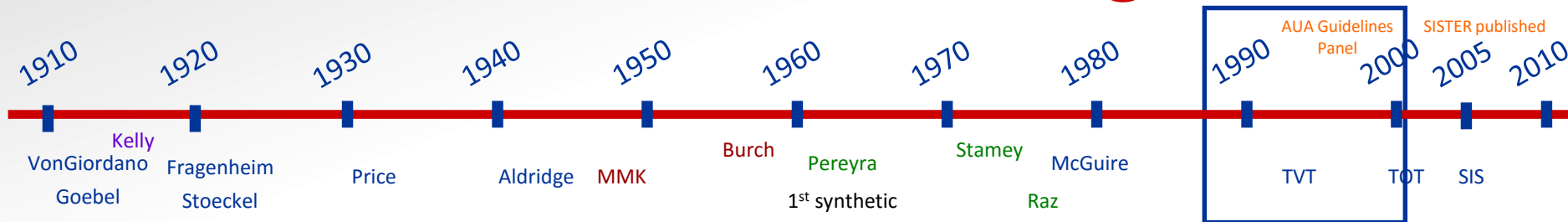
# Integral Theory

Laxity causes:

- Dissipation of muscle contraction
- Stimulation of stretch receptors at bladder base

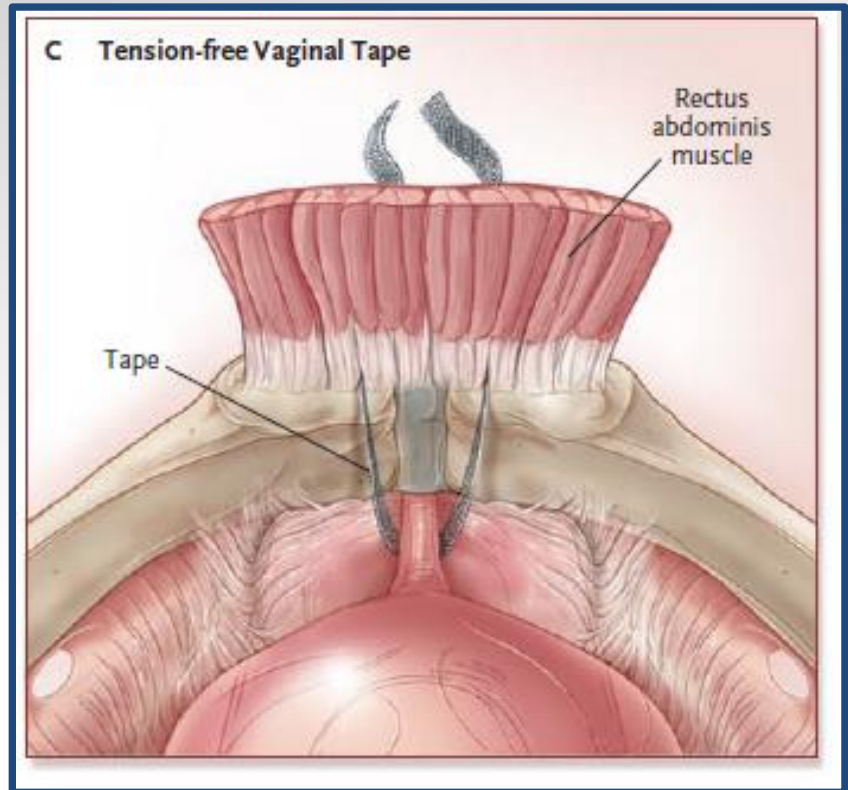
SUI

Urge

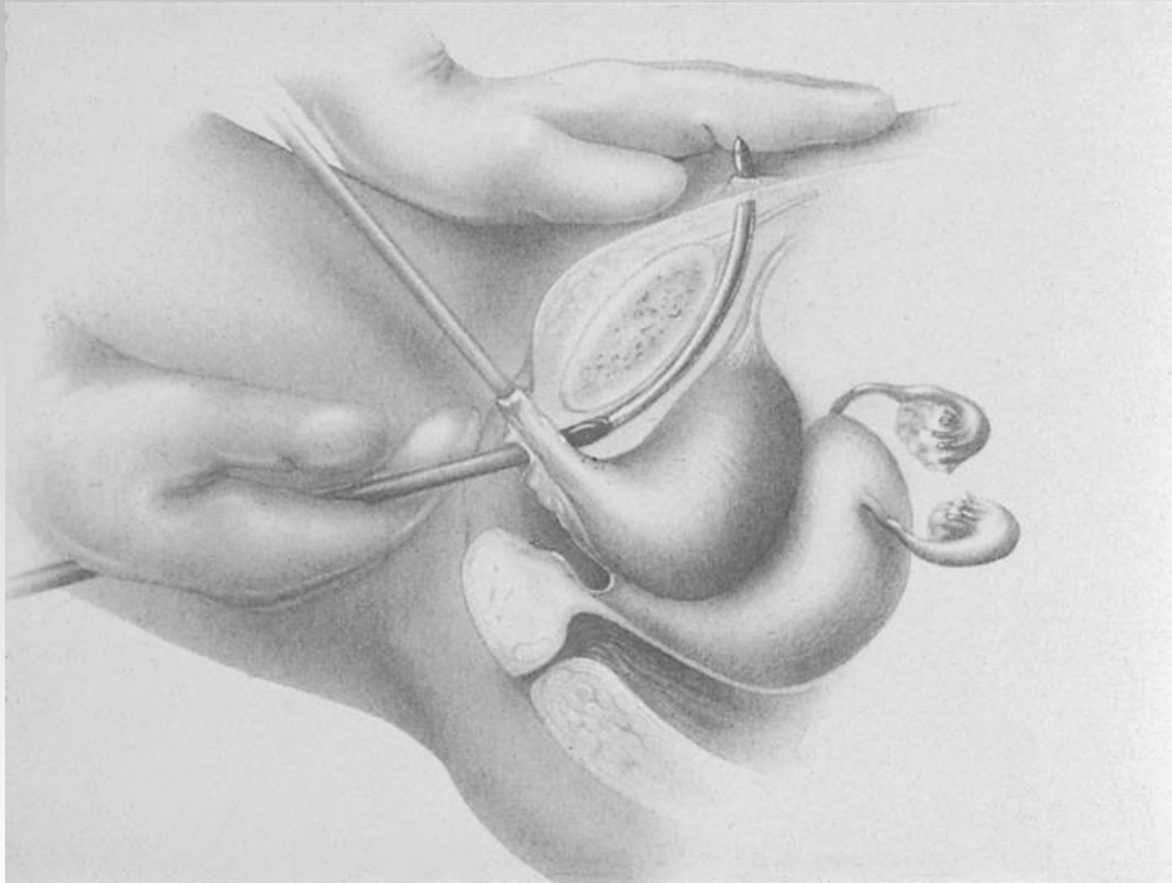


# Mesh Slings SUI

- Minimally invasive
- Incisions are very small
- Procedural pain is minimal
- Outpatient surgery
- Designed to reduce recovery time
- Patients can resume normal, non-strenuous activities 4-6 weeks after the procedure.



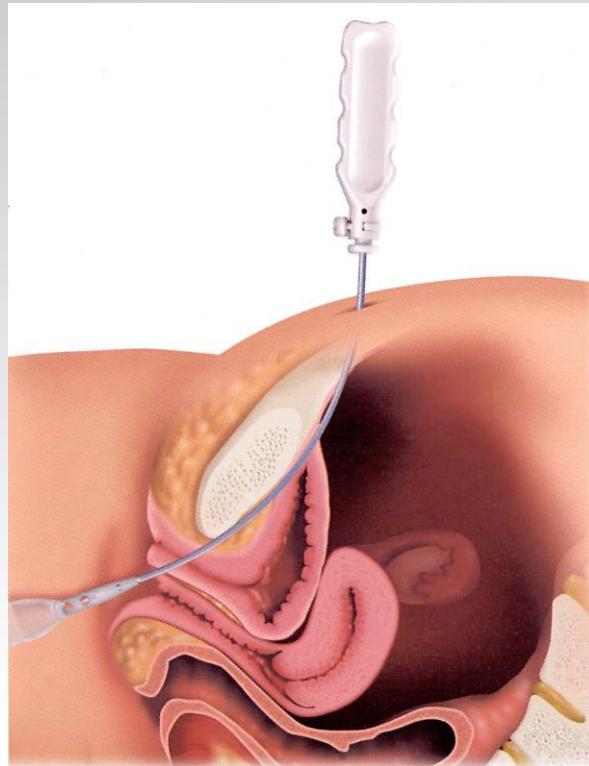
# TVT



- Type I polypropylene mesh
- Placed loosely at the mid-urethra



# SPARC





# Mechanism of Action

- 40 pts had perineal ultrasound before/after TVT –at rest and with Valsalva
- The tape
- Bladder r
- Dynamic
- Compression of the symphysis

Function  
dependent on  
urethral  
hypermobility

Sarlos d, et al: *Int Urogynecol J* 2003;14:395-8.



# TVT Outcomes

Authors	n	F/U (mos)	Cured % (n)	Improved % (n)	Retention % (n)
Ulmsten et al., 1998	131	≥12	91 (119)	7 (9)	3 (4)
Wang & Lo, 1998	70	3-18	87 (61)	4 (3)	17 (12)
Olsson & Kroon, 1999	51	36	90 (46)	6 (3)	Few
Wang, 2000	39	19	90 (35)*	-	-
Haab, 2001	46	12-24	86.9 (40)	10.9 (5)	0
Jeffry et al., 2001	88	25	91 (80)	9 (8)	4 (4)

\*Cured/improved reported together



# TVT Long-Term Results—11.5 years

- Prospective Cohort 90 patients who had TVT
- At 11.5 years, 79% of the original 90 were evaluated with:
  - Cough stress test
  - 24h pad test
  - Incontinence questionnaires data
  - Patient Global Impression of Improvement score
  - Pelvic exam to evaluate for erosion



# TVT Long-Term Results—11.5 years

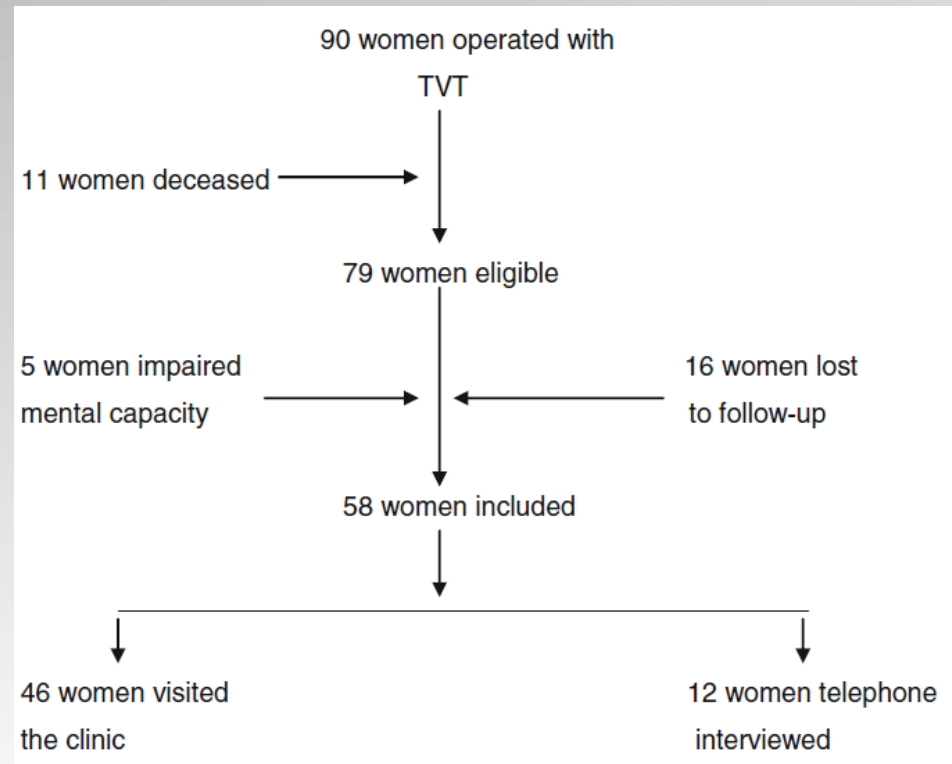
## Conclusions:

- Objective Cure Rate = 90%
  - Negative cough stress test
  - Negative pad test
- Subjective Cure Rate (PGI-I)
  - Cured = 77%
  - Improved = 20%
  - Failed = 3%
- No distinct decline in cure rates occurs over 11 years
- No late adverse effects of the mesh material were found
- Tape erosion into adjacent tissue did not occur

Nillson et al, Int Urogynecol J (2008) 19: (1043-1047)



# TVT Long Term Results--17 years

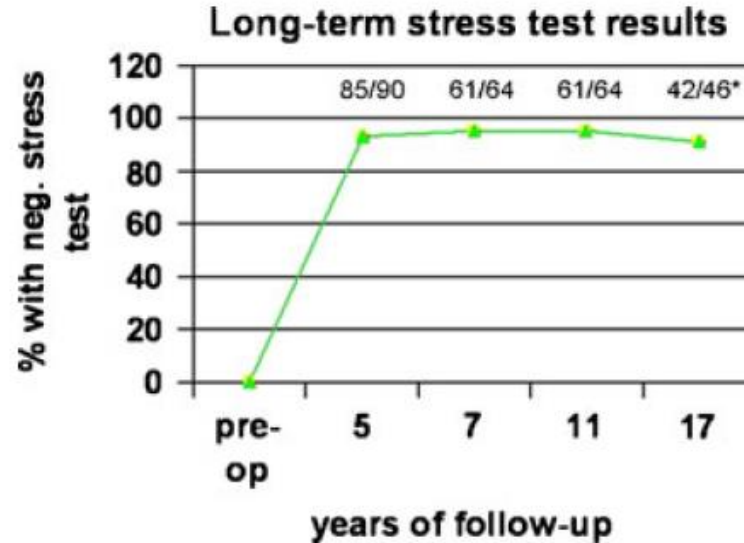


**Fig. 1** Flow chart of the study

Nilsson et al, Int Urogynecol J (2013) 24: 1265-1269



# TVT Long Term Results--17 years



**Fig. 2** Cough stress test results during 17 years of follow-up after a trans-vaginal tape (TVT) operation. \*number of performed stress tests per available women

Nilsson et al, Int Urogynecol J (2013) 24: 1265-1269



# TVT Long Term Results--17 years

**Table 2** Patients' global impression of improvement at 5, 7, 11, and 17 years of follow-up

	5 years	7 years	11 years	17 years
Percentage cured or improved	95.3	97.6	97.0	87.2
Number available for evaluation	85/90	78/80	67/69	48/55

Nilsson et al, Int Urogynecol J (2013) 24: 1265-1269



# TVT—17 year follow up

- At 17 years, only 1 woman had a vaginal mesh extrusion in the right para-urethral area. She was asymptomatic, vaginal tissue was noted to be atrophic, and she was treated with vaginal estrogen.

Nilsson et al, Int Urogynecol J (2013) 24: 1265-1269



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# COMPLICATIONS OF MIDURETHRAL SLINGS

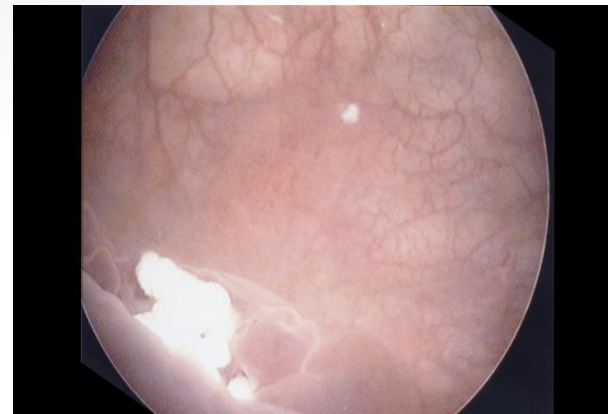
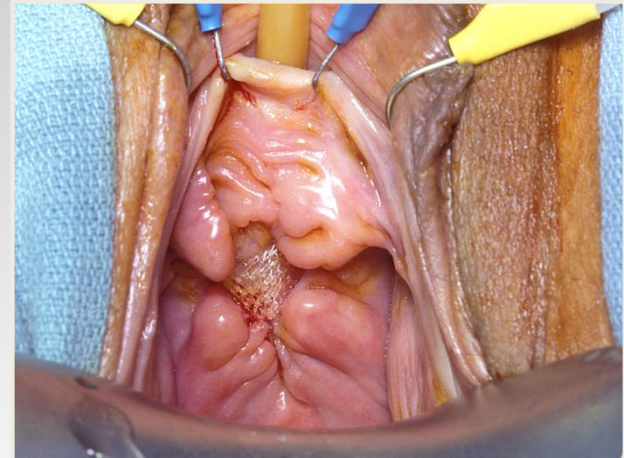


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# Complications of Mid-Urethral Slings

- De novo urgency
- Vaginal extrusion
- Urinary tract erosion
- Retention
- Visceral or neurologic injury
- Hemorrhage



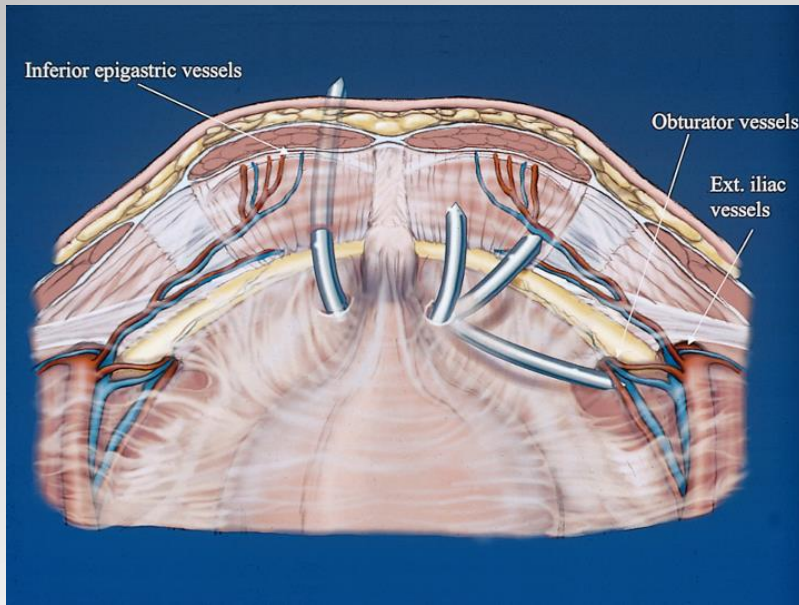
# TVT Complications

- **Multicenter retrospective review of 241 patients who underwent TVT (22 patients had a secondary procedure)**
- **Mean Follow-up 6 months**
- **Intraoperative**
  - Bladder perforation 5.8%
  - Blood loss >500mL 2.5%
- **Immediate**
  - Pelvic hematoma 1.9%
  - Catheter >48h 6.2%
  - Sling Lysis 4.1%
- **Late**
  - De Novo Urgency 15%
  - Intravaginal Tape Erosion 0.4%

Abouassaly et al, BJU, 2004:94, 110-13

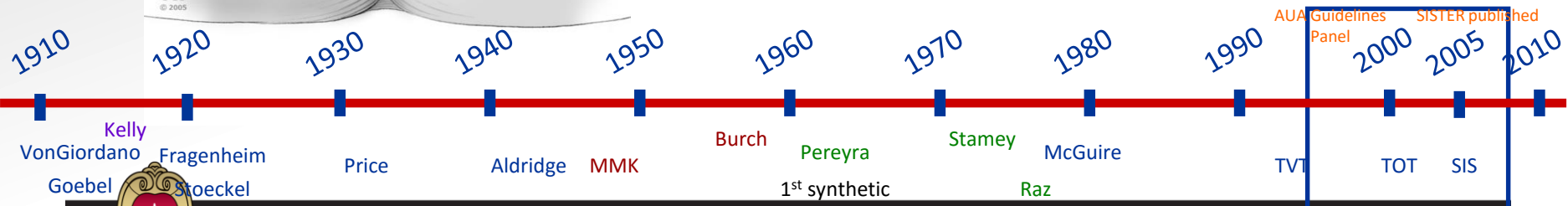
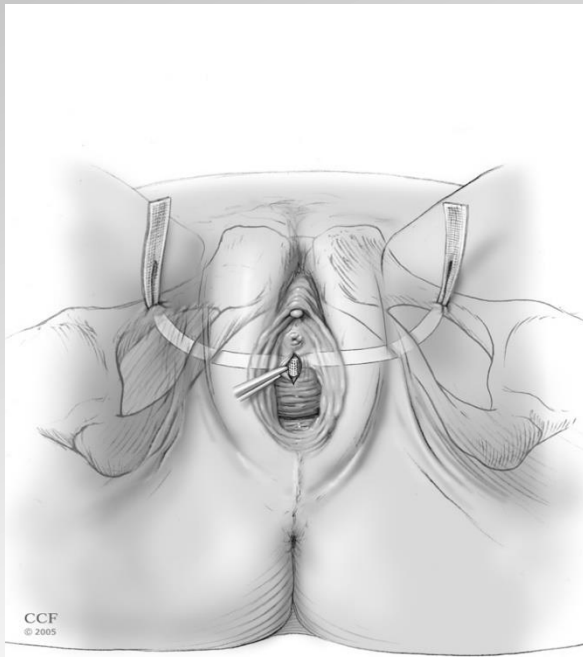


# Vascular Injury

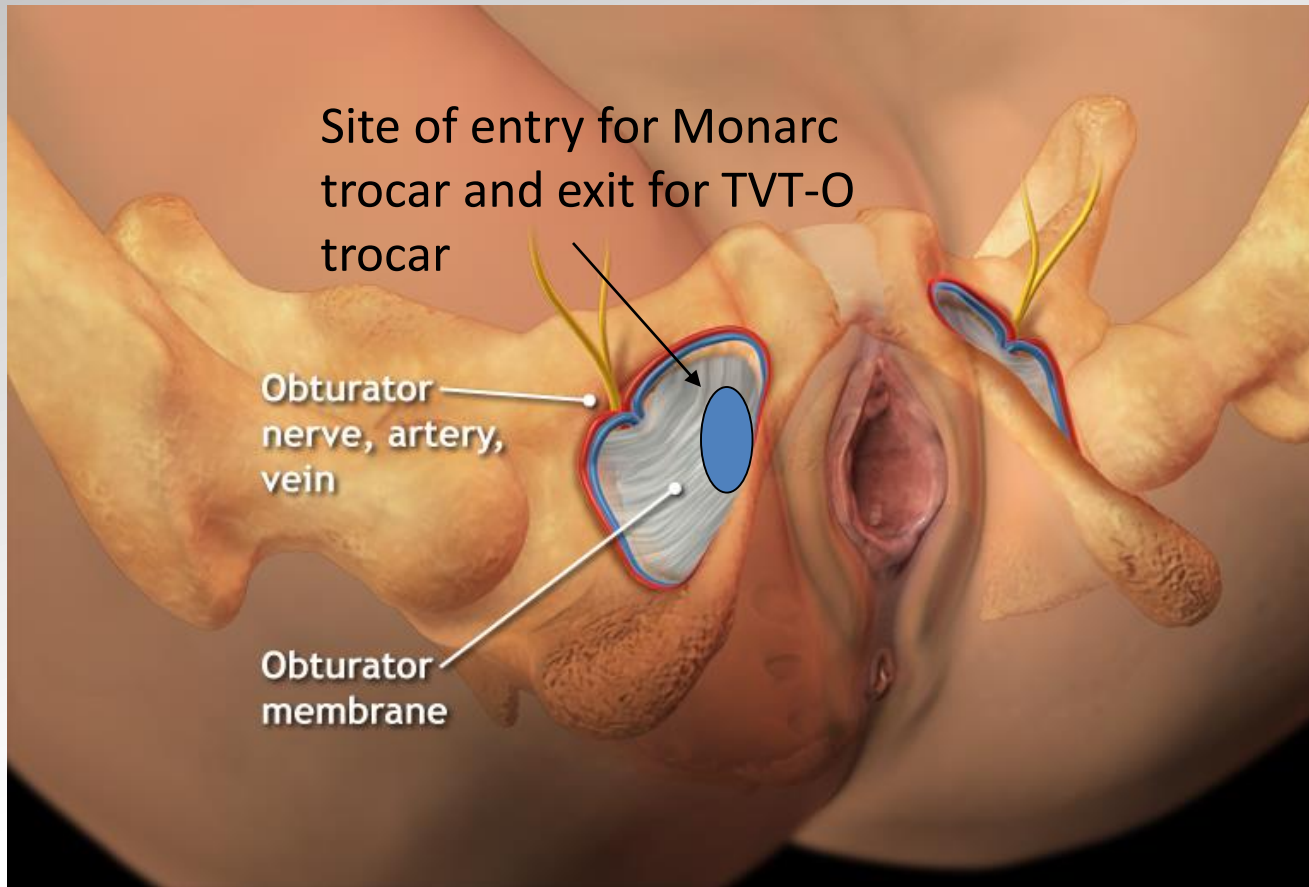


# Transobturator Approach

- Preserve mid-urethral position
- Avoid the retropubic space

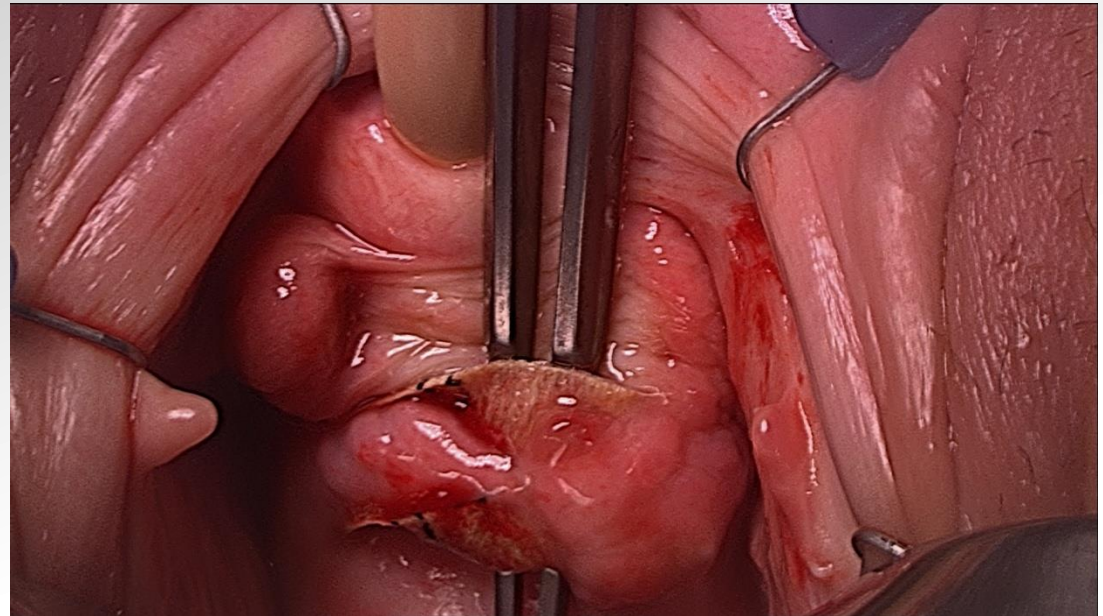


# Transobturator Trocar Passage



# Complications

Transvaginal View  
at Excision of  
Protegen Sling



# Mesh Slings SUI

The screenshot shows the FDA website interface. At the top left is the FDA logo and the text "U.S. Food and Drug Administration Protecting and Promoting Your Health". To the right are links for "A to Z Index", "Follow FDA", and "FDA Voice Blog", along with a search bar and a "SEARCH" button. Below this is a navigation menu with buttons for "Home", "Food", "Drugs", "Medical Devices", "Radiation-Emitting Products", "Vaccines, Blood & Biologics", "Animal & Veterinary", "Cosmetics", and "Tobacco Products".

