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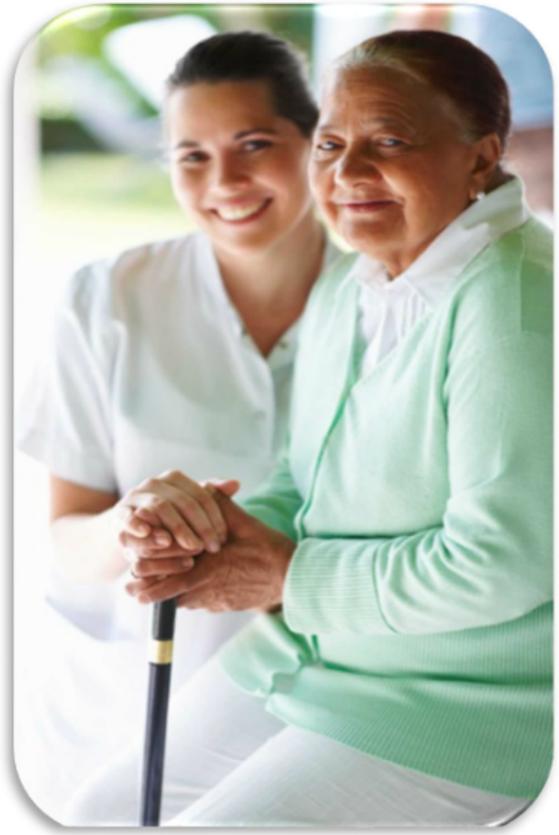
GERIATRIC WORKFORCE ENHANCEMENT PROGRAM (GWEP)

Learn@Lunch

Geriatric Education Series



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Stemming the Flood: Treatment for Urinary Incontinence

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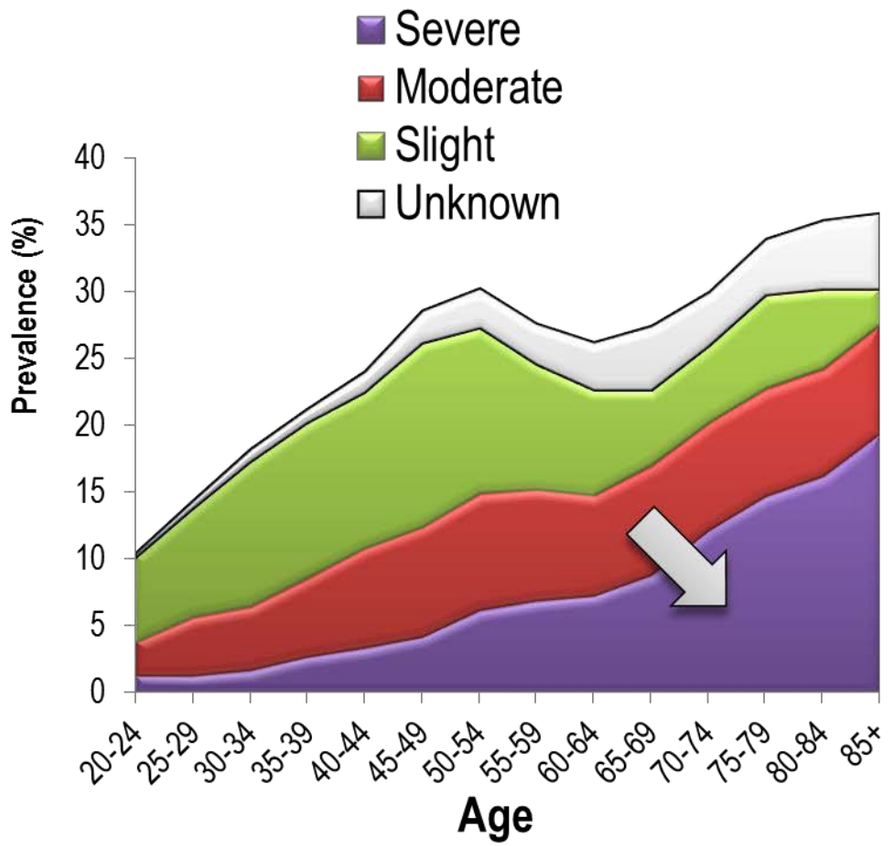
University of North Carolina Chapel Hill