A yellow banner for "Archived Content" contains a search bar labeled "Search Archive" and a disclaimer: "The content on this page is provided for reference purposes only. It was current when produced, but is no longer maintained and may be outdated."

The main content area is titled "Medical Devices" and includes a breadcrumb trail: "Home > Medical Devices > Medical Device Safety > Safety Communications". On the right are icons for printing, social media, and email. A sidebar on the left lists "Medical Device Safety", "Safety Communications", and "Public Health Notifications (Medical Devices)".

The main article title is "FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence". Below the title is a text block: "For updated information about Surgical Mesh for Pelvic Organ Prolapse, see: [UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse](#), released July 13, 2011."





About 157,000 results (0.38 seconds)

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by Vanessa Blanco - in 36 Google+ circles

Dec 10, 2013 - The FDA has issued warnings about the dangers of **vaginal mesh**, used to treat ... Learn about the serious **complications** it can cause.

Bladder Slings - Transvaginal Mesh Lawsuit - Transvaginal Mesh Recall

### [Troubling Signs and Symptoms of Transvaginal Mesh Problems](#)



[www.potts-law.com/transvaginal-mesh-symptoms/](http://www.potts-law.com/transvaginal-mesh-symptoms/) ▾

by Derek Potts

If you have had problems or **complications** as a result of **transvaginal mesh**, you may be entitled to compensation for the emotional and physical toll the ...

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1 (855) 234 7795

# Mesh Slings SUI

- Long term durability, safety, and efficacy up to 17 years
- 2,000 publications in the scientific literature
- The mid-urethral (mesh) sling is associated with less pain, shorter hospitalization, faster return to work, and reduced cost
- Over 3 million have been placed worldwide
- *FDA: “The safety and efficacy of multi-incision slings is well-established in clinical trials that followed patients for up to one year”*
- *Position Statement on Mesh Midurethral Sling for Stress Urinary Incontinence, AUGS SUFU*



# FDA & Mesh for SUI--2011

- The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year. Longer follow-up data is available in the literature, but there are fewer of these long-term studies compared to studies with one-year follow-up.



**U.S. Food and Drug Administration**  
Protecting and Promoting *Your* Health



# RETROPUBIC VERSUS TRANSOBTURATOR



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# TOMUS: Trial Overview

- Multicenter, randomized, equivalence trial comparing outcomes of retropubic vs. transobturator midurethral slings
- Primary Outcome
  - Treatment success at 12 months
    - **Objective criteria** (neg stress test, neg pad test, no retreatment)
    - **Subjective criteria** (self-reported absence of symptoms, no leakage episodes recorded, no retreatment)
  - Pre-determined equivalence margin
    - +/- 12 percentage points

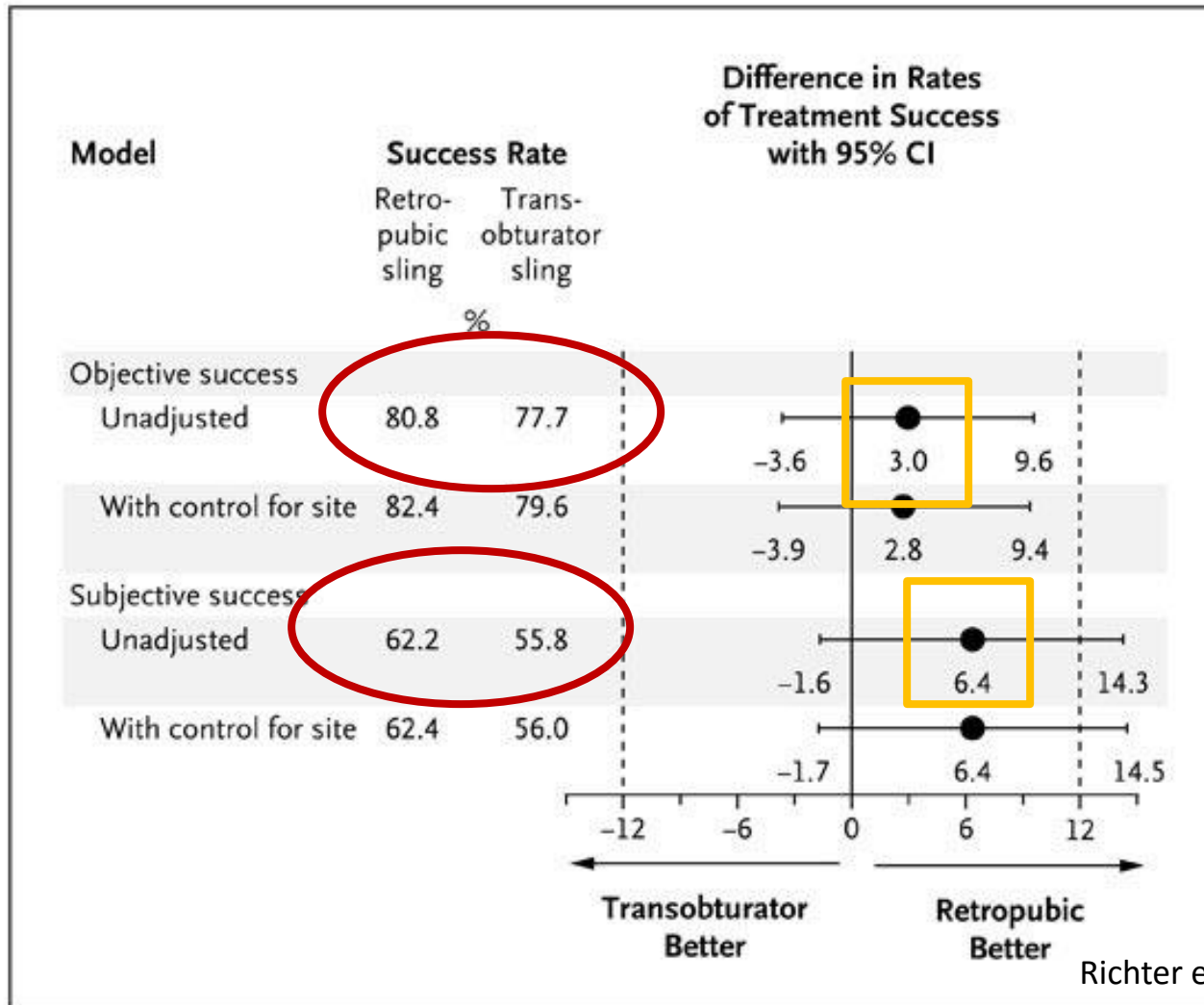


# TOMUS: Trial Overview

- 597 women randomized
  - 298 retropubic, 299 transobturator
- 565 completed the 12 month assessment
- Inclusion criteria:
  - 3 month h/o stress-predominant incontinence
  - Positive cough stress test  $\leq$  300mL
    - (urodynamic stress incontinence not required)
  - Concomitant vaginal surgery was permitted.



# TOMUS: Assessment of Equivalence at 12 months



Richter et al, NEJM 2010; 362:2066-76



# TOMUS: Primary Outcome

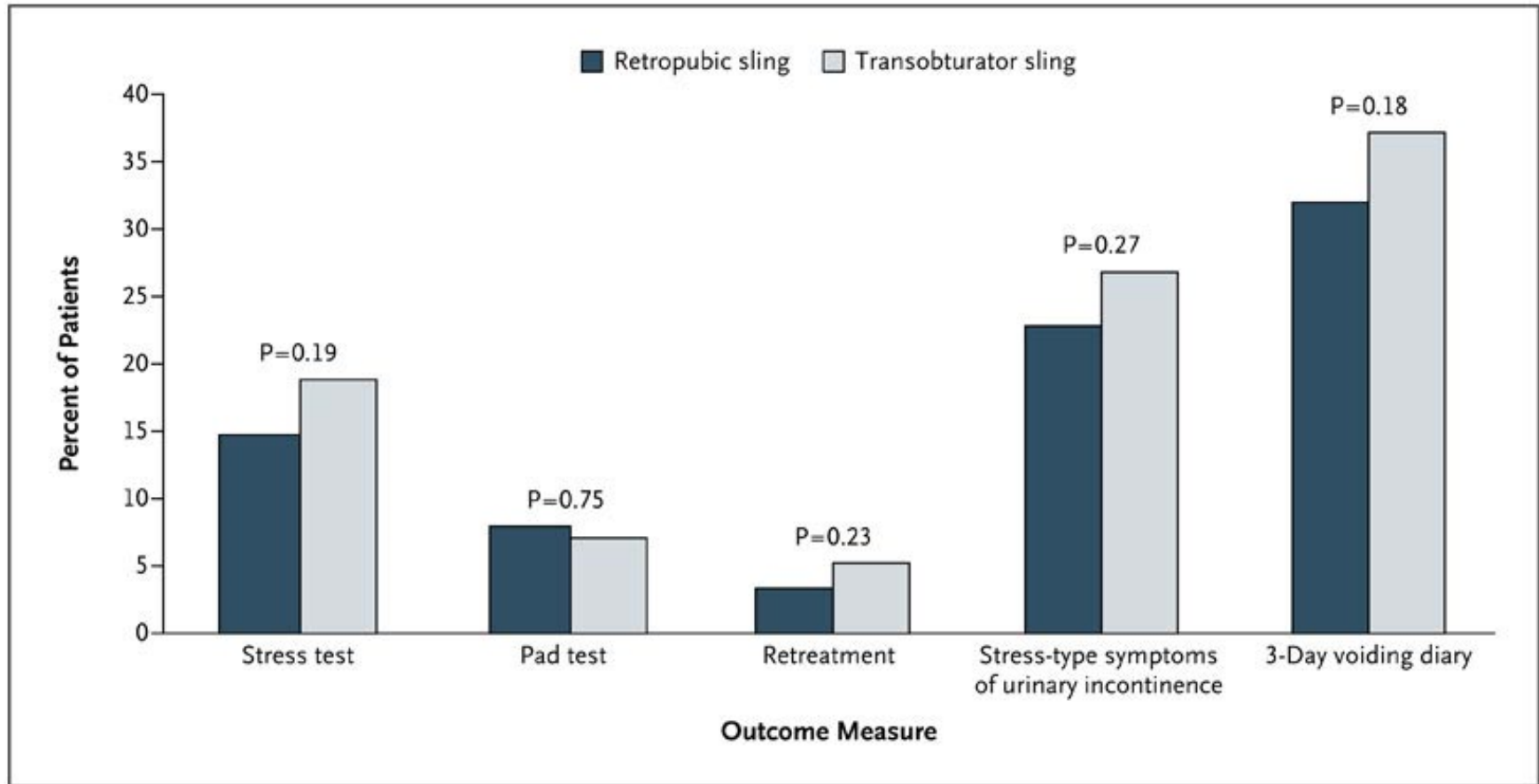
- Objective criteria—two approaches are equivalent
- Subjective criteria—success rates similar but did not meet the criteria for equivalence.

Richter et al, NEJM 2010; 362:2066-76





# Proportion of Patients with Treatment Failure at 12 mos



# TOMUS: Complications

- Retropubic group—more voiding dysfunction requiring surgery
- Transobturator group—more neurologic symptoms



# TOMUS: Complications (Grade III & IV)

Richter et al, NEJM 2010; 362:2066-76

**Table 2. Adverse Events, According to Treatment Group, Severity, and System.\***

Adverse Event	Retropubic Sling (N = 298)		Transobturator Sling (N = 299)		P Value
	Events	Patients	Events	Patients	
	no.	no. (%)	no.	no. (%)	
Serious adverse event	43	41 (13.8)	20	19 (6.4)	0.003
Wound-related event	10	9 (3.0)	5	5 (1.7)	0.30
Mesh exposure†	9	8 (2.7)	1	1 (0.3)	
Mesh erosion‡	1	1 (0.3)	1	1 (0.3)	
Surgical-site infection	0	0	2	2 (0.7)	
Granulation tissue	0	0	1	1 (0.3)	
Genitourinary event	23	23 (7.7)	13	13 (4.3)	0.09
Urethral perforation	1	1 (0.3)	0	0	
Bladder perforation¶	15	15 (5.0)	0	0	
Vaginal epithelial perforation	6	6 (2.0)	13	13 (4.3)	
Recurrent cystitis, leading to diagnostic cystoscopy¶¶	1	1 (0.3)	0	0	
Vascular or hematologic event	1	1 (0.3)	1	1 (0.3)	>0.99
Pulmonary embolus	0	0	1	1 (0.3)	
Postoperative bleeding	1	1 (0.3)	0	0	
Neurologic symptoms	1	1 (0.3)	0	0	0.50
Voiding dysfunction requiring surgery, use of catheter, or both	9	8 (2.7)	0	0	0.004
Other (urothelial abrasion)	0	0	1	1 (0.3)	0.50



# TOMUS: Complications (Grade I & II)

**Table 2. (Continued.)**

Adverse Event	Retropubic Sling (N = 298)		Transobturator Sling (N = 299)		P Value
	Events	Patients	Events	Patients	
	<i>no.</i>	<i>no. (%)</i>	<i>no.</i>	<i>no. (%)</i>	
Adverse events, grades I and II	151	110 (36.9)	132	89 (29.8)	0.07
Wound-related event	6	6 (2.0)	5	5 (1.7)	0.77
Mesh exposure†	4	4 (1.3)	3	3 (1.0)	
Surgical-site infection	2	2 (0.7)	2	2 (0.7)	
Genitourinary event	46	40 (13.4)	27	24 (8.0)	0.04
Vascular or hematologic event	20	18 (6.0)	7	7 (2.3)	0.03
Neurologic symptoms	15	12 (4.0)	31	28 (9.4)	0.01
Numbness	8	6 (2.0)	9	7 (2.3)	
Weakness	7	7 (2.3)	22	21 (7.0)	
Voiding dysfunction	16	10 (3.4)	5	4 (1.3)	0.11
Self-reported pain ≥6 wk after procedure	7	7 (2.3)	7	6 (2.0)	0.79
New urge incontinence**	0	0	1	1 (0.3)	0.50
Persistent urge incontinence††	54	36 (12.1)	55	30 (10.0)	0.44
Other‡‡	7	6 (2.0)	6	6 (2.0)	>0.99



# TOMUS: Patient Satisfaction

- Assessed at 12 months with question:
  - *“How satisfied or dissatisfied are you with the result of bladder surgery related to urine leakage?”*
- Retropubic 85.9%
- Transobturator 90% ( $p = 0.14$ )
- No significant differences between the groups between baseline and postoperative
  - “distress” scores
  - “bother” scores
  - Effect of these symptoms on quality of life



# TOMUS: Conclusions

- The 12-month rates of objectively assessed success of treatment for stress incontinence with the retropubic and transobturator approaches met the pre-specified criteria for equivalence; the rates of subjectively assessed success were similar between groups but did not meet the criteria for equivalence
- Differences in the complications associated with the two procedures should be discussed with patients who are considering surgical treatment for incontinence

Richter et al, NEJM 2010; 362:2066-76



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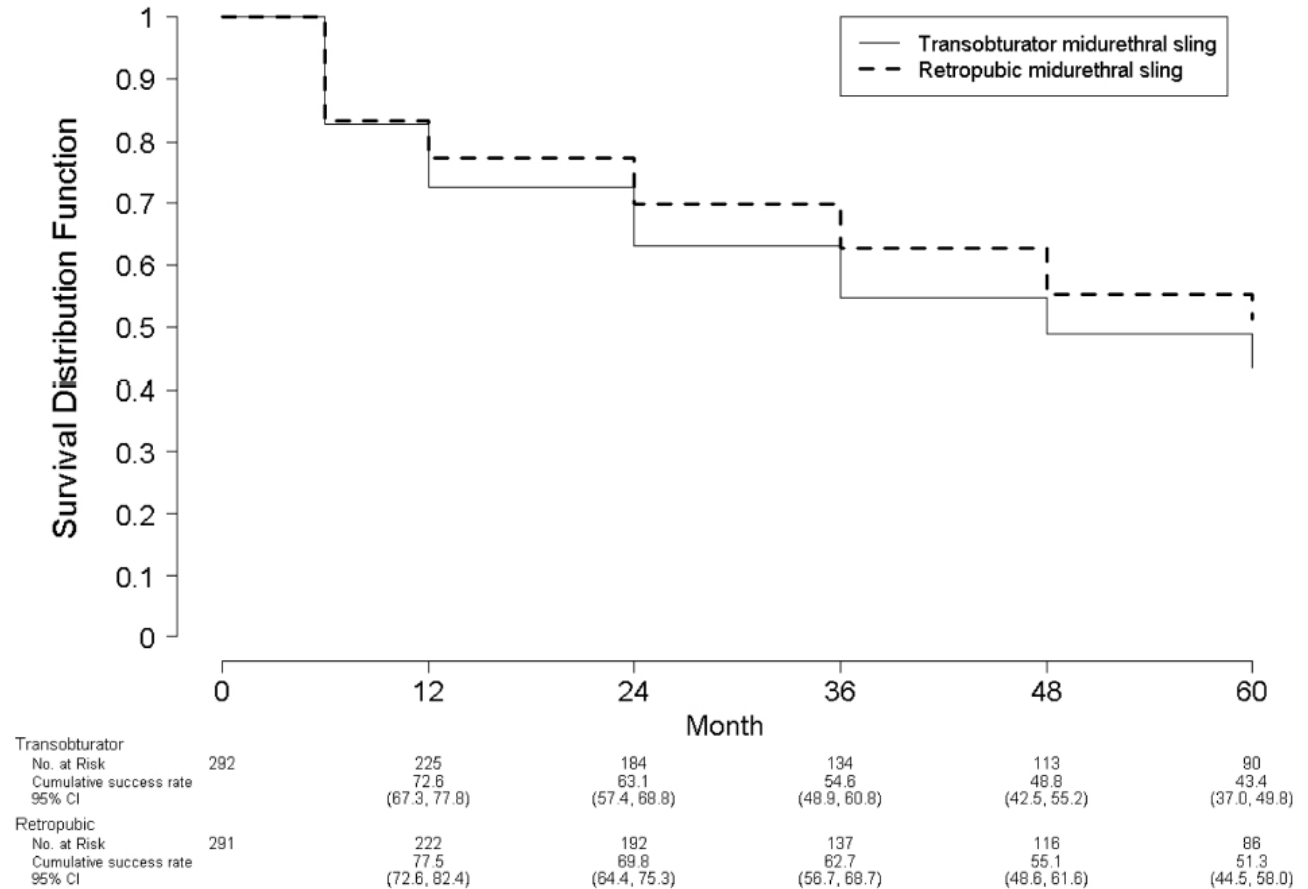
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# 5-Year Longitudinal follow-up TOMUS

- 404 of 597 (67.7%) of original participants enrolled in follow-up study
- Composite outcome of questionnaires and pelvic exam
- There were 7 new mesh exposures in years 3-5 after surgery.
- Total rate of mesh exposures = 1.7%



Treatment success declines with time—even with synthetic slings



**Figure 2.** Treatment Success Rates Over Time for Women Randomized to Retropubic and Transobturator Midurethral Sling (N=583)

Kenton, et al, J Urol, 2015





# 5-Year Longitudinal follow-up TOMUS

TIME	RETROPUBIC	TRANSOBTURATOR
1 YEAR	77.5%	72.6%
2 YEARS	69.8%	63.1%
5 YEARS	51.3%	43.4%

- “Early in the introduction of polypropylene slings, surgeons suggested the use of “permanent” mesh would result in more durable outcomes compared to procedures with autologous, donor allograft, and xenograft slings. **Our data refutes that initial belief: just as with biological materials, permanent mesh slings show a progressive decline in efficacy over time.**”



## 5-Year Longitudinal follow-up TOMUS

- Treatment success declined over 5 years for both retropubic and transobturator slings
  - (sling benefit retropubic)
- Patient satisfaction remained high in both arms
- New mesh erosions occurred in both arms over time, although at a similarly low rate.



# Pro/Con Mid-urethral Slings

## Advantages

- Simplicity
- Excellent early efficacy
- Low morbidity
- Less voiding dysfunction?
- Less outlet obstruction?

## Disadvantages

- Visceral injuries
- Neurovascular injuries
- Vaginal extrusion
- Urinary tract erosion
- Voiding dysfunction



# How to Choose?

- Retropubic Mid-urethral Sling:
  - Healthy woman bothered by SUI
  - Hypermobility/mobility on exam
  - PVR <100mL
  - +/- need for concomitant prolapse surgery (OPUS trial, *NEJM* 2012)
  - Regardless of the following urodynamic parameters
    - VLPP
    - Detrusor overactivity
    - Voiding mechanism (Valsalva or not)



# How to Choose?

- Transobturator Mid-urethral sling:
  - Candidates for retropubic mid-urethral slings
  - Those at high risk for retropubic scarring or with a history of multiple procedures
  - (McAchnan only)—morbid obesity with a BMI > 45



# How to Choose?

- Autologous pubovaginal sling:
  - High risk for erosion
  - History of radiation therapy
  - Immobile urethra
  - ISD
  - Recurrent / Reoperative SUI



# How to Choose?

- Burch urethropexy
  - Patients undergoing simultaneous abdominal prolapse repair
  - Limited vaginal access (Burch)



# How to Choose?

- Urethral bulking agent:
  - Poor operative candidates
  - Inadequate outcome from prior anti-incontinence procedure





# QUESTIONS?



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# OVERACTIVE BLADDER (OAB)



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# OAB Symptoms

## Urgency

- Sudden, strong desire to urinate

## Frequency

- 8+ visits to the toilet per 24 hours
- 2+ visits to the toilet during sleeping hours (nocturia)

## Urge Incontinence

- Sudden & involuntary loss of urine



# Overactive Bladder Triggers

- Hearing or touching running water
- Seeing a bathroom
- Placing your feet on the floor when you first get out of bed
- Putting your key in the door when you get home
- Anxiety or stressful situations
- Exposure to cold

[www.urologyhealth.org](http://www.urologyhealth.org)

g



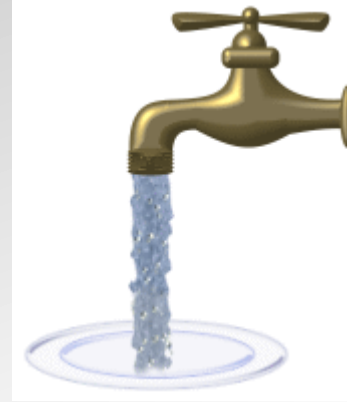
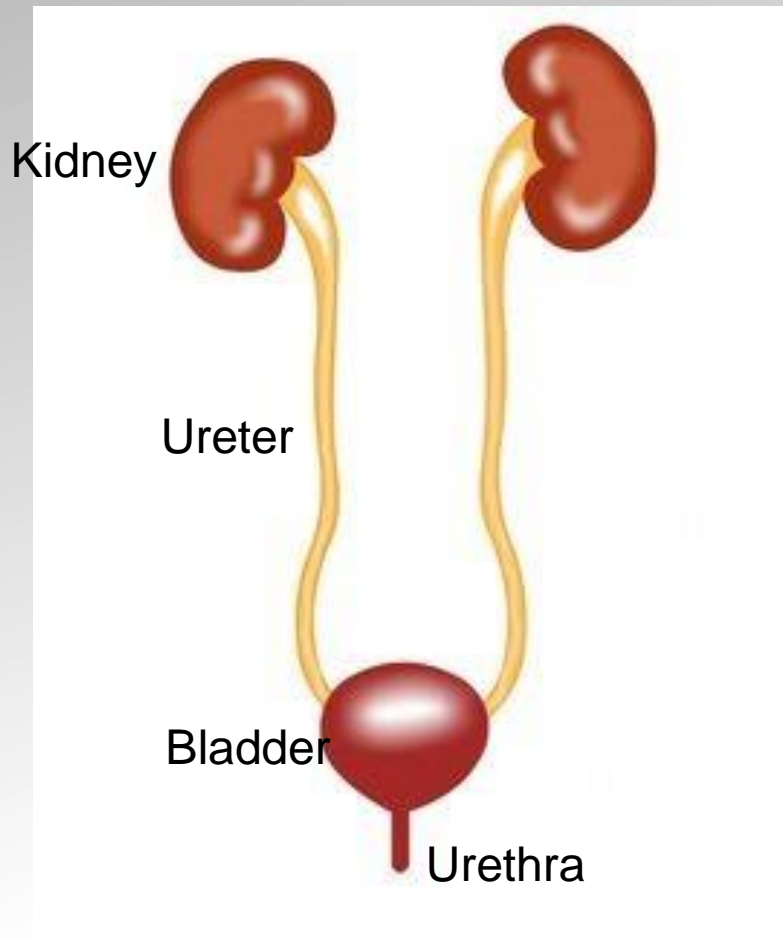
# THE LOWER URINARY TRACT

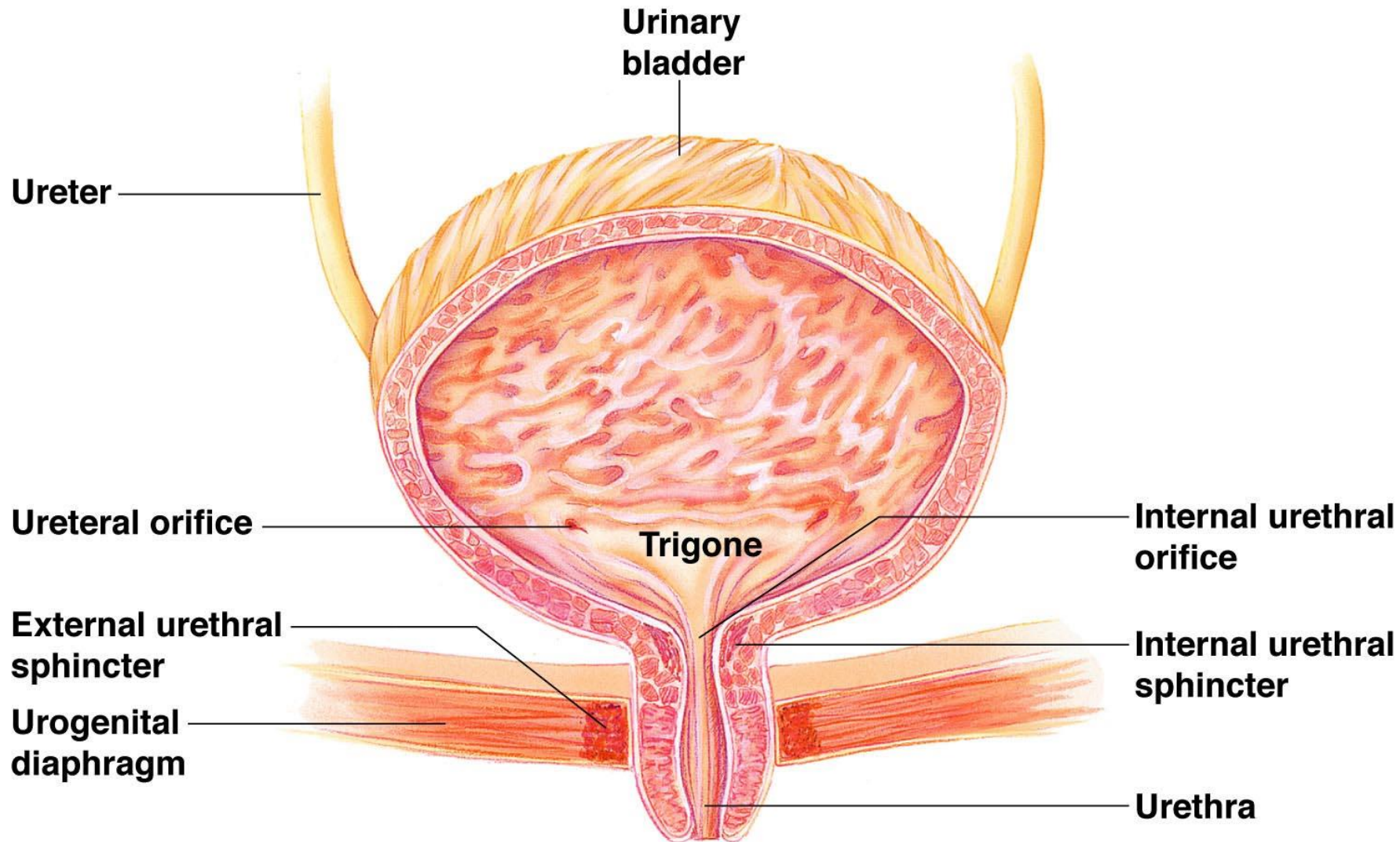


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# The Urinary Tract





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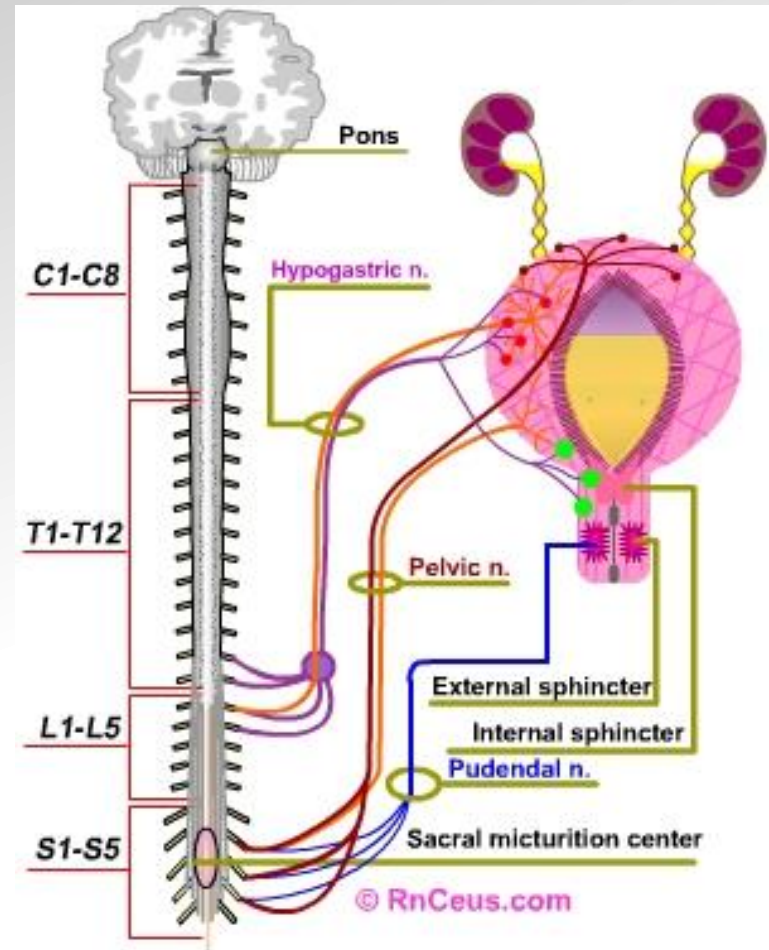


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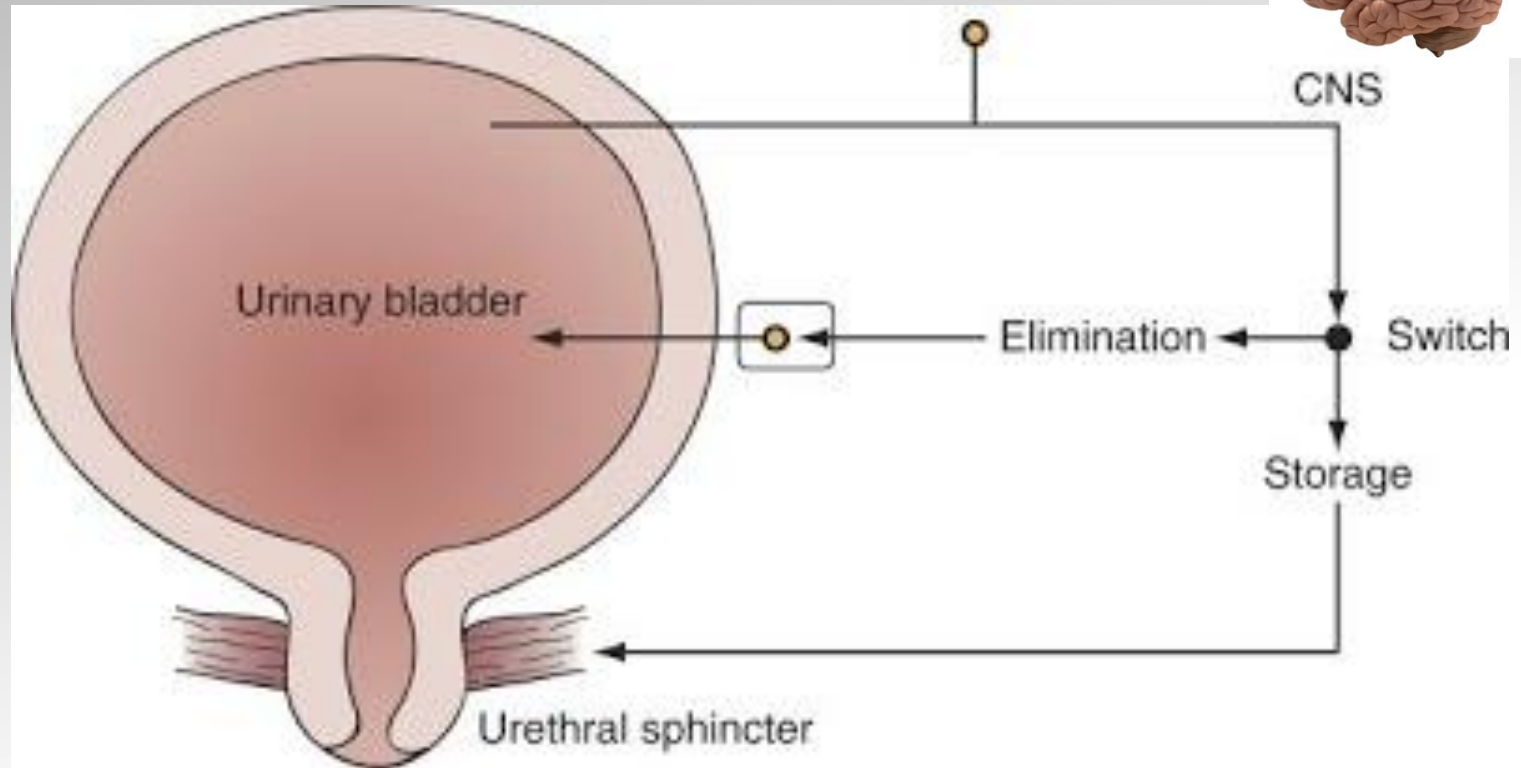
# Normal Urination

- Normally urination doesn't require much thought.
- It's a combination of both voluntary (conscious) and involuntary (automatic) muscle actions that coordinate to hold and release urine

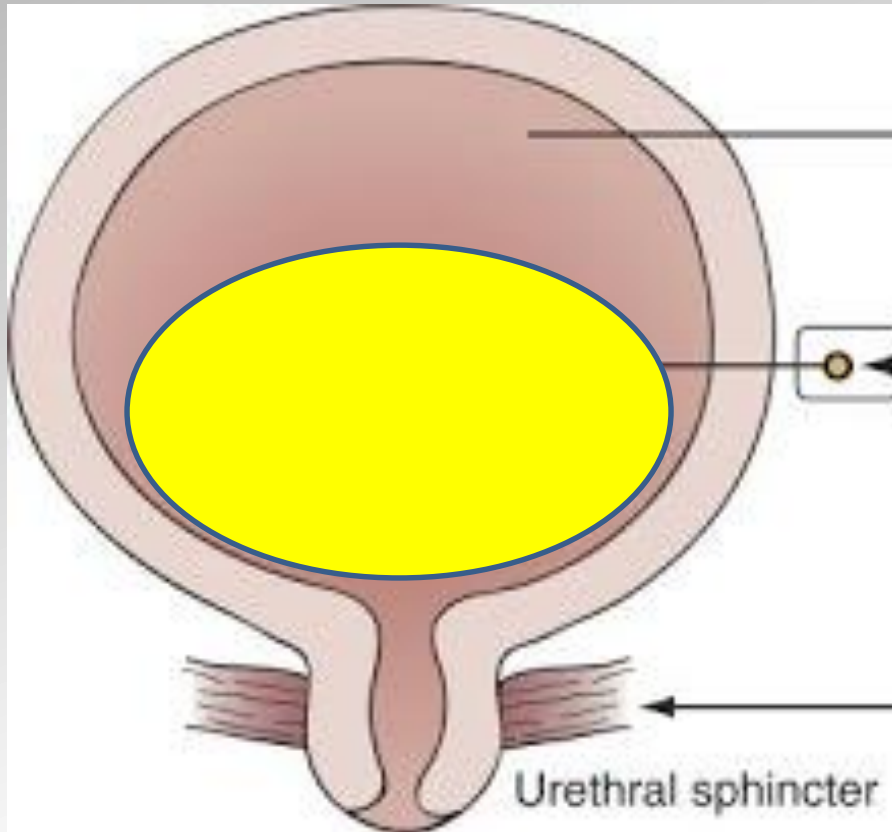




# Normal Urination



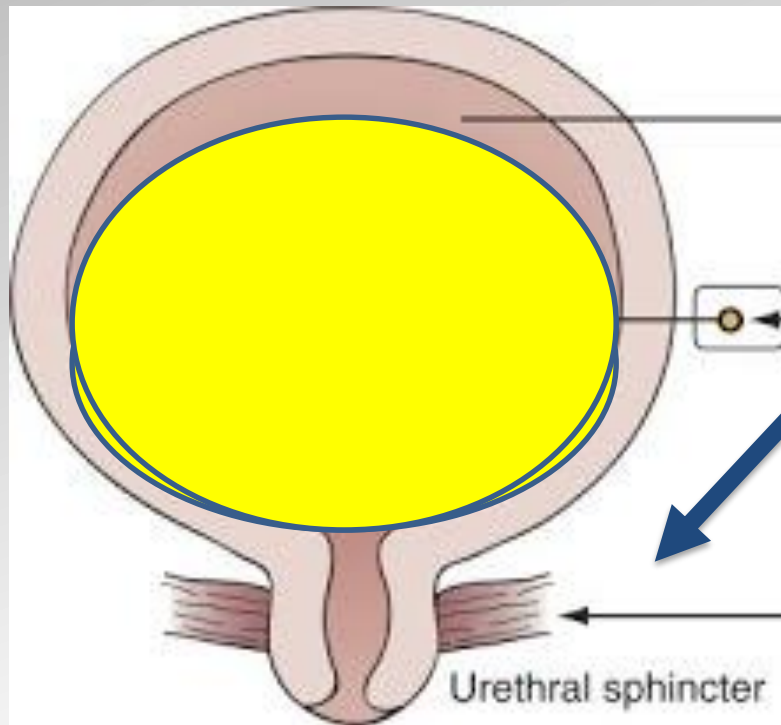
# Normal Urination



- Over several hours the bladder fills with urine and the bladder muscle is relaxed and stretches.
- The sphincter stays tightly closed
- When the bladder reaches 8-10 oz, the nerves along the bladder send a message to the brain. **This is an urge.**



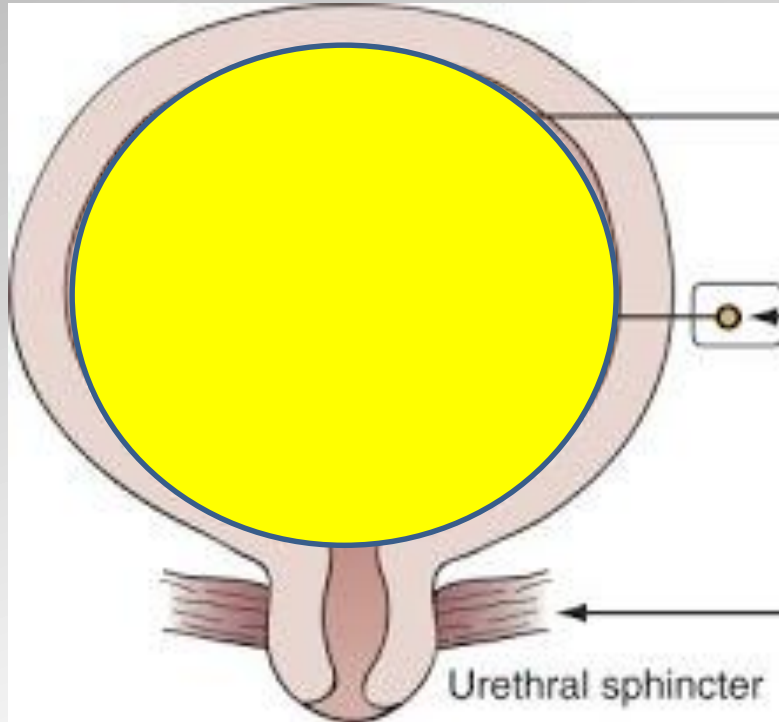
# Normal Urination



- If it's not a convenient time to go the bathroom, you consciously tighten your sphincter.
- This signals the bladder to relax.
- It can then continue to fill and stretch



# Normal Urination



- When you decide it's a good time to urinate, your brain flips the switch from STORAGE MODE to EMPTY MODE.
- You consciously relax your sphincter and the bladder muscle then contracts to squeeze out urine.



# OVERACTIVE BLADDER

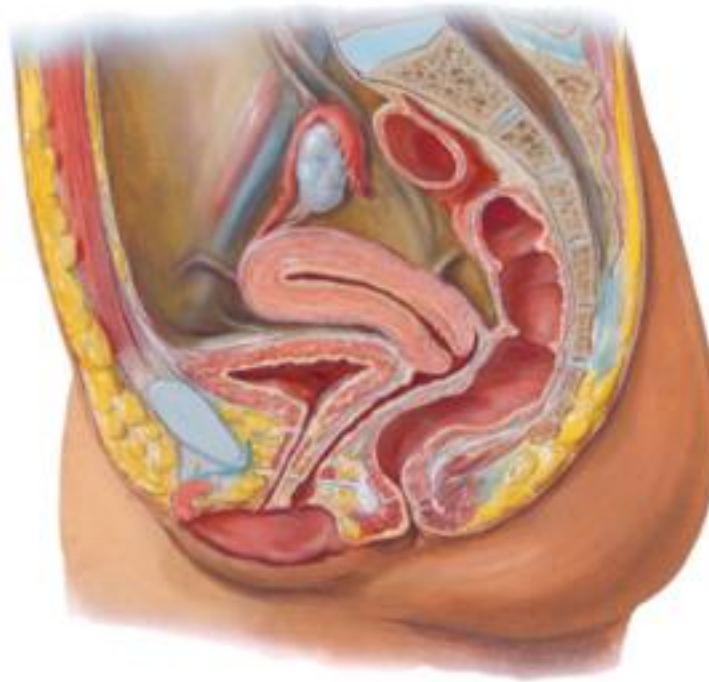


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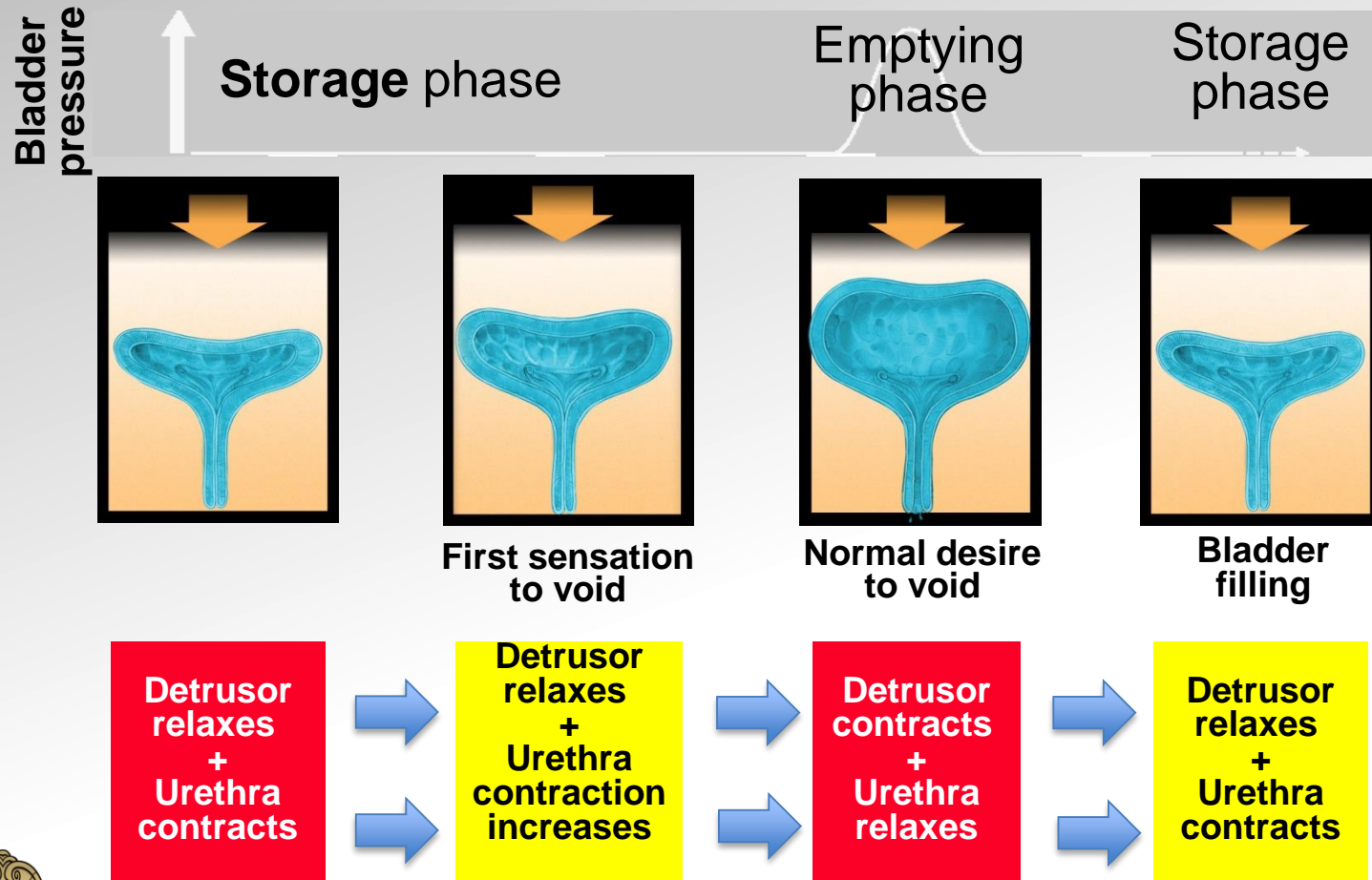
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# OAB is a bladder problem

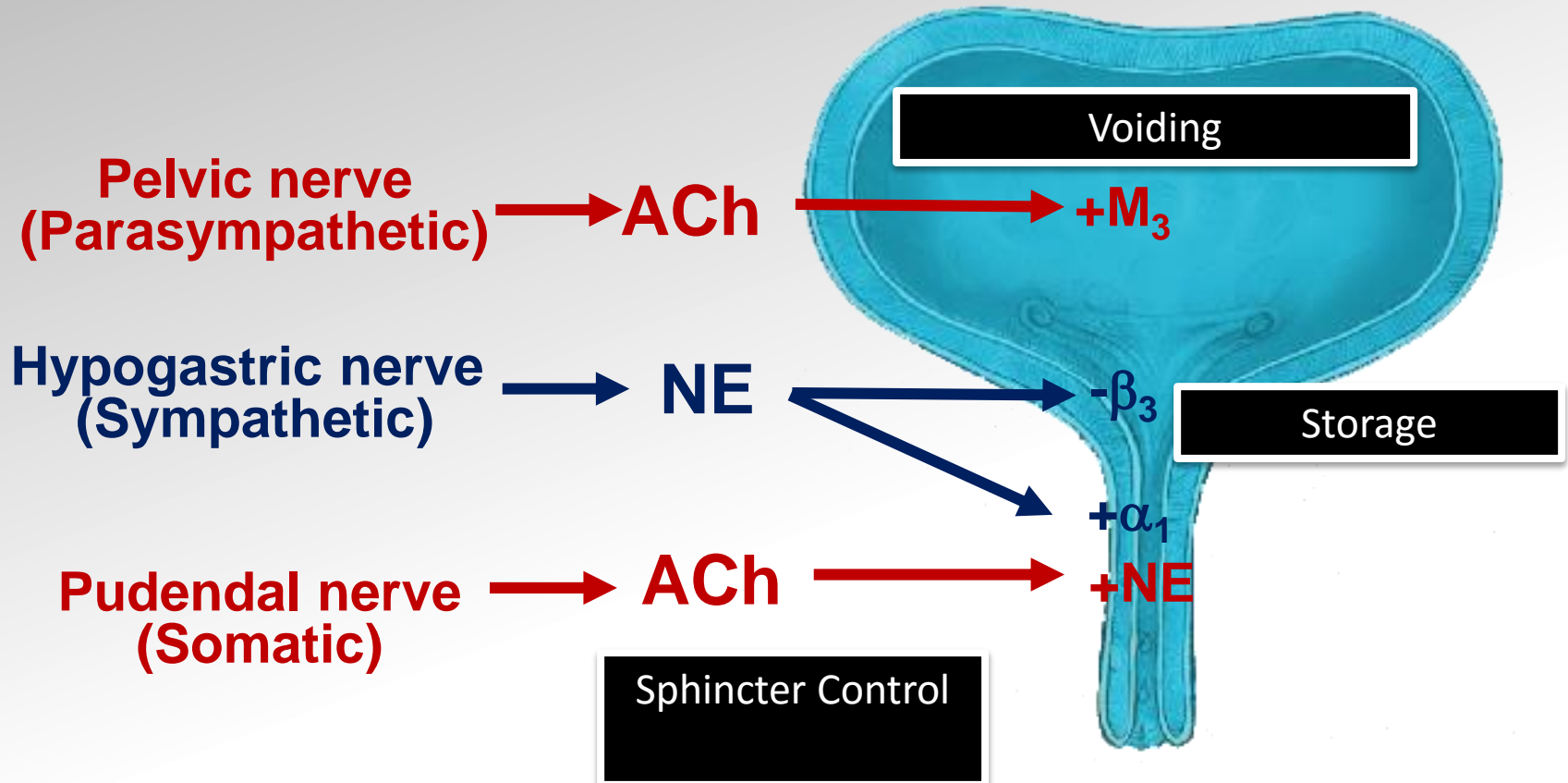
Pelvic Viscera and Perineum of Female  
Median (Sagittal) Section



# Normal Lower Urinary Tract (LUT) Function: Reciprocal Activities



# LUT Peripheral Motor Innervation



Adapted from: de Groat WC and Yoshimuran N. *Annu Rev Pharmacol Toxicol.* 2001;41:691-721





# NOBLE Study

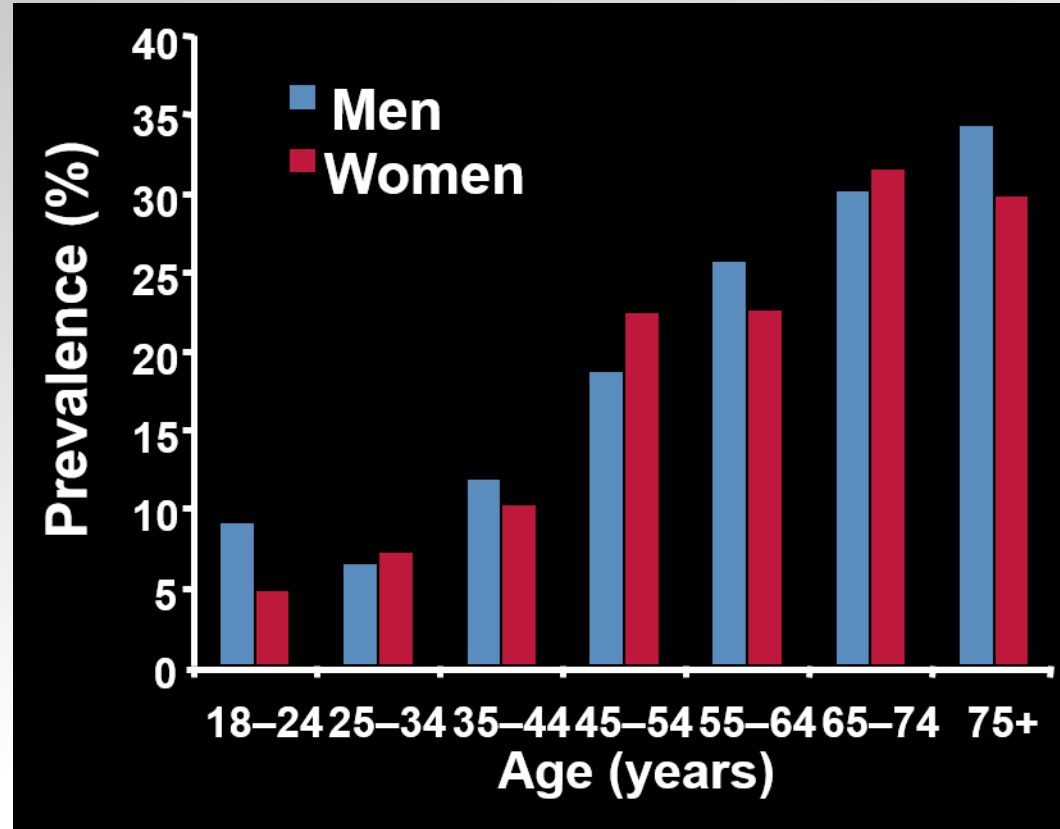
- National Overactive Bladder Evaluation
- Published 2002
- Questionnaire based study
  - OAB instruments, SF-36, Depression index, sleep instrument
- 5,204 US citizen sample
- To evaluate the prevalence and burden of OAB in the United States

Stewart W et al. *World J Urol.* 2003;20:327-336



# Prevalence of OAB in the US

- Men 16% and Women 16.9%
- Prevalence of OAB increases with age



Adapted from Stewart W et al. *World J Urol.* 2003;20:327-336.



# NOBLE Results

- Prevalence between men & women was roughly equal
- Severity of symptoms worse for women, with women having more OAB-wet and men more OAB-dry
- OAB *with and without* UI was associated with clinically and significantly:
  - lower SF-36 quality of life scores
  - higher CES-D depression scores
  - poorer quality of sleep



# EVALUATION OF OAB



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# ICIQ-UI Short Form

- How often do you leak urine?
- How much urine do you usually leak?
- Overall, how much does leaking urine interfere with your everyday life?
- When does urine leak? (self diagnosis items that discern urge incontinence from stress incontinence)

<http://www.iciq.net>



# OAB Symptom Quiz

1

I feel frustrated or embarrassed about my frequent urination (i.e. the number of times I visit the bathroom in one day).

*Never*

*Sometimes*

*Often*

2

I have sudden urges to urinate that make me rush to the bathroom.

*Never*

*Sometimes*

*Often*

3

I have urges to urinate that end in urine leakage.

*Never*

*Sometimes*

*Often*

4

When I leave my house, I plan my activities around the nearest bathroom.

*Never*

*Sometimes*

*Often*



# Physical Exam

- Assessment of mobility and cognitive function
- Pelvic examination
  - Evaluate for atrophy, prolapse beyond the vaginal introitus, prior surgery
- Assessment of post-void residual urine volume
- Cough stress test
- Urinalysis
  - hematuria, pyuria, bacteriuria, glucosuria



# TREATMENT



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# AUA Guidelines on OAB, 2012

## **DIAGNOSIS AND TREATMENT OF OVERACTIVE BLADDER (Non-Neurogenic) IN ADULTS: AUA/SUFU GUIDELINE**

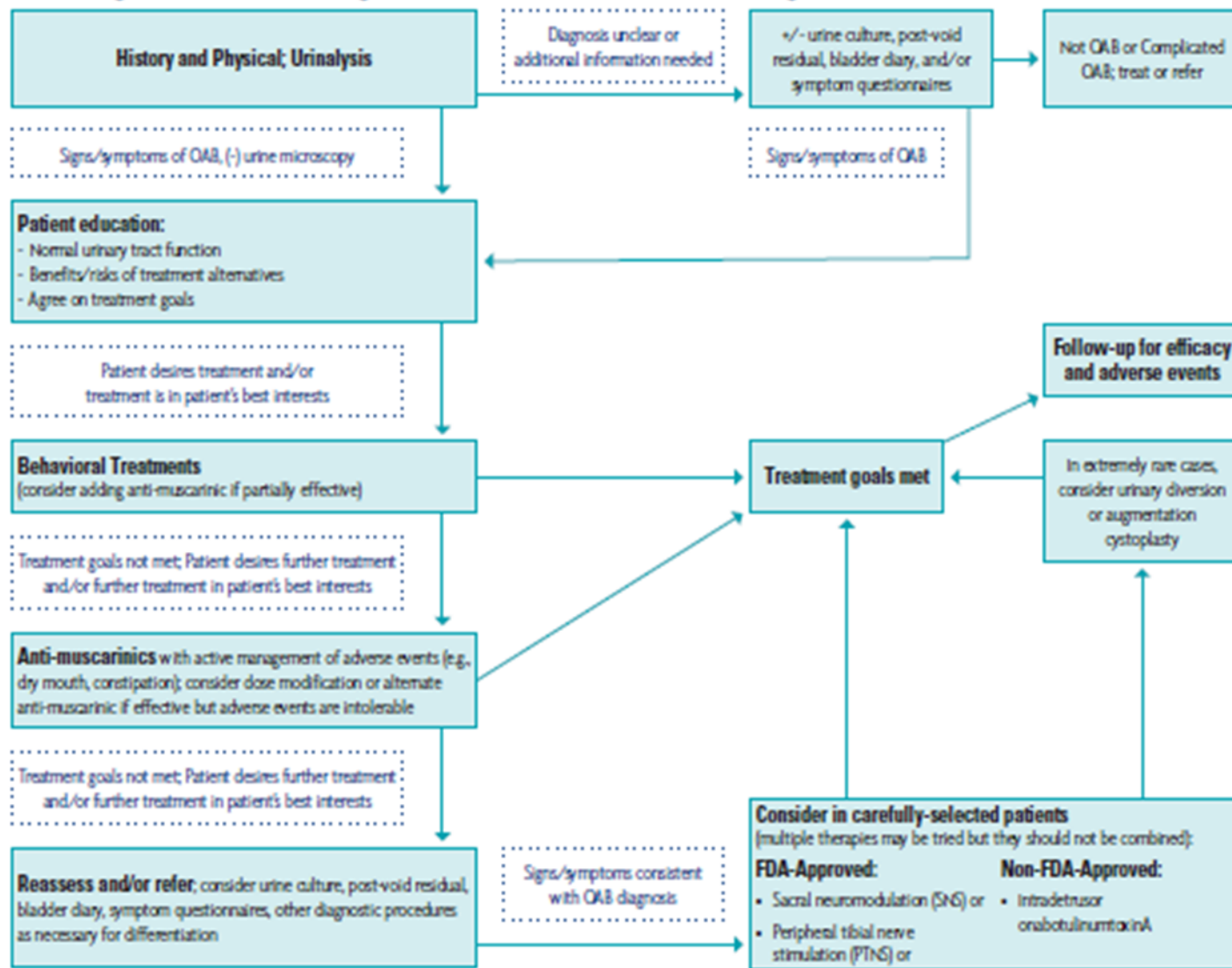
E. Ann Gormley, Deborah J. Lightner, Kathryn L. Burgio, Toby C. Chai, J. Quentin Clemens, Daniel J. Culkin, Anurag Kumar Das, Harris Emilio Foster, Jr., Harriette Miles Scarpero, Christopher D. Tessier, Sandip Prasan Vasavada



# AUA/SUFU OAB Diagnosis & Treatment Algorithm 2012

[www.auanet.org](http://www.auanet.org)

## Diagnosis & Treatment Algorithm: AUA Guideline on Non-Neurogenic Overactive Bladder in Adults.



The complete OAB Guideline is available at [www.AUAnet.org/Guidelines](http://www.AUAnet.org/Guidelines).

This resource is supported by an educational grant from Astellas Scientific and Medical Affairs, Inc.

# Treatment Algorithm for OAB

## Conservative Therapy

Behavioral  
Diet Modification  
Pelvic Floor PT

## Pharmacotherapy

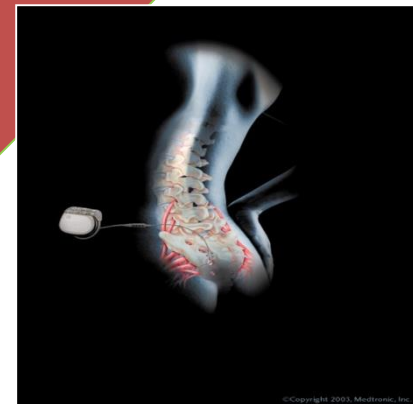
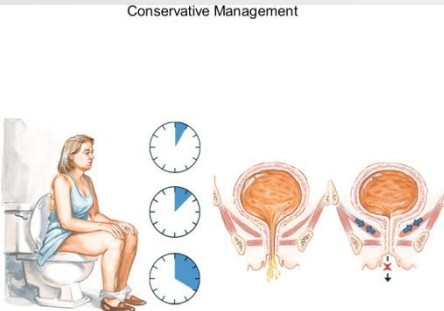
## Neuromodulation

*Botox*  
*PTNS*  
*Sacral Neuromodulation*

## Surgical Intervention

Urinary Diversion,  
Augmentation  
Cystoplasty

Conservative Management



©Copyright 2005, Medtronic, Inc.



# Conservative Therapy

- Lifestyle changes
  - Caffeine reduction
  - Fluid management
- Prevent constipation
- Maintain a healthy weight
- Re-train the bladder--Mind Over Bladder
  - Work with a pelvic floor physical therapist
  - There are home programs as well
    - [www.accidentalsisterhood.com](http://www.accidentalsisterhood.com)
- Pelvic Floor Physical Therapy
  - Strengthening, urge suppression
- Bladder diary—app or paper:
  - 24 hour record of volume in, out, leakage episodes, triggers



# Voiding Diary

3-Day Voiding Diary					
Time of day	Fluid intake	Toilet urinations	Amount of urine drained via a catheter	Leaks	Pad changes
circle bedtime and wake up times below; also fill in events at right in the time slots when they occurred	write down amount of liquid you drank - in oz - from one toileting event to next	write down oz urinated into urinary hat sitting inside toilet seat each time you urinate	if using a catheter, record amount in oz, ml, or cc; indicate if this was catheter [C] residual [R]	place check mark in column if you leaked urine before making it to toilet	at each toileting event write "D" if pad is dry or if wet, write down amount: small, mod., large
7 am					
8 am					
9 am					
10 am					
11 am					
noon					

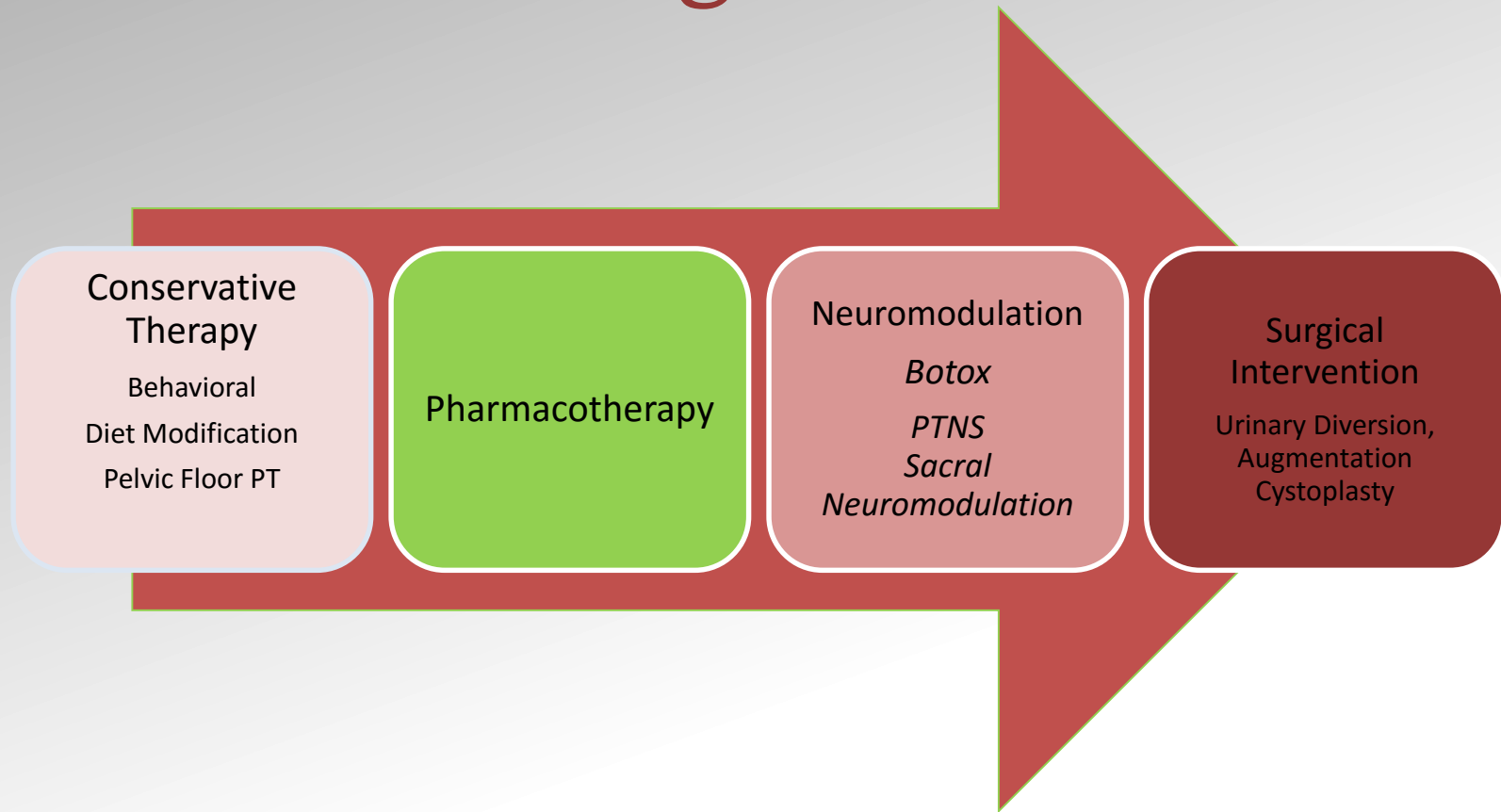
[www.sufuorg.com](http://www.sufuorg.com)



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# Treatment Algorithm for OAB



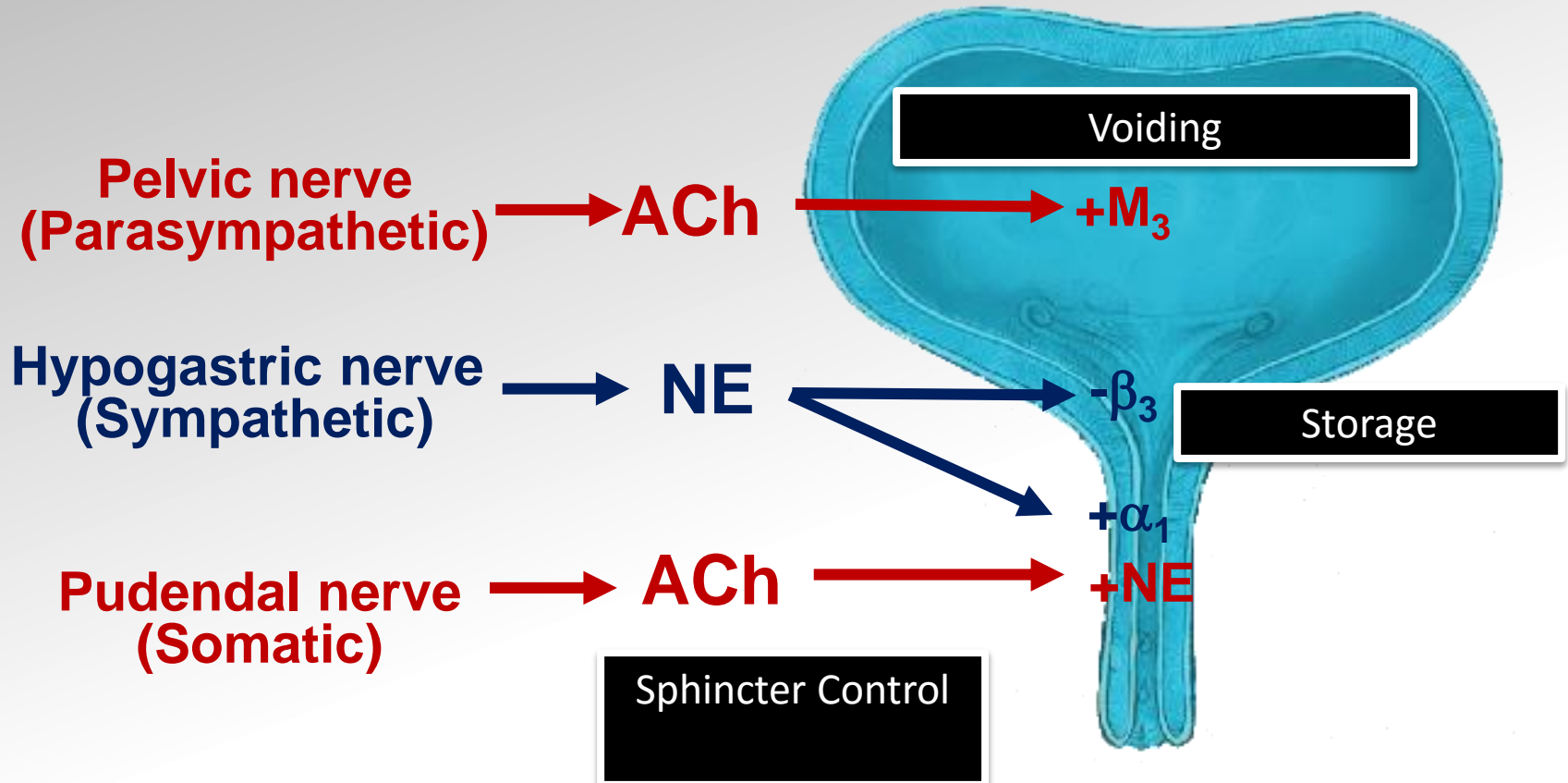
# Anticholinergics

- Oxybutynin Chloride – Immediate Release
- Oxybutynin Chloride XL (Ditropan XL)
- **Transdermal Oxybutynin Patch (Oxytrol)**
- **Oxybutynin Chloride Gel (Gelnique)**
- Tolterodine – Immediate Release
- Tolterodine LA (Detrol LA)
- **Fesoterodine fumarate (Toviaz)**
- Trospium (Sanctura)
- Trospium Chloride XR (Sanctura XR)
- Solifenacin (Vesicare)
- Darifenacin (Enablex)

*Introduced 2009*  
*OTC since 2013*



# LUT Peripheral Motor Innervation



Adapted from: de Groat WC and Yoshimuran N. *Annu Rev Pharmacol Toxicol.* 2001;41:691-721



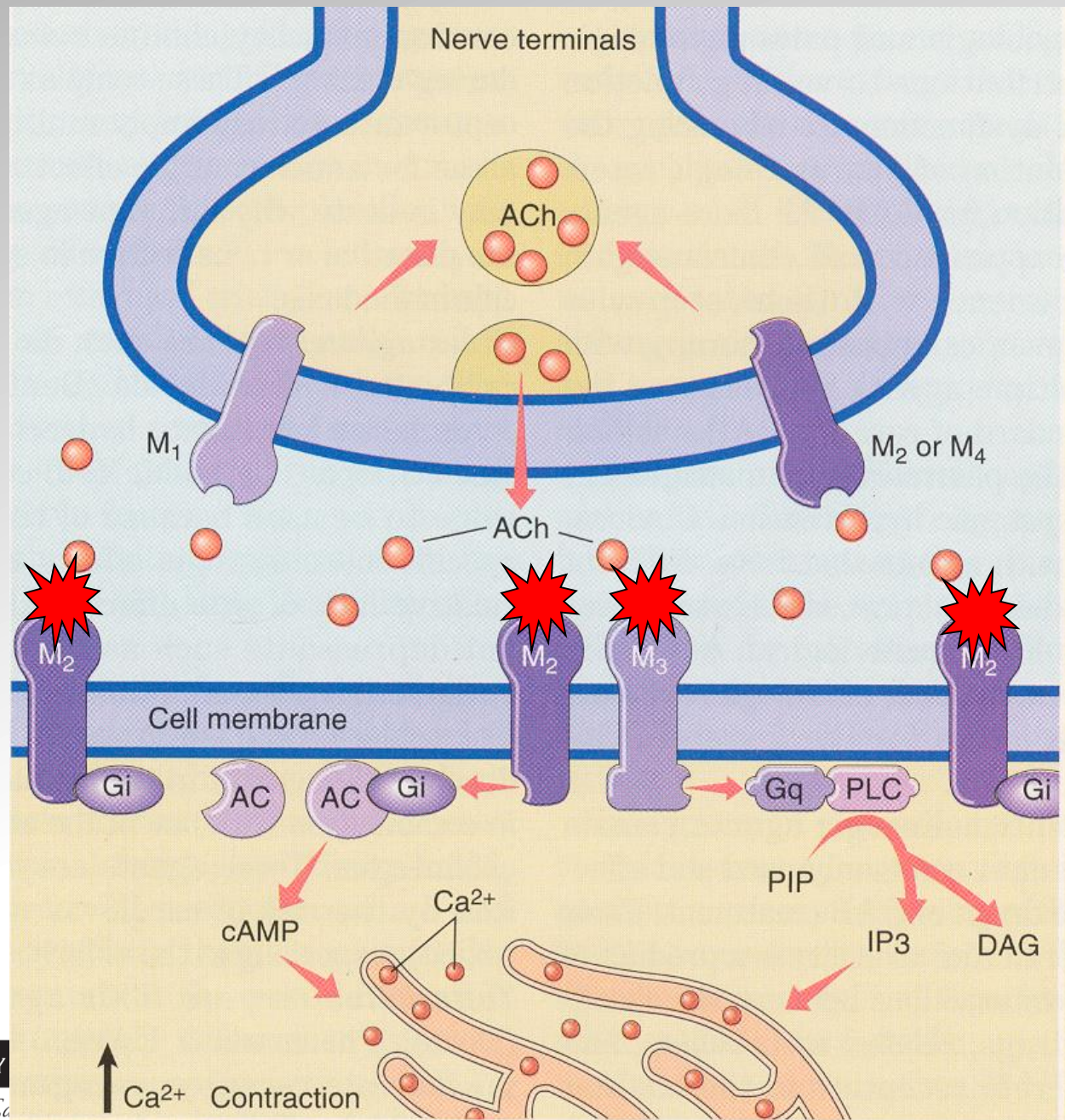


# Anticholinergics: Mechanism of Action

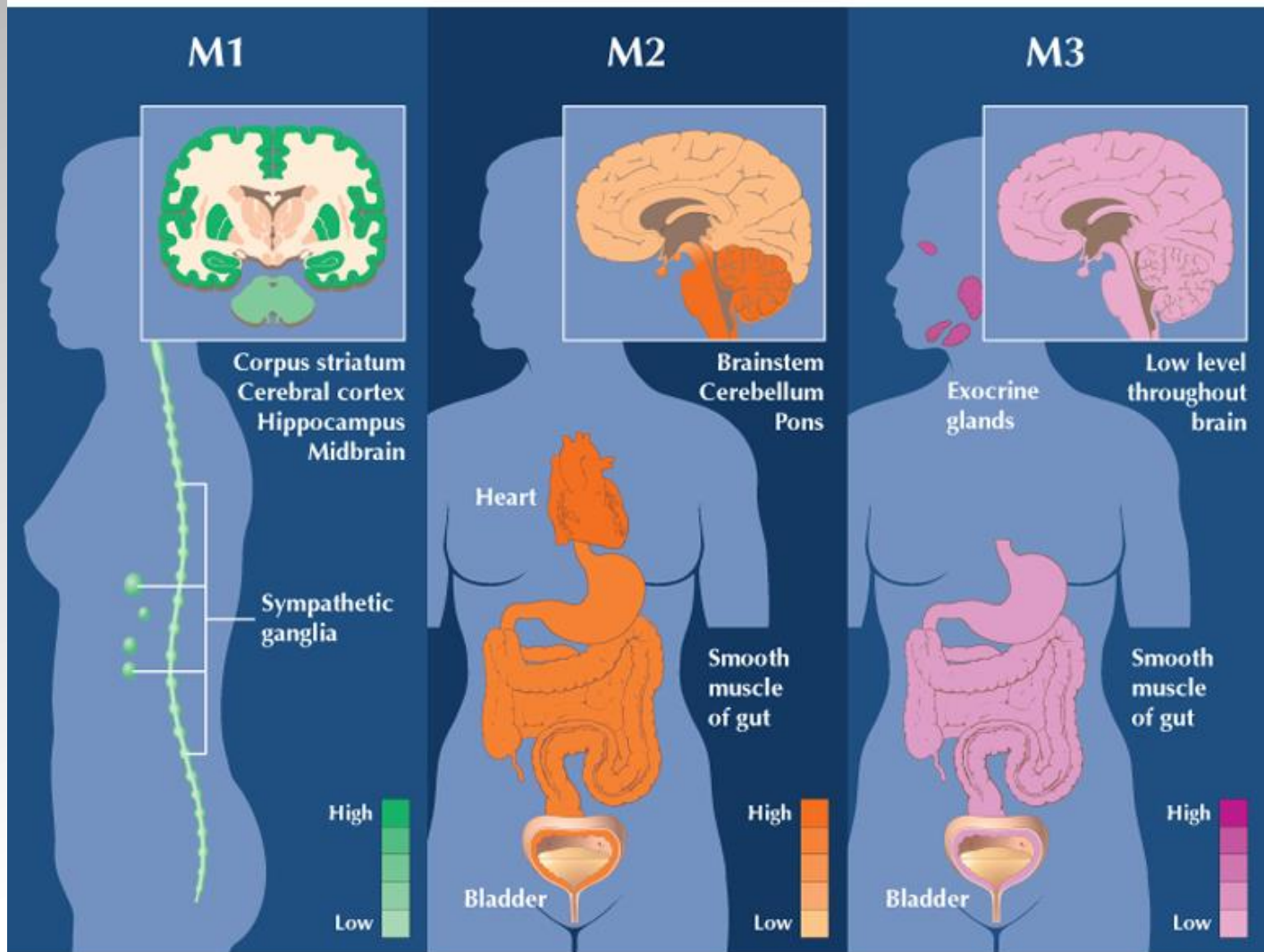
- Detrusor (bladder) muscle rich in cholinergic/muscarinic receptors
- Medications block muscarinic receptors in detrusor
  - stabilize bladder muscle
- ? Influence suburothelial receptors as well
  - Mediate urgency
- Multiple muscarinic subtypes have been identified



# Comparative Receptor Presence in Detrusor Wall



# Distribution of Muscarinic Receptors Throughout the Body



# Receptor Activity

- M2 receptors make up 2/3 of M receptors in detrusor, but M3 receptors appear to facilitate contractile response in **normal** bladders
- Research suggests facilitation via M2 in certain disease states and aging

Ruggieri et al. *Auton Autacoid Pharmacol* 2006;26:311–325.



# Antimuscarinic Class Side Effects

- Dry mouth
- Constipation
- Blurred vision
- Headache
- Cognitive Impairment



# Oxybutynin

- Some selectivity for M3 and M1 receptors
- Other bladder activity
  - Direct smooth muscle relaxation
  - Local anesthesia
- Active metabolite: N-Desethyloxybutynin (N-DEO)
  - Potent antimuscarinic
  - Responsible for significant side effects
- Used for decades
- **Side effects limit use**
- May cause cognitive dysfunction



# Long-term Evaluation of Oxybutynin IR for OAB

- Prospective randomized trial to compare oxybutynin 2.5 mg bid or 5 mg qhs
- Titrate doses up
- 53% overall reported improvement or cure
- **2/3 stopped medication within 4 months**

Salvatore et al. *Eur J Obstet Gynecol Reprod Biol* 2005;119:237–241.



# Oxybutynin Extended Release

- Oxybutynin placed in slow-release vehicle
- Release of all medication takes 24 hours
- More released in distal GI tract with less metabolism
- Better efficacy, fewer side effects
- Available in 3 doses: 5, 10, 15 mg
  - Can be titrated
- Approved at doses up to 30 mg
  - Usually for patients with neurogenic overactivity





# Tolterodine (Detrol)

- First drug developed to specifically treat OAB
  - Greater selectivity for bladder
- Low potential to cross blood-brain barrier
  - Thought to have fewer cognitive side effects
- Extended-release form found to have increased efficacy with fewer side effects



# Trospium (Sanctura)

- Nonselective quaternary amine
  - More highly charged and hydrophilic
  - Should not cross blood brain barrier
- Minimal metabolism—most drug renally excreted unchanged
  - Does not interact with drugs metabolized by cytochrome P450 system
- Available in once/day dosing; must be taken on an empty stomach



# Solifenacin (Vesicare)

- M3 selective antimuscarinic
- Available in 2 doses: 5 and 10 mg
  - Can be titrated
- Long half-life = 50 hours



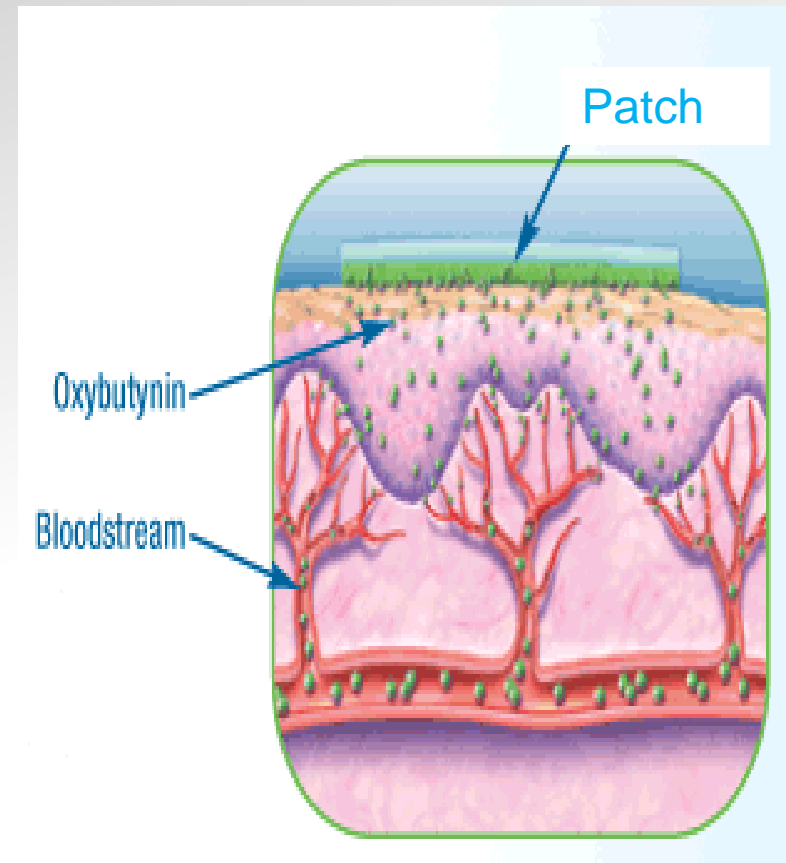
# Darifenacin (Enablex)

- Relatively M3 selective
- Low affinity for M1 receptor
  - Much of CNS cholinergic activity involves M1 receptors
  - Few CNS side effects
  - No QT interval prolongation
- Available in 2 doses: 7.5 and 15 mg
  - Can titrate



# Oxybutinin Transdermal System (Oxytrol)

- Apply every fourth day
- Avoids first-pass metabolism, therefore lower N-DEO metabolite
- Fewer systemic side effects
  - Dry mouth and constipation = placebo
  - 17% incidence of skin reactions
    - Contact dermatitis
    - Erythema resolves
    - Pruritus –moisturizer and rotate location



# Oxytrol

## Oxytrol® For Women.

The first over-the-counter treatment for overactive bladder (OAB) in women — in an easy-to-use patch.

LEARN MORE ▶



**\$19.99 for a one month supply at  
Target—NOT ANYMORE**



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# Oxybutinin Topical Chloride Gel (Gelnique)

- Once daily gel formulation
- Similar systemic side effect profile to patch
- Less local skin reaction



# Fesoterodine (Toviaz)

- Pro-drug, rapidly metabolized to 5-HMT, the major active metabolite of tolterodine
- Available as 4mg and 8mg once daily doses





# Anticholinergic Side Effects

Agent	Chemical Structure	Dry Mouth	Constipation	Cognition	Sleep
Oxybutinin (IR)	Tertiary amine	93%	50%	Yes	Yes
Tolterodine (LA)	Tertiary amine	24.3%	6.1%	Minimal effects on EEG, case reports of night terrors, hallucinations	Yes
Darifenacin	Tertiary amine	20-31%	19-24%	None reported	None reported
Solifenacin	Tertiary amine	14-21%	7%	None reported	None reported
Tropium chloride	Quaternary amine	22%	9.5%	No, minimal effects on quantitative EEG	None reported

Staskin DR, Drugs Aging 2005; 22(12): 1013-1028



Table 1. Incidence Rates of Adverse Events.

Drug	Dry Mouth (%)	Constipation(%)
Fesoterodine		
4mg	19	4
8mg	35	6
Darifenacin		
7.5mg	20	15
15mg	35	21
Solifenacin		
5mg	11	5
10mg	28	13
Trospium		
20mg BID	20	10
XR 60mg	11	9
Tolterodine		
ER 4mg	23	6
Oxybutynin		
IR 5-20mg/day	71	13
XL 10mg	29	7
Gel	8	1

# “Head to Head” Studies

- Lack of direct comparison studies
- Most current data based on comparisons of single agents with placebo



# Anticholinergic Discontinuation

- Database Study from UK (1991-2005)
  - 49,419 episodes of anticholinergic therapy
  - Overall discontinuation rate
  - Drug specific discontinuation rate

Gopal et al, Obstet Gynecol 2008; 112:1311-8



# Anticholinergic Discontinuation

- Median time to discontinuation = **4.76 months** (all drugs)
- 50% of women prescribed anticholinergics discontinue the medication at 6 months
  - 75% by 1 year
- Rates of discontinuation increase with duration of use

Gopal et al, Obstet Gynecol 2008; 112:1311-8



# Anticholinergics (Ach) & Cognitive Impairment

- Acute impairment in:
  - Working memory
  - Attention
  - Psychomotor speed
- Global cognitive impairment
- Elderly patients are more susceptible due to age-related changes of pharmacokinetics.
- Cholinesterase inhibitors may precipitate incontinence and pharmacologically directly oppose the action of Ach  
*(Boudreau et al, JAGS 59:2069-2076)*



# Cumulative Use of Strong Anticholinergics and Incident Dementia

## A Prospective Cohort Study

Shelly L. Gray, PharmD, MS<sup>1</sup>; Melissa L. Anderson, MS<sup>2</sup>; Sascha Dublin, MD, PhD<sup>2,3</sup>; Joseph T. Hanlon, PharmD, MS<sup>4</sup>; Rebecca Hubbard, PhD<sup>2,5,6</sup>; Rod Walker, MS<sup>2</sup>; Onchee Yu, MS<sup>2</sup>; Paul K. Crane, MD, MPH<sup>7</sup>; Eric B. Larson, MD, MPH<sup>2,7</sup>

[\[+\] Author Affiliations](#)

*JAMA Intern Med.* 2015;175(3):401-407. doi:10.1001/jamainternmed.2014.7663.

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- Cognitive effects thought to be reversible upon discontinuation.
- Longitudinal study followed patients from 1994-2004.
- 10 year cumulative dose-response relationship was observed for dementia (0.9 vs. 1.54) and Alzheimer disease



Original Investigation

# Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults

Shannon L. Risacher, PhD; Brenna C. McDonald, PsyD, MBA; Eileen F. Tallman, BS; John D. West, MS; Martin R. Farlow, MD; Fredrick W. Unverzagt, PhD; Sujuan Gao, PhD; Malaz Boustanli, MD, MPH; Paul K. Crane, MD, MPH; Ronald C. Petersen, MD, PhD; Clifford R. Jack Jr, MD; William J. Jagust, MD; Paul S. Aisen, MD; Michael W. Weiner, MD; Andrew J. Saykin, PsyD; for the Alzheimer's Disease Neuroimaging Initiative

- Longitudinal study of 2 cohorts of cognitively normal adults.
- Use of anticholinergics was assessed

JAMA Neurol Published online 4/18/16



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Original Investigation

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- Use of medications with medium or high anticholinergic activity was associated with poorer memory, executive function, brain hypometabolism, brain atrophy, and increased risk of clinical conversion to cognitive impairment.
- Study concludes--"Use of medication with significant anticholinergic activity should likely be discouraged in older adults if alternative therapies are available.

JAMA Neurol Published online 4/18/16



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# COMBINATION THERAPY



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# Combined PFE and Drug Therapy for Urge Incontinence in Older woman

Randomized crossover

N = 35

PFE → PFE + Drug

57.5% → 88.5%

Drug → Drug + PFE

72.% → 84.3%

Burgio K et al. *J Am Geriatr Soc.* 2000;48:370-374.



# Combined Behavioral and Drug Therapy for Urge Incontinence

“Whether drug and behavioral therapy are combined from the onset or used sequentially in a stepped program, the evidence from the present study is that *two interventions combined have a greater potential to enhance outcome than could be achieved by either intervention alone.*”

Burgio K et al. *J Am Geriatr Soc.* 2000;48:370-374.



# Behavioral Therapy: BE-DRI Study

- 307 woman with urge-predominant incontinence
  - 153 tolterodine ER alone
  - 154 tolterodine ER + Behavioral Therapy
    - Pelvic floor exercises
    - Behavioral strategies to diminish urgency, suppress bladder contractions
    - Delayed voiding
    - Individualized fluid management
  - Drug discontinued at 10 weeks in both groups, behavior therapy continues
  - Reassessed at 6 months

Burgio et al, Ann Intern Med 2008: 149: 161-169



# Behavioral Therapy: BE-DRI Study

*Table 4. Adjusted Mean Incontinence Episodes per Week\**

Variable	Incontinence Episodes, <i>n</i>	
	Combination Therapy ( <i>n</i> = 154)	Drug Therapy Alone ( <i>n</i> = 153)
Pretreatment	23.1	23.2
End of stage 1	2.7	4.7
Mean reduction	20.4	18.5
Difference between groups (95% CI), <i>percentage points</i>	1.9 (–2.0 to 5.9)	

\* Computed from mixed-model analysis of variance, controlling for randomization stratum and site.

Burgio et al, Ann Intern Med 2008: 149: 161-169



# Behavioral Therapy: BE-DRI Study

- Combination therapy reduces incontinence frequency during active treatment
- Behavioral therapy *does not allow* patients to discontinue drug therapy and still maintain incontinence improvement
- Combination therapy leads to higher patient satisfaction, perceived improvement, and reduction of other bladder symptoms



# NEW TARGETS: BETA 3 RECEPTOR AGONISTS



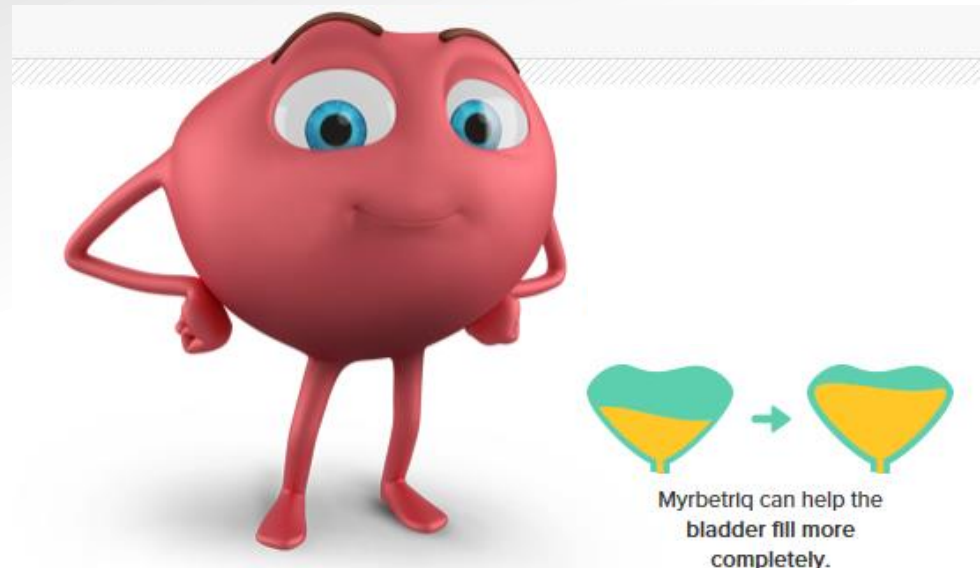
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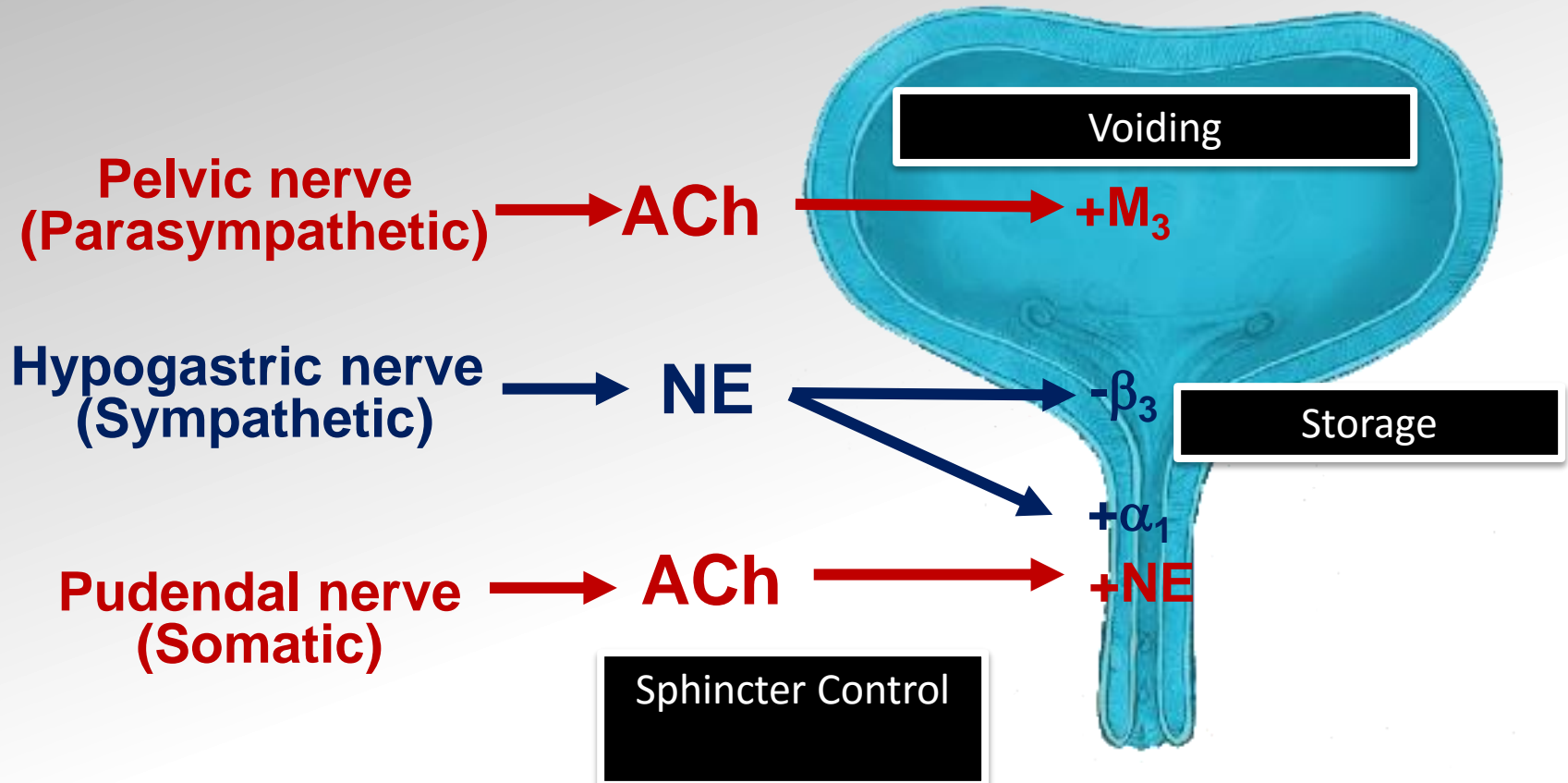


# Beta 3 Receptor Agonist (Mirabegron)

- Novel Target for OAB
- Introduced October 22, 2012
- Brand name = Myrbetriq



# LUT Peripheral Motor Innervation

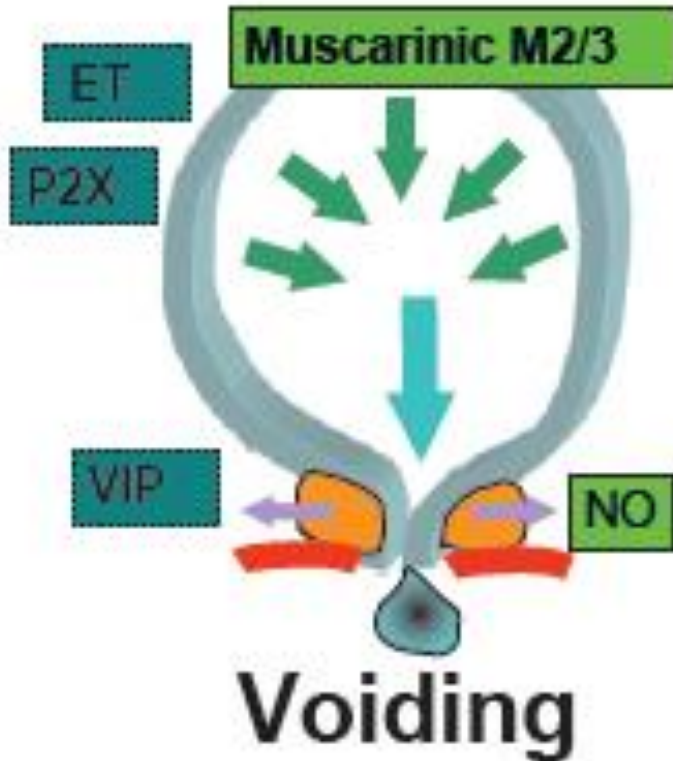


Adapted from: de Groat WC and Yoshimuran N. *Annu Rev Pharmacol Toxicol.* 2001;41:691-721

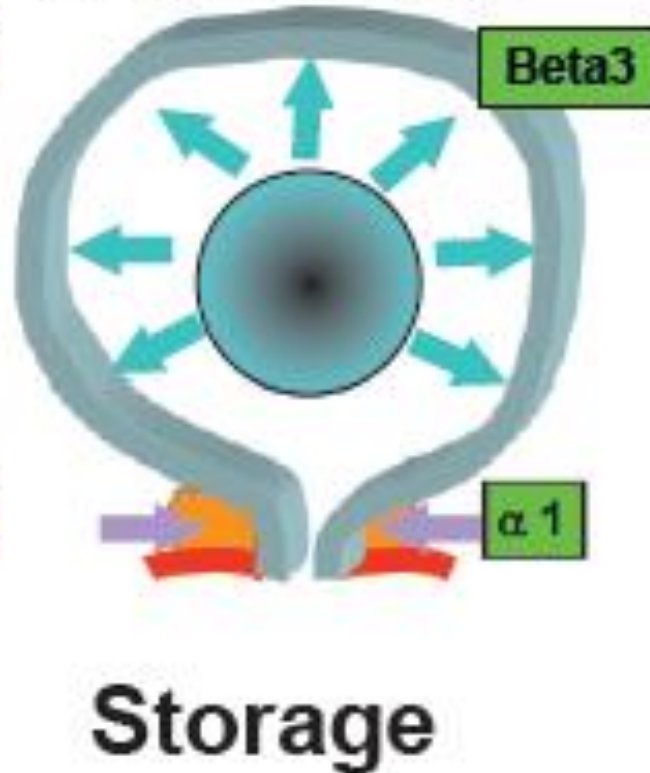


# How it Works

Pelvic Nerve  
(Parasympathetic Nerve)



Hypogastric Nerve  
(Sympathetic Nerve)



Takeda, et al J Pharmcol Sci, 112, 121-127 (2010)



# U.S. Phase III Trial

- Nitti et al, *Results of a Randomized Phase III Trial of Mirabegron in Patients with OAB*, J Urol, Accepted Manuscript 2012

	Placebo	50mg	100mg
Mean decrease in incontinence episodes/24h	-1.13	-1.47	-1.63
Mean decrease in micturition/24 h	-1.05	-1.66	-1.75

- *Magnitude of improvement is similar to that of anticholinergic medication*



# European-Australian Phase III Trial

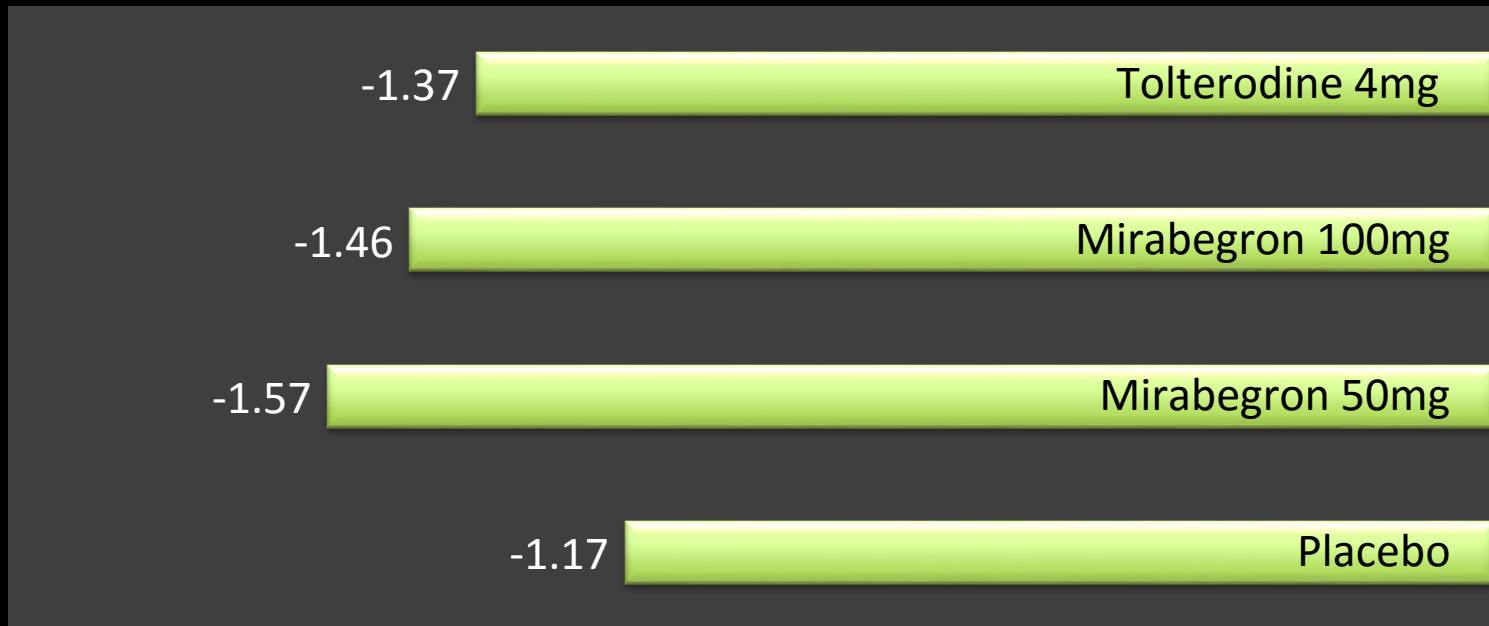
- Compared placebo, 50mg, 100mg, & tolterodine ER 4mg
- 1,978 patients randomized
  - 549 men & 1,429 women
- Primary endpoints
  - Assess safety and tolerability
  - Compare efficacy and safety with once daily tolterodine



# European-Australian Phase III Trial

## Mean change from baseline in Number of incontinence episodes

■ Mean change from baseline in Number of incontinence episodes



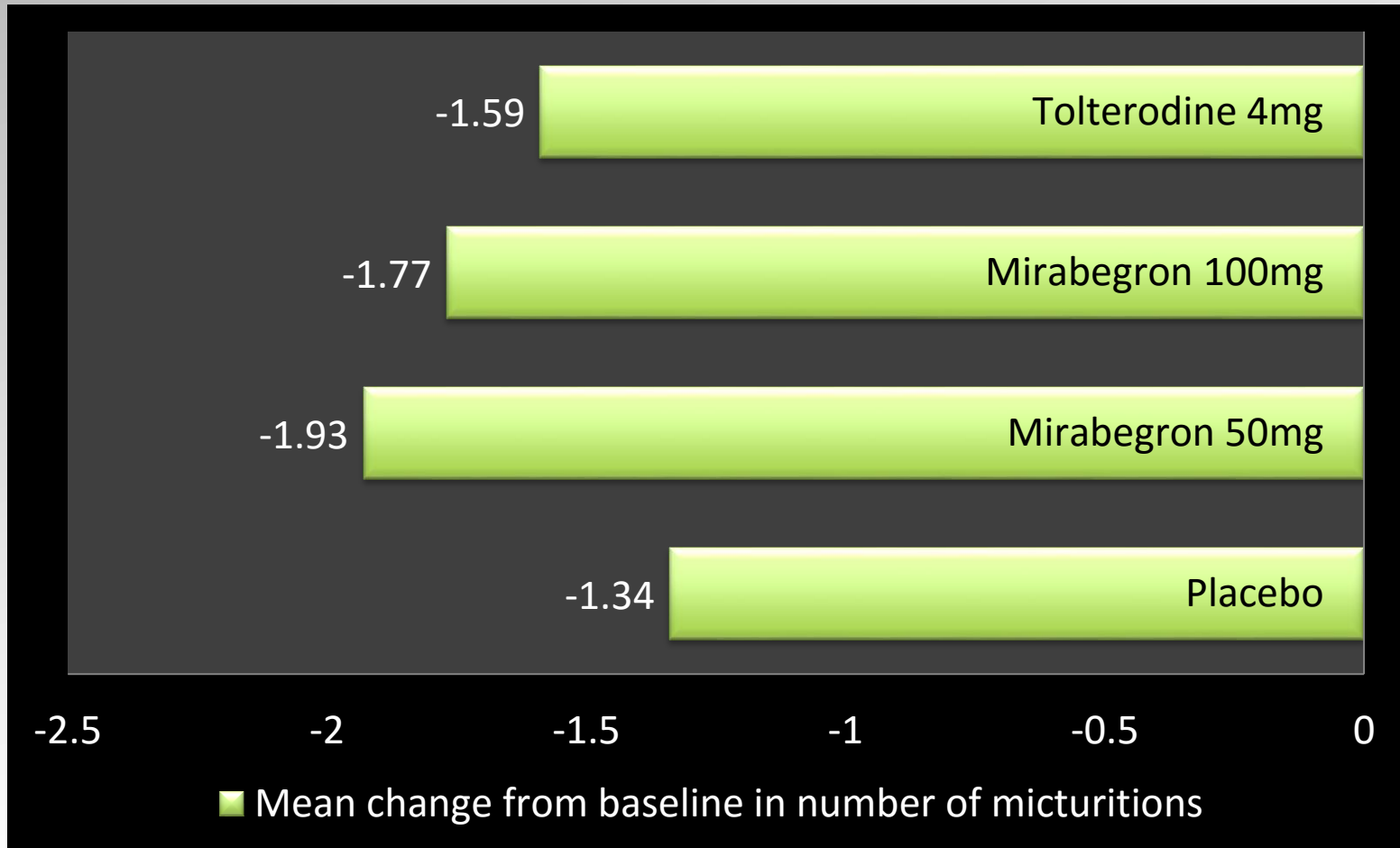
Khullar et al, Abstract Annual Congress of EUA, 2011, Vienna



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# European-Australian Phase III Trial



# European-Australian Phase III Trial

Adverse Events (%)	Placebo (n=494)	50mg (n=493)	100mg (n=496)	Detrol (n=495)
Hypertension	7.7	6.9	6.4	8.1
Nasopharyngitis	1.6	2.8	2.8	2.8
Dry Mouth	2.6	2.8	2.8	10.1
Headache	2.8	3.7	1.8	3.6
Influenza	1.6	2.2	2.0	1.4
UTI	1.4	1.4	1.8	2.0
Constipation	1.4	1.6	1.6	2.0





# Prescribing Issues

- Beta receptors
  - B1 Heart muscle contraction
  - B2 Smooth muscle relaxation
  - B3 Enhance lipolysis, Promotes relaxation of detrusor muscle in the bladder



# Prescribing Issues

- Small increase in BP
  - At 50mg dose in healthy volunteers, **the maximum increase in SBP/DBP = 4.0/1.6 mmHg** greater than placebo
  - Dose dependent
  - Reversible upon discontinuation
  - Caution in patients with hypertension



# Prescribing Issues

- Inhibitor of CYP2D6
- Can increase systemic exposure to:
  - Metoprolol
  - Desipramine
- Use caution when prescribed with:
  - Thioridazine
  - Flecainide
  - Propafenone



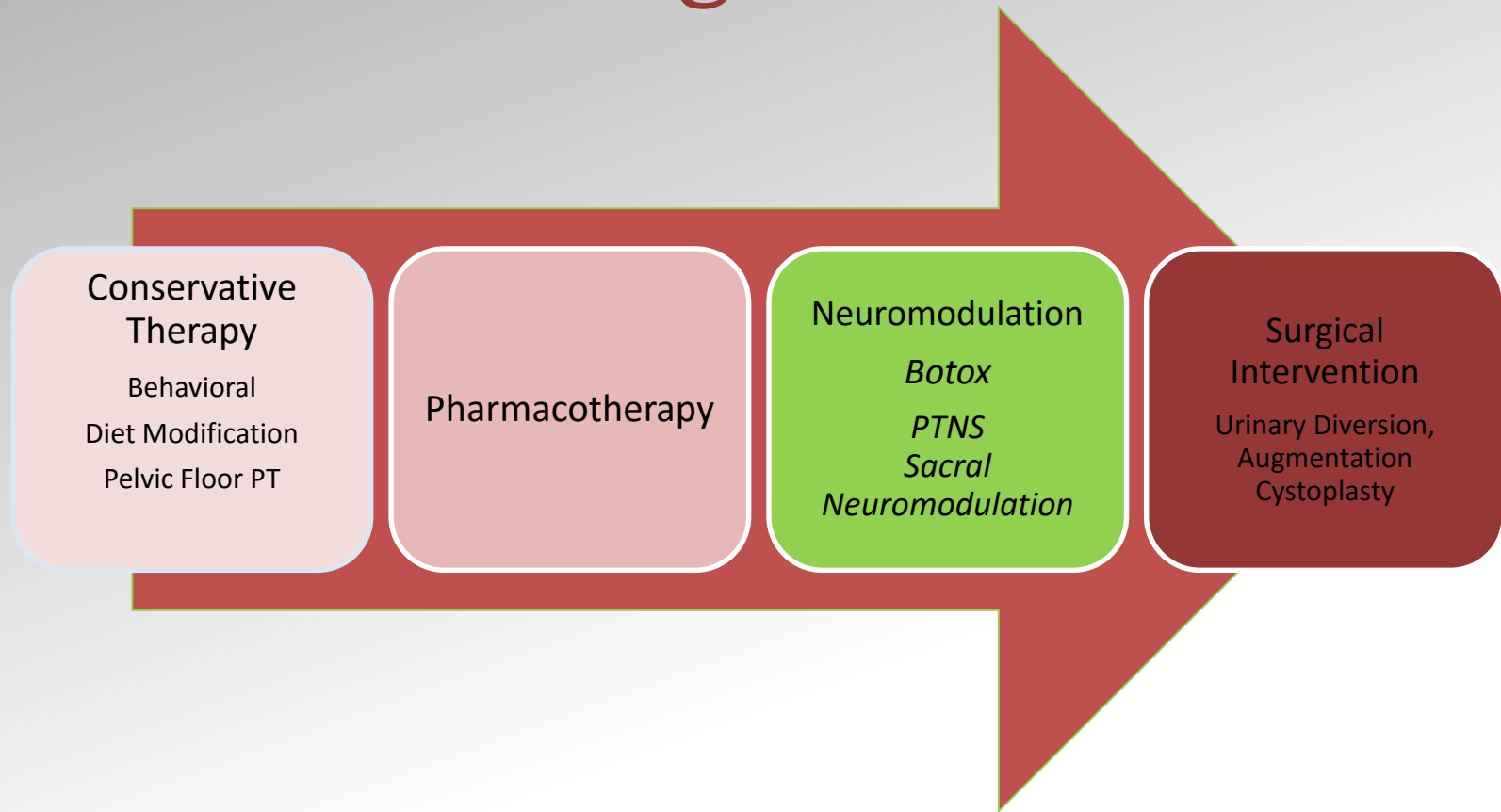
# NEUROMODULATION CHEMICAL & ELECTRICAL



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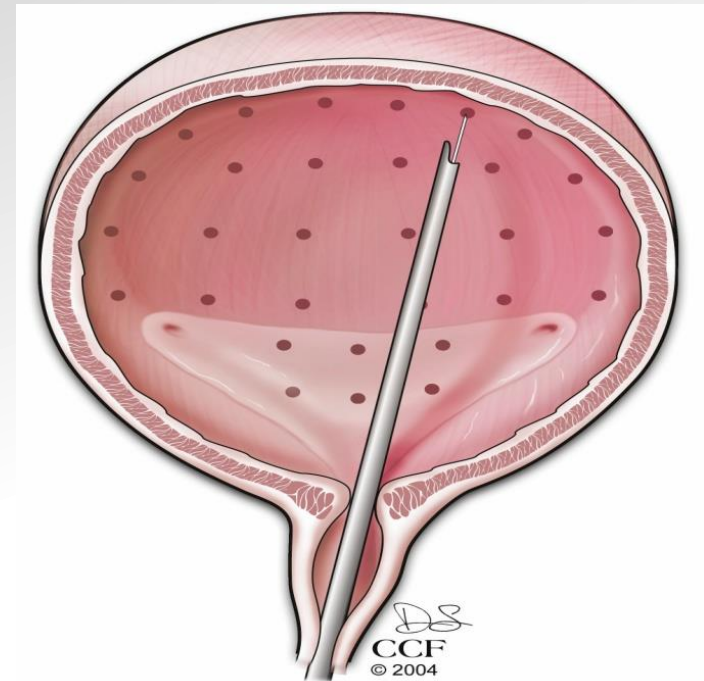
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# Treatment Algorithm for OAB



# Botulinum Toxin - Botox

- Decreases bladder muscle's ability to contract
  - Inhibits acetylcholine release at presynaptic cholinergic junction
  - Regional decreased muscle contractility and atrophy
- Can be done in the office with local anesthetic or in the OR with sedation
- Reversible in 5-8 months (detrusor)



# Trials of Botox for Idiopathic OAB

- 4 Randomized, placebo controlled
  - Brubaker et al, 2008
  - Dmochowski et al, 2010
  - Flynn et al, 2009
  - Sahai et al, 2007
- 2 Randomized, without placebo control
- 15 Observational studies
  - Without control groups
- *Significant reductions in incontinence episodes and in urgency were reported in all active treatment groups*



# Botox for Refractory Idiopathic OAB

- 28 patients 200 units BoNT-A
- 15 patients placebo injections
- 60% BoNT-A documented improvement (questionnaire)
- Median response duration = 373 days
- **Trial placed on clinical hold**
  - *43% women had post-void residual >200mL requiring CIC*
  - *Mean duration of CIC = 62 days*

Brubaker et al, J. Urol 2008 180(1) 217-222





# Botox In Older Women

- Limited Data
- 21 patients aged 75-92 were assessed one month after Botox injection (200 units)
  - 16/21 patients (76%) reported greater than 50% improvement in symptoms
  - Frequency decreased from 11-5 voids/day
  - Pad use decreased from 4-1 pad/day
  - No complications reported

White et al, J Urol, 2008; 180(6): 2522-6



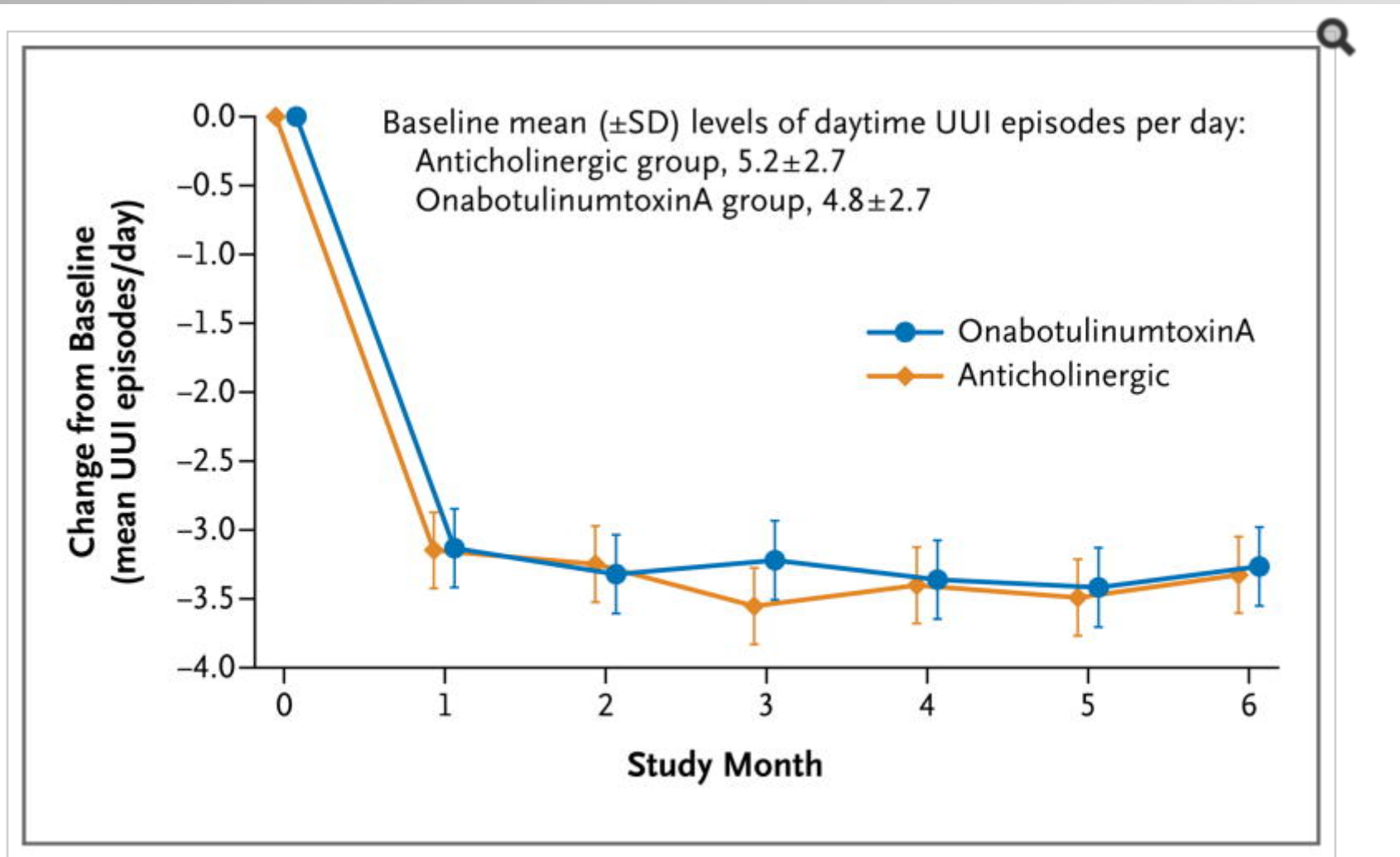
# ABC Study

- The ABC study was designed to compare treatment with an anticholinergic medication (Solifenacin or Trospium) to a single Botox A<sup>®</sup> injection into the bladder.
- 242 women participated  
100 units Botox used

Visco AG, Brubaker L et al. [Anticholinergic therapy vs. onabotulinum toxin A for urgency urinary incontinence](#). New England Journal of Medicine November 8 2012;367(19):1803



# ABC Study



**Reduction from Baseline in Number of Episodes of Urgency Urinary Incontinence (UUI) per Day**



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# ABC Study

- Both groups of women had less urge urinary incontinence episodes.
  - Decrease from about 5 episodes per day to about 1.5 episodes.
- Women who received the Botox A<sup>®</sup> injection were more likely than those taking the oral medication to report no incontinence episodes (they were completely dry).
  - Botox 27% at 6 months vs. 13% oral medication
- Both groups of women had improved quality of life after treatment.
- Side effects differed between groups. **Women in the Botox group needed to use a catheter intermittently to help them empty their bladder (5%). They were also more likely to get treatment for urinary tract infections (33%).** The women in the anticholinergic medication group reported more dry mouth.

Visco AG, Brubaker L et al. Anticholinergic therapy vs. onabotulinum toxin A for urgency urinary incontinence. New England Journal of Medicine November 8 2012;367(19):1803



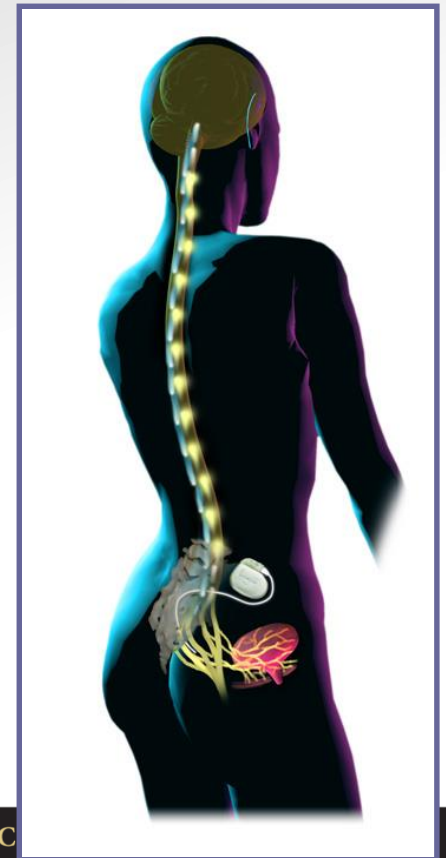
# AUA OAB Guidelines on Botox

- FDA-approved for Idiopathic OAB (1/18/13)
- Symptoms improve
- *Risk of adverse events requiring secondary interventions is substantial (UTI, retention)*
- Patients must be willing to perform self-catheterization for long periods
- Clinician must be able to measure PVR
- Repeat injections are necessary to maintain improvement



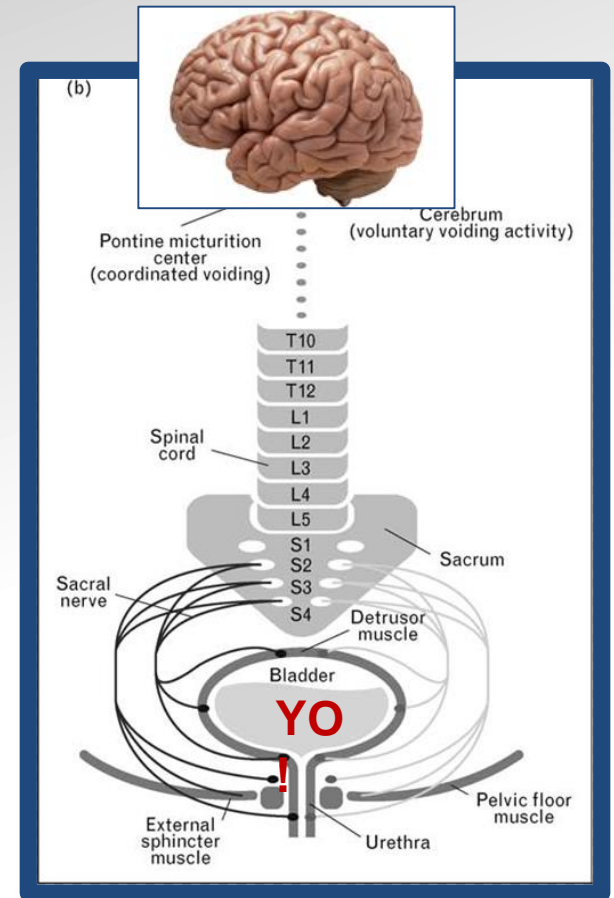
# Sacral Neuromodulation (Interstim)

- FDA approved in 1997 for refractory:
  - Urgency/frequency
  - Urge incontinence
  - Idiopathic urinary retention

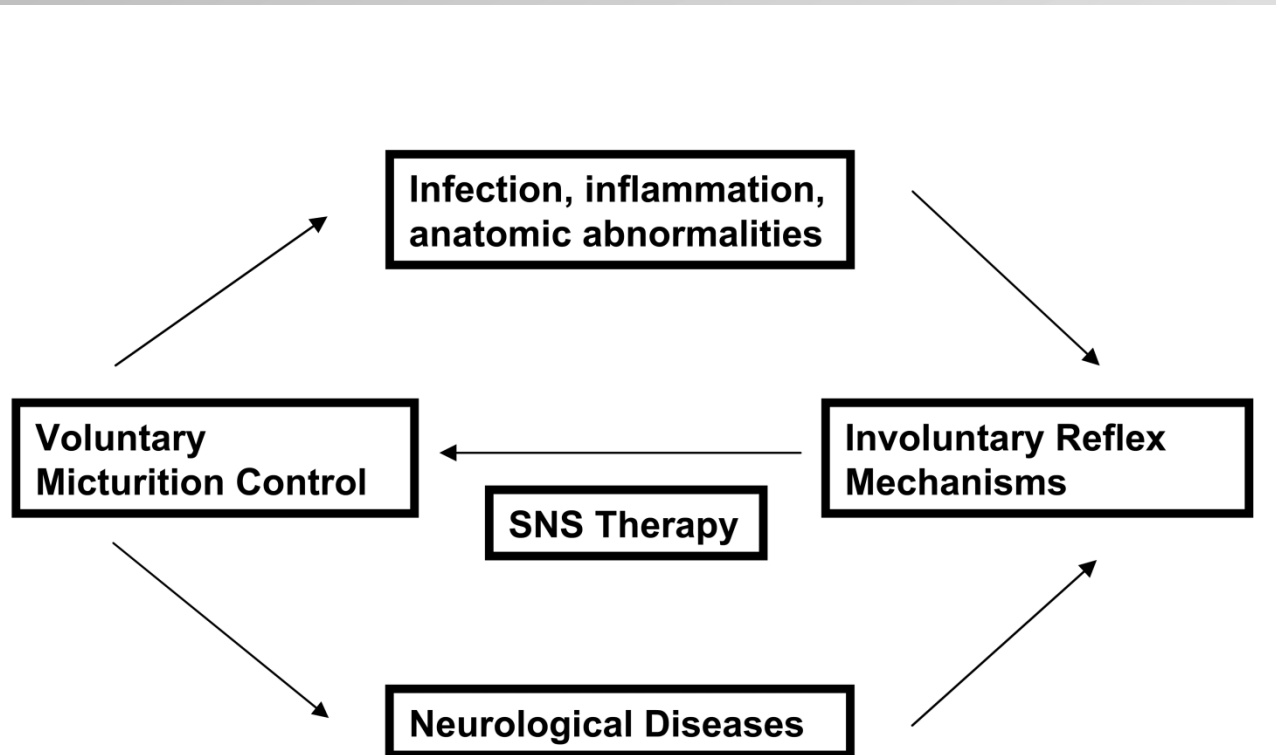


# Sacral Neuromodulation

- Neuromodulation of sacral nerves
- Mechanism not fully understood
- Theory:
  - Alters the nerve signals going from the bladder back to the spinal cord ultimately leading to less frequent bladder contractions



# Sacral Neuromodulation





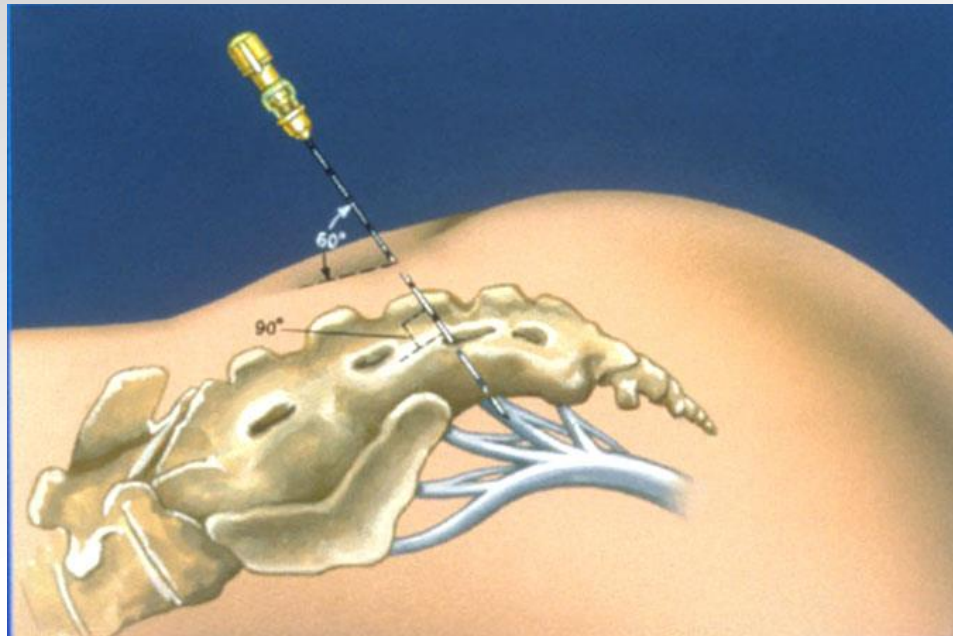
# Interstim--Medtronic

- <http://www.everyday-freedom.com/women/about/therapy/index.htm>



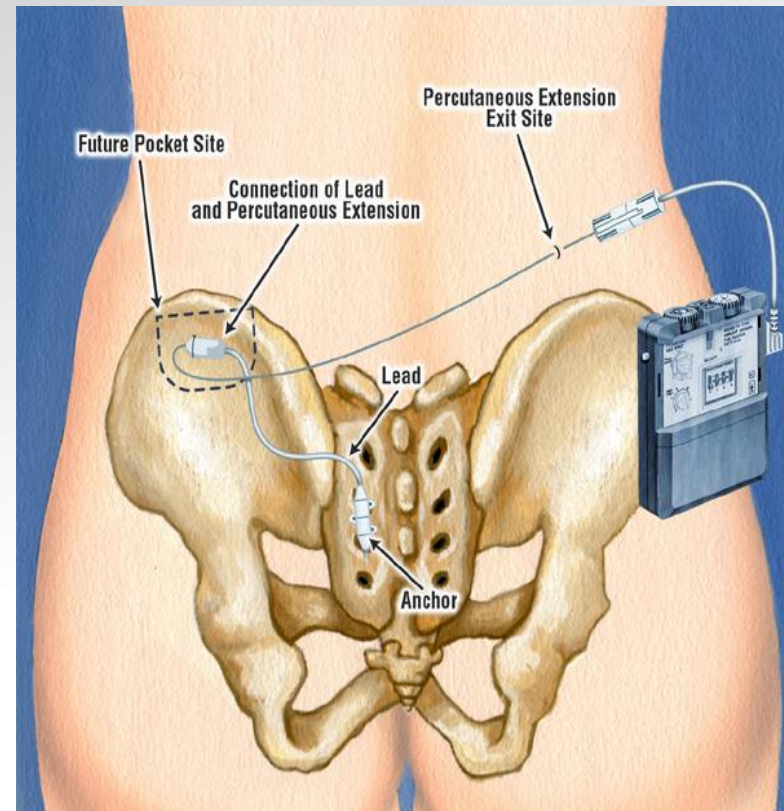
# InterStim Test Stimulation Procedure

Simple outpatient procedure  
Done under local anesthetic



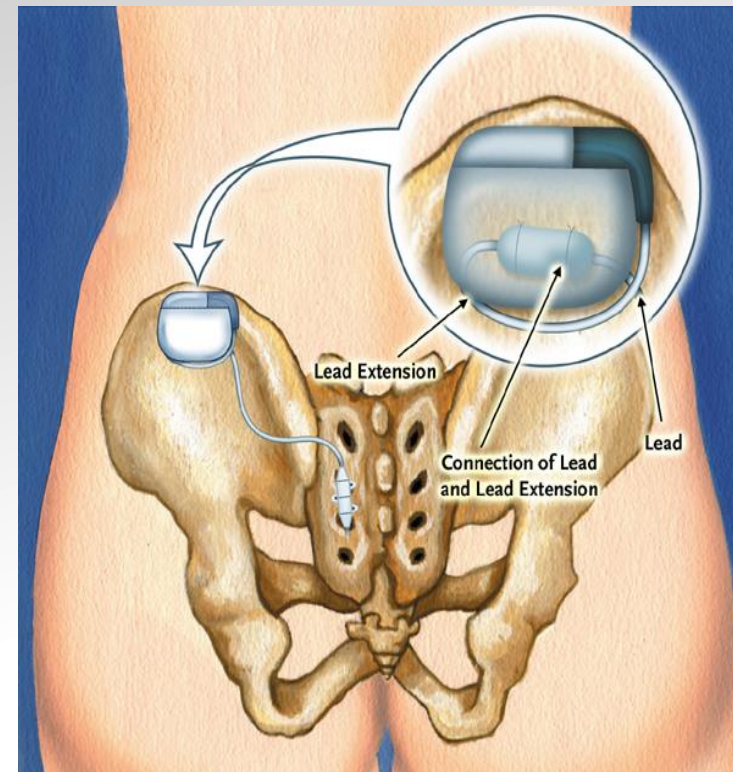
# Staged Implant Procedure

- In the OR, the permanent lead is implanted and connected to a percutaneous extension for the home test stimulation.



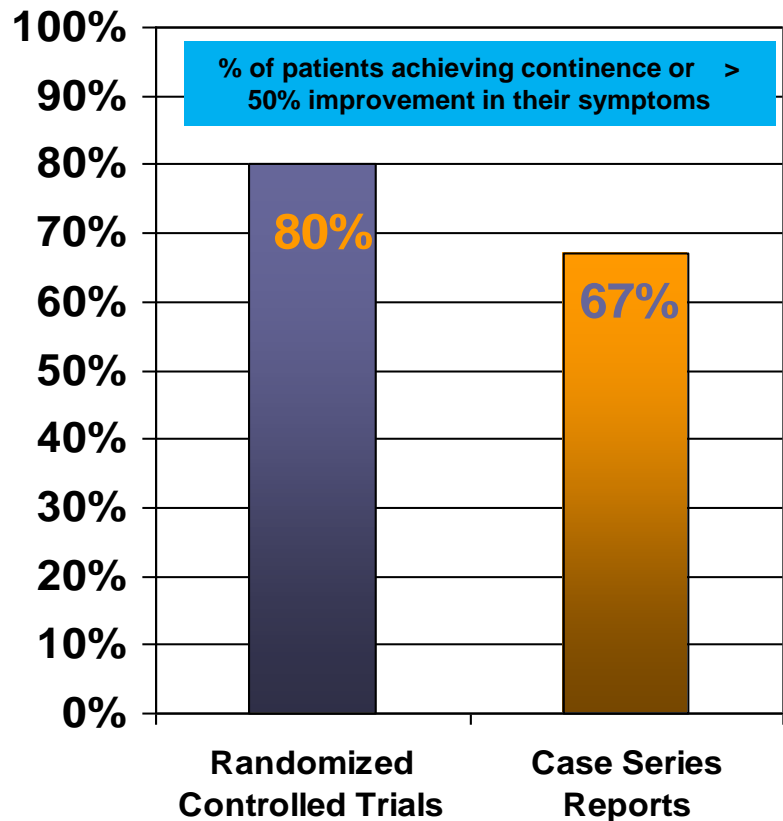
# Implant Procedure

- Patients with a successful test stimulation go on to implantation of neurostimulator.



# Current Literature: Systematic Review: Urge Incontinence

## Randomized Controlled Trials vs. Case Series Reports

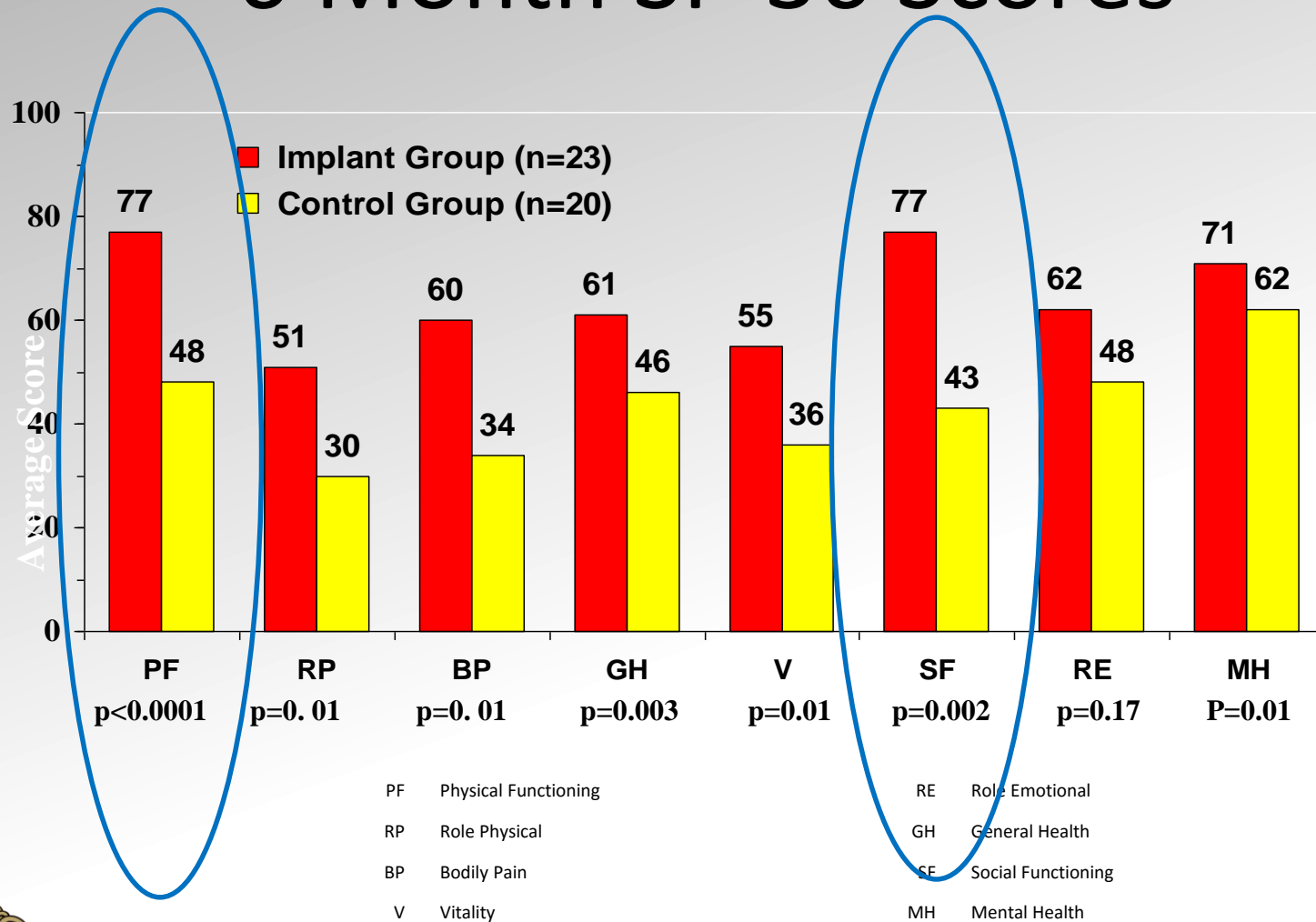


- In an independent investigation of 1,827 implants from 34 clinical trials, InterStim Therapy was shown to be an effective treatment option for the treatment of urinary urge incontinence<sup>1</sup>

Brazelli, M. et al. Journal of Urology. 2006



# Urgency-Frequency 6 Month SF-36 Scores



# Implantation: Ranking of Adverse Events in first 12 Months Post-implant

- Pain at neurostimulator site 15.3%
- New pain 9.0%
- Suspected lead migration 8.4%
- Infection 6.1%
- Transient electric shock 5.5%
- Pain at lead site 5.4%
- Adverse change in bowel function 3.0%
  
- Note: Additional events occurred – each less than 2.0%



# Contraindications to Interstim

- Bony sacral abnormality
- *Cognitive impairment*
  - *Can't operate the device*
  - *Can't provide appropriate feedback about stimulation*
- Non-compliant patients
- Patients with functional incontinence
- Patients with known need for future MRI (below neck)





# Sacral Neuromodulation in Elderly Patients

- 2002 Study by Amundsen evaluated SNS in elderly patients
  - 25 patients > 55 years underwent test implantation
    - 12 responded and were implanted
  - Low morbidity, comparable to younger patients
  - *Lower complete dry rate (17% vs 40%)*

Amundsen CL, Webster GD. *Am J Obstet Gynecol.* Dec 2002;187(6):1462-1465; discussion 1465.



# Sacral Neuromodulation in Elderly Patients

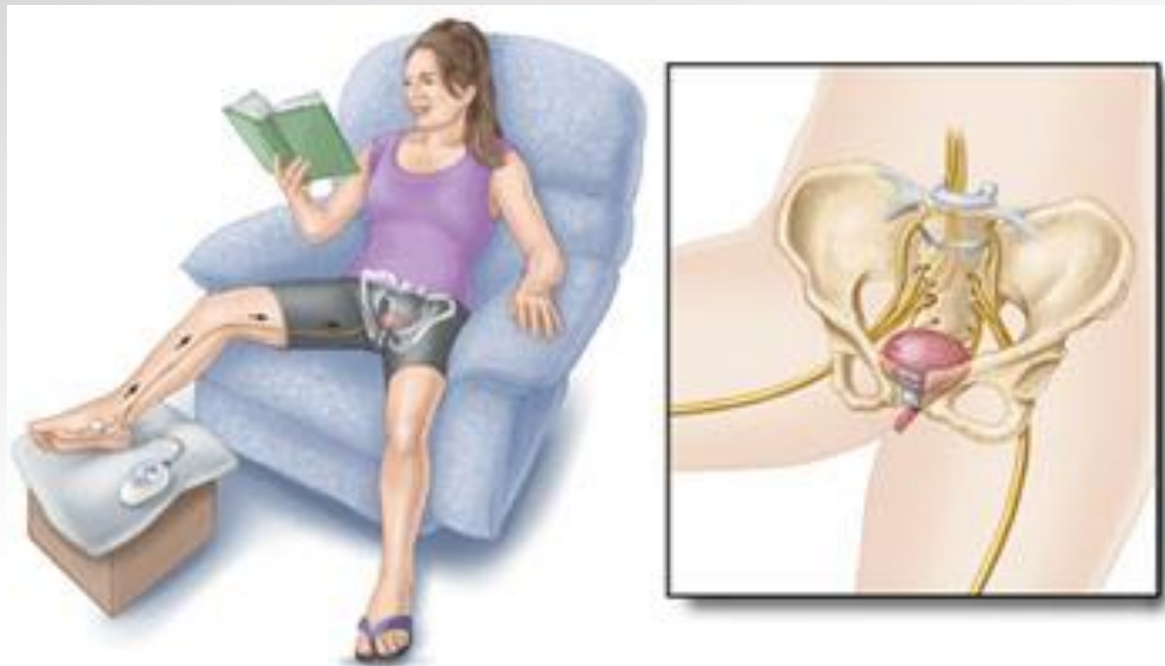
- Prospective evaluation of pre-operative risk factors for failure of neuromodulation found the following associated with failure :
  - *Age > 55 years (cure rate of 37% vs. 65%)*
  - *3 or more chronic conditions*
  - *Neurologic conditions*

Amundsen CL, Romero AA, Jamison MG, Webster GD. *Urology*. Oct 2005;66(4):746-750.



# Percutaneous Tibial Nerve Stimulation (PTNS)

- Based on translational findings of traditional Chinese acupuncture techniques
- First described by Dr. Ed McGuire in 1983



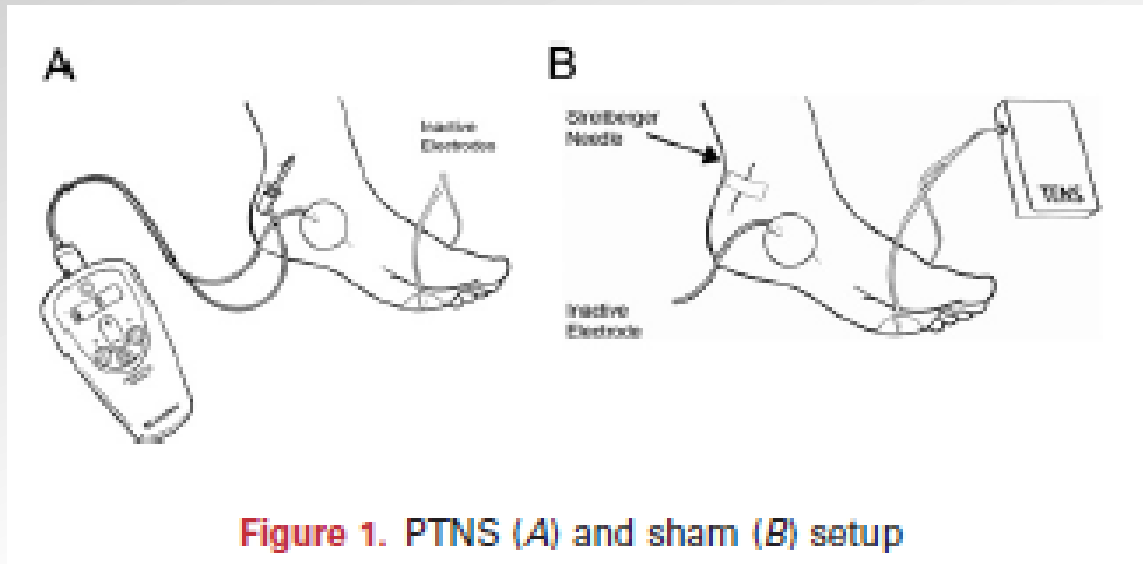
# PTNS

- Posterior Tibial Nerve
  - Mixed sensory and motor nerve
  - Fibers originating from spinal roots L4-S3
    - Modulate the somatic and autonomic nerves to the pelvic floor muscles, bladder and urinary sphincter.



# PTNS: SUmiT Trial

- Multicenter, double blinded, randomized controlled trial comparing the efficacy of PTNS to sham through 12 weeks of therapy
- 220 patients not on OAB drugs during study



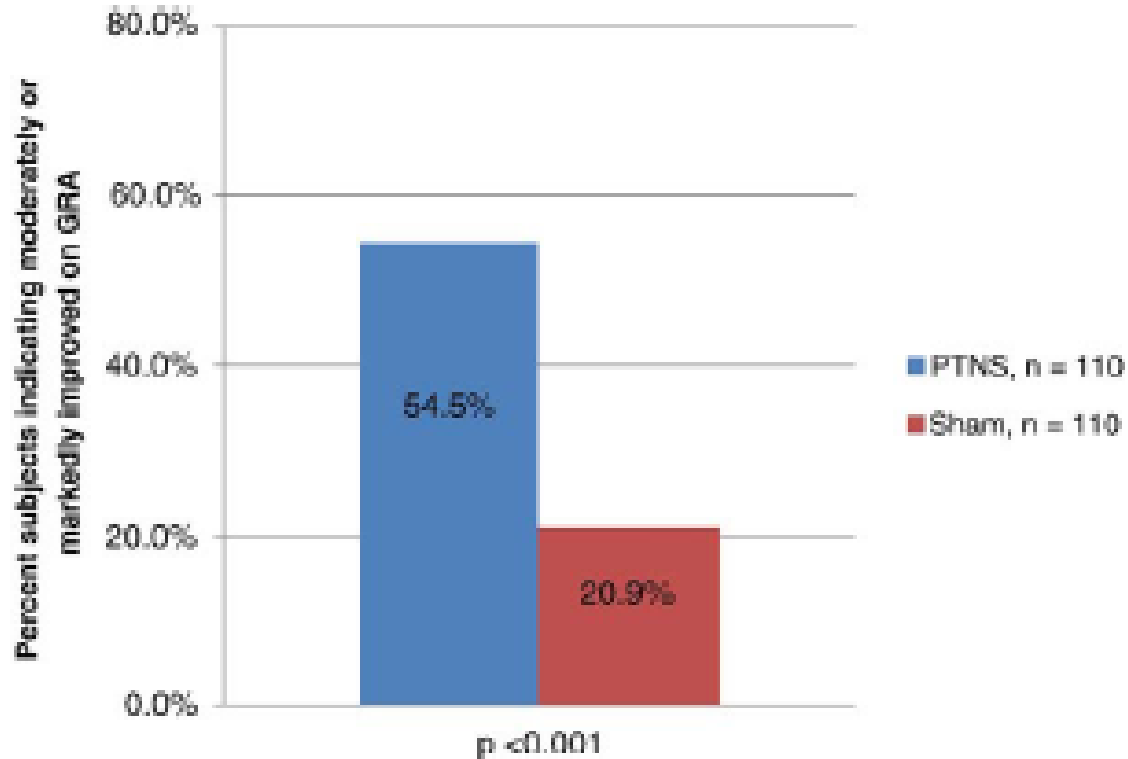
Peters et al, J. Urology, 183 (1438-1443, 2010



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# PTNS: SUmiT Trial



**Figure 3.** Intent to treat analysis comparing PTNS and sham GRA at week 13 assessment.



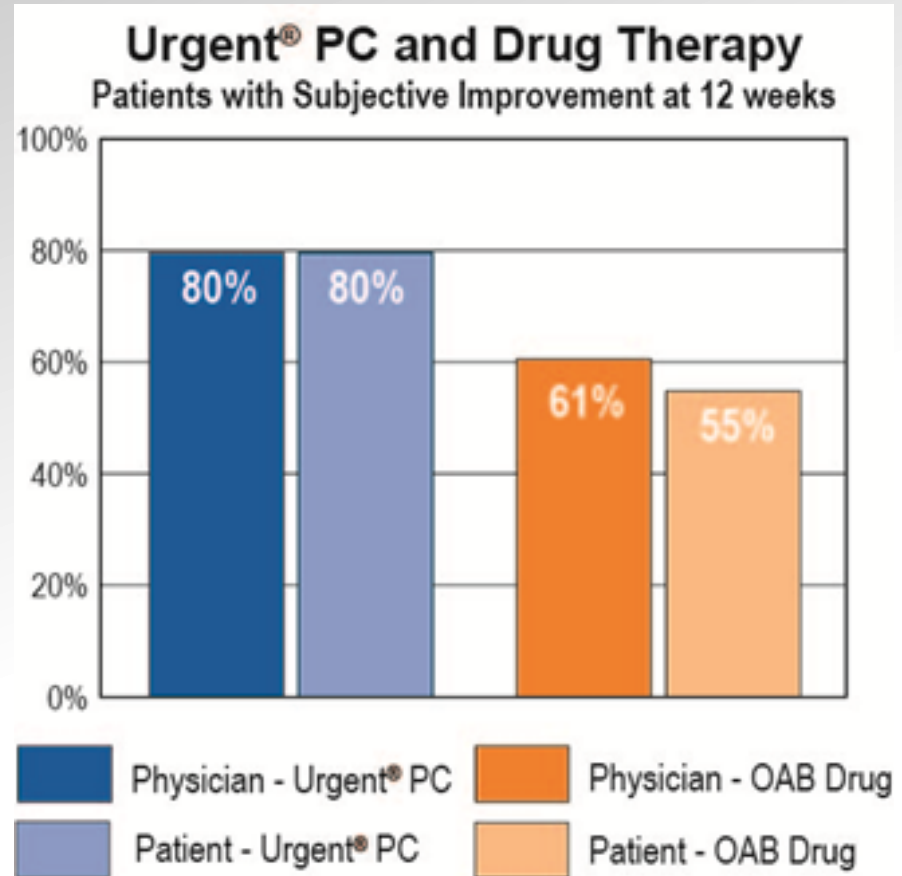
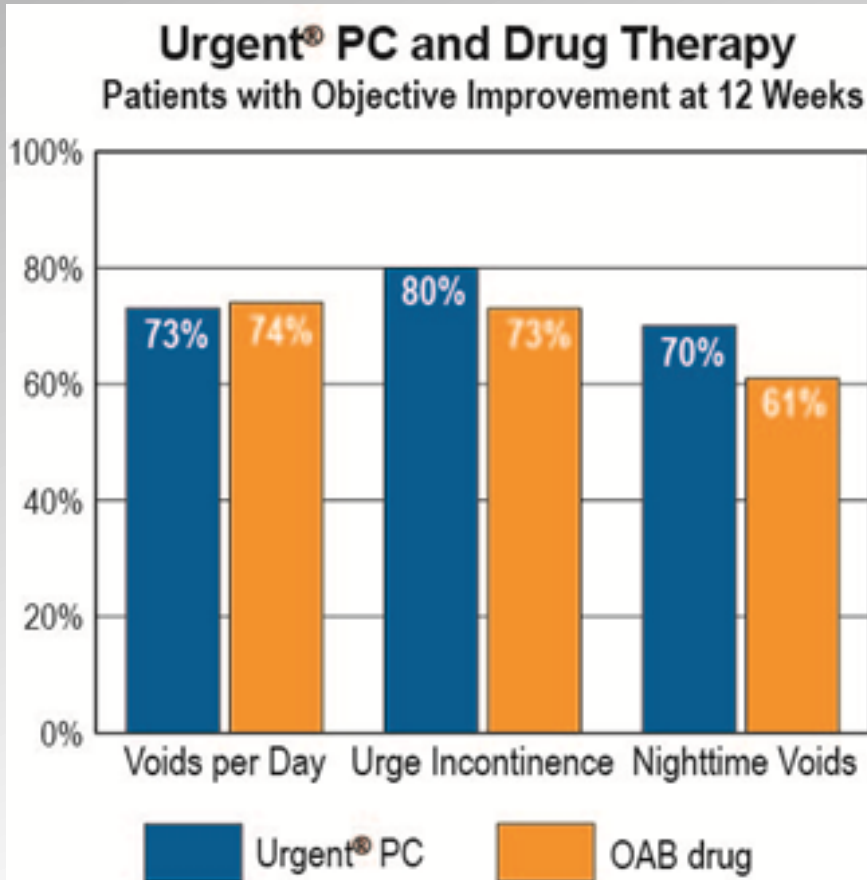
# PTNS: OrBIT Trial

- Phase 1 compared PTNS to tolterodine
  - 79.5% improvement in OAB symptoms PTNS
  - 54.8% improvement for Tolterodine
- Phase 2 evaluated sustained efficacy at 12 months
  - Initial 12 week course
  - Ongoing therapy at tapering intervals
    - Avg of  $12 \pm 4.9$  further treatments over 9 months

MacDiarmid et al, J. Urol 183, 234-240, 2010



# PTNS: OrBIT Trial

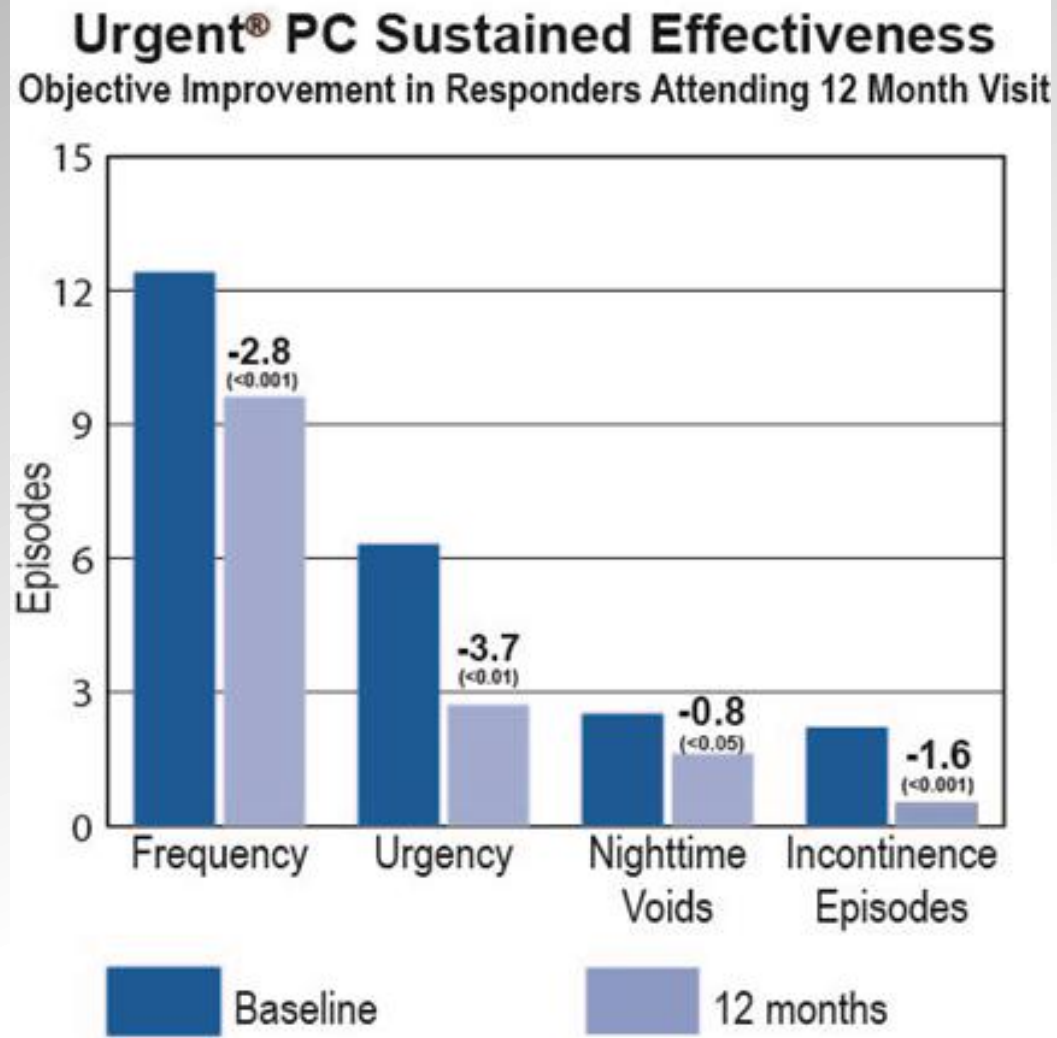


MacDiarmid et al, J. Urol 183, 234-240, 2010





# PTNS: OrBIT Trial Results, Long Term



# PTNS Risks of Treatment

- Transient pain at/near the stimulation site
- Transient mild pain or skin inflammation at or near the stimulation site
- Transient mild bleeding at needle insertion site.



# AUA OAB Guidelines on PTNS

- For carefully selected patients with moderately severe symptoms
- Willingness and resources to make frequent office visits
- Grade C evidence
  - Observation designs
  - Varying patient inclusion criteria
  - Short follow-up for most studies



# Comparisons of Neuromodulation Therapies

## Sacral Neuromodulation:

Restores function

Not NOAB

Treats retention

Helps GI conditions

One Treatment

No carry over effect

Immediate use of BTX if fails

Long term benefit

Safety: proven

Revisions: 25-50% over 2-10y

Not MRI compatible

Simple: not totally office based yet

Time Consuming

FDA Approved

## Botulinum Toxin Injections:

Takes away function

ALL OAB pts

Potential to cause retention

No GI benefit

60-70% need repeat rx

30% have a permanent x-over effect

Wait 3-6 months for adjuvant rx

Temporary

Safety: not fully known

Frequent retreatment ~6 months

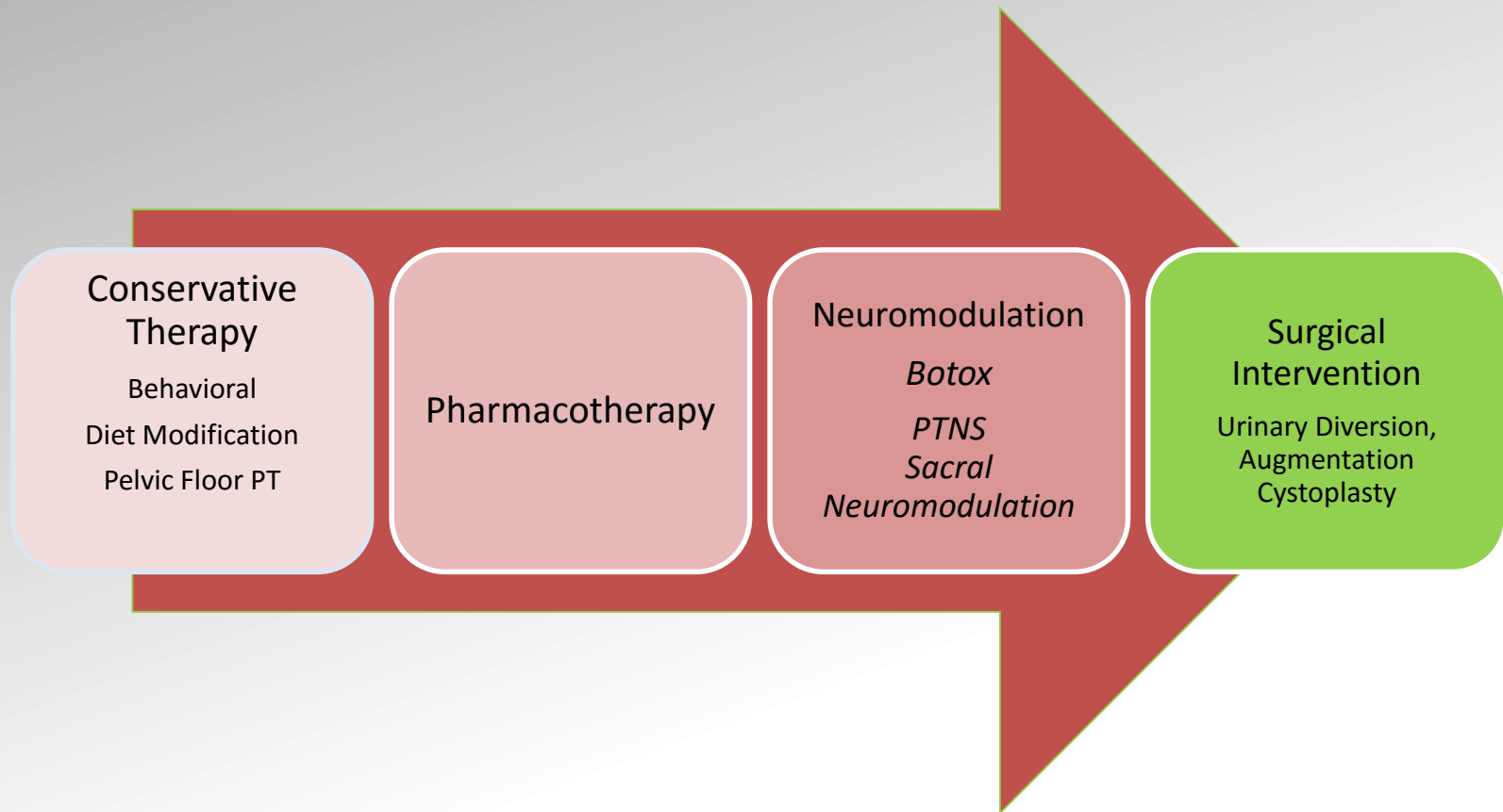
MRI compatible

Simpler: office based (sometimes)

Less time consuming

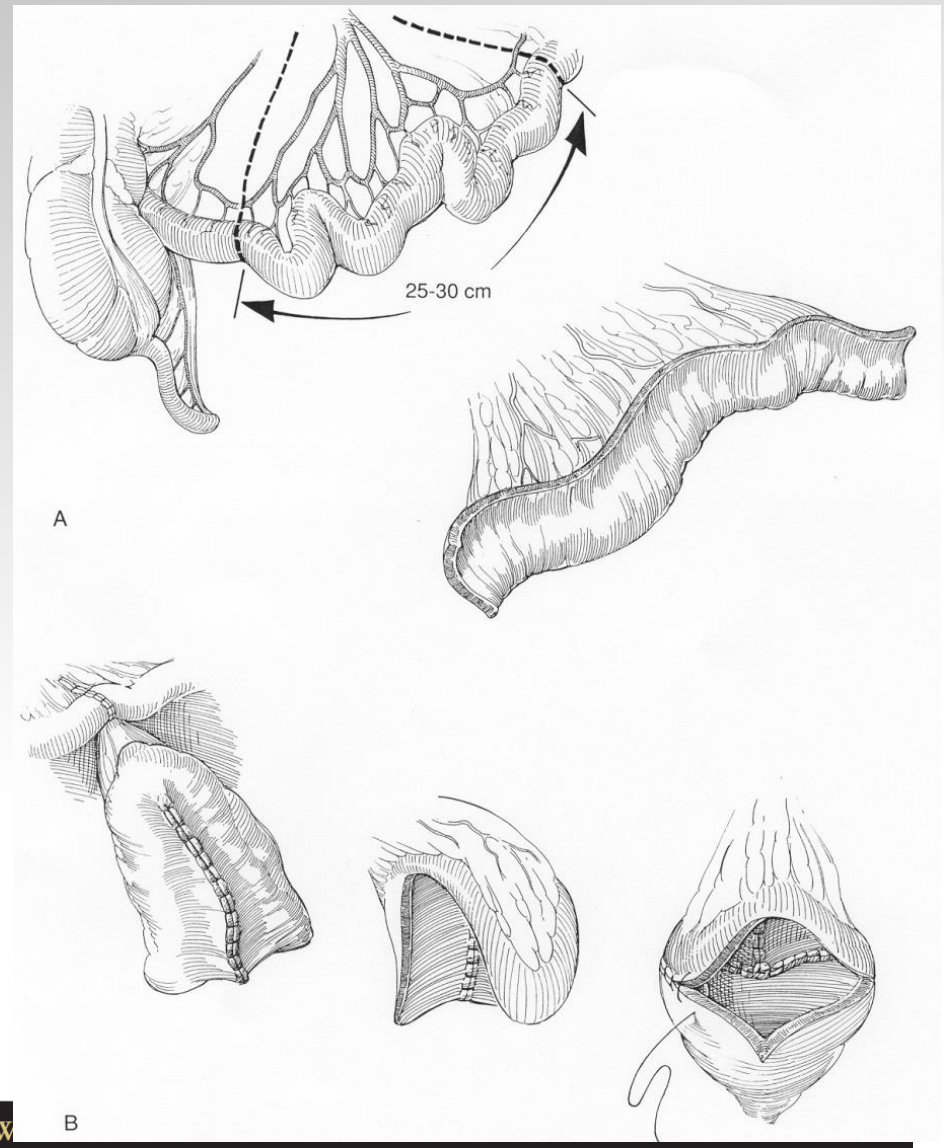
FDA Approved

# Treatment Algorithm for OAB



# Enterocystoplasty

- Increase bladder capacity
- Interruption of coordinated detrusor contractions
- Low pressure system



# OAB

Modify Risk Factors



Behavioral Therapy

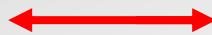


Pelvic floor exercises



Anticholinergics

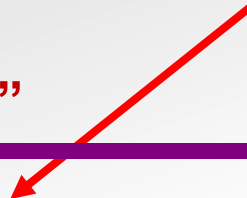
**B3 –  
adrenoreceptor  
agonist**



Other  
anticholinergics

Imipramine

**“REFRACTORY OAB”**



Sacral  
neuromodulation  
or PTNS



Botox



Experimental Protocol



Bladder Augmentation



# Talk to your Doctor

- Every woman's situation is different
- Patients respond differently to treatments—work with your doctor to find the best treatments for you
- Success or failure of someone else's operation should never be the deciding factor for you





# QUESTIONS?



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# Online Resources

- Urology Care Foundation [www.UrologyHealth.org](http://www.UrologyHealth.org)
- The Simon Foundation for Continence  
[www.SimonFoundation.org](http://www.SimonFoundation.org)
- Society of Urodynamics Female Pelvic Medicine and Urogenital Reconstruction (SUFU) [www.sufu.org.com](http://www.sufu.org.com)
- American Urogynecologic Society (AUGS)  
[www.VoicesForPFD.org](http://www.VoicesForPFD.org)
- National Association for Continence (NAFC) [www.NAFC.org](http://www.NAFC.org)



# High-n-Dry

I called to my bladder  
What could be the matter?  
You're acting so suddenly strange.

You don't let me know  
When I so need to go,  
Then you wait 'til the pot's out of range.

It's awfully naughty  
When you act so haughty  
Causing me all kinds of grief.

So do be a dear  
And when I have a beer,  
Please don't make me pee in my briefs.

Alas I have friends  
Who will work to the end  
To save me from this awful mess.

Drs. Bennett and Moore  
(whom both I adore)  
Have lifted me from the duress

And now as I chatter  
About aforesaid bladder  
I'm on such a giggly high.

There's no room to quibble,  
I no longer dribble;  
I'm smiling, I'm happy, I'm dry!





In order to maintain the beauty  
of the artwork, please do not  
climb the cow.



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