Objectives

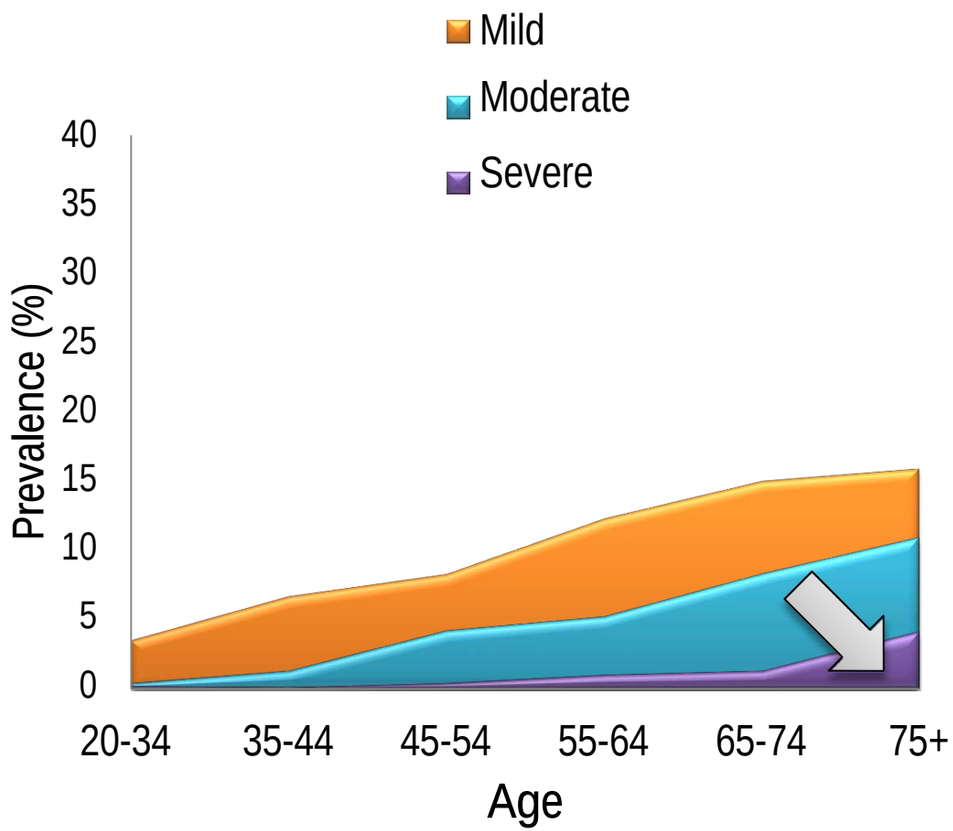
- Describe the pathophysiology of UI.
- Discuss the evaluation and referral criteria for UI.
- Describe behavioral and pharmacologic treatments for UI.
- Discuss neuromodulation and sphincter replacement therapies for UI.

Prevalence of Urinary Incontinence:

Women & Men



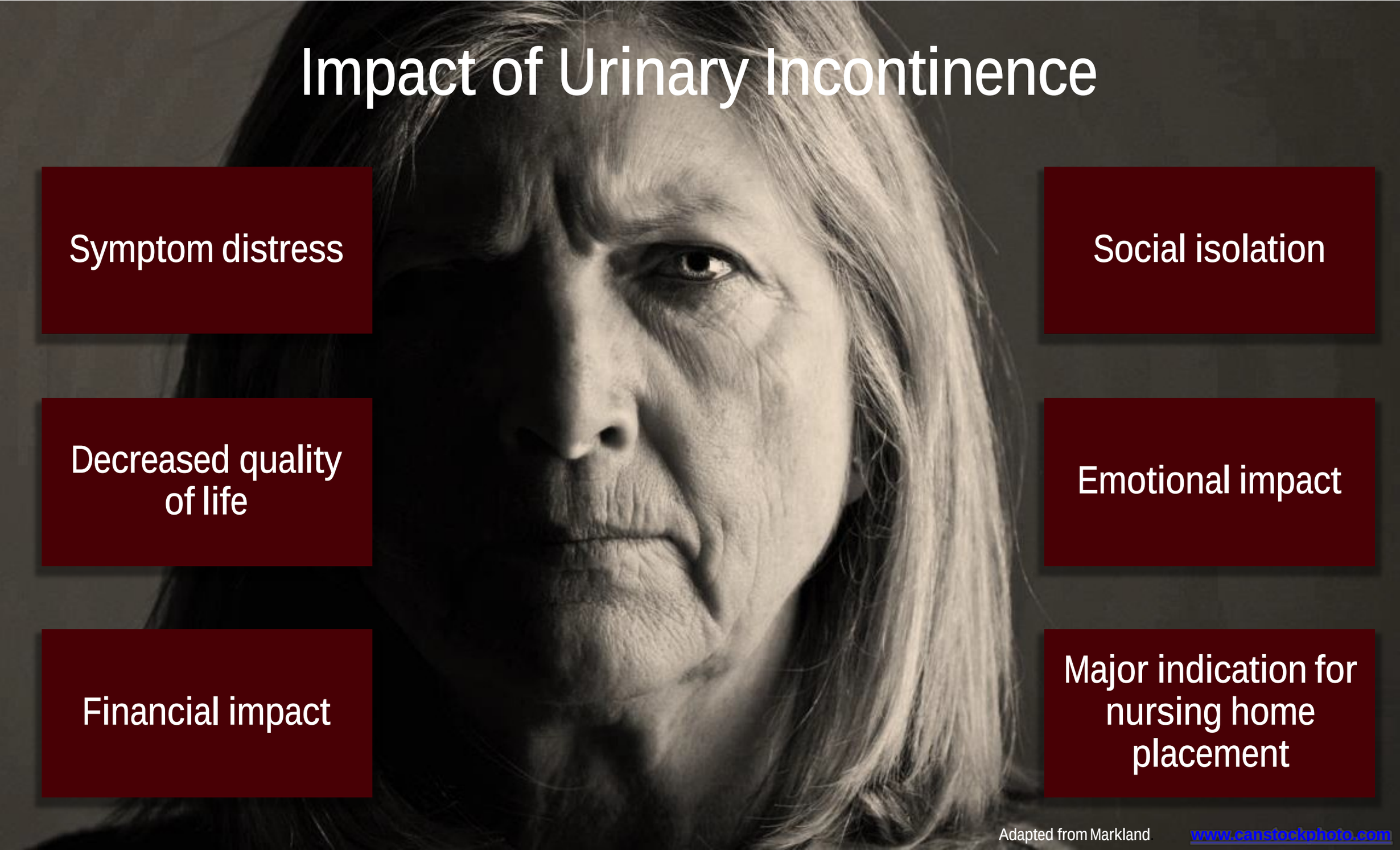
WOMEN



MEN

Burgio, K. L., K. A. Matthews, and B. T. Engel. *The Journal of urology* 146.5 (1991): 1255-1259.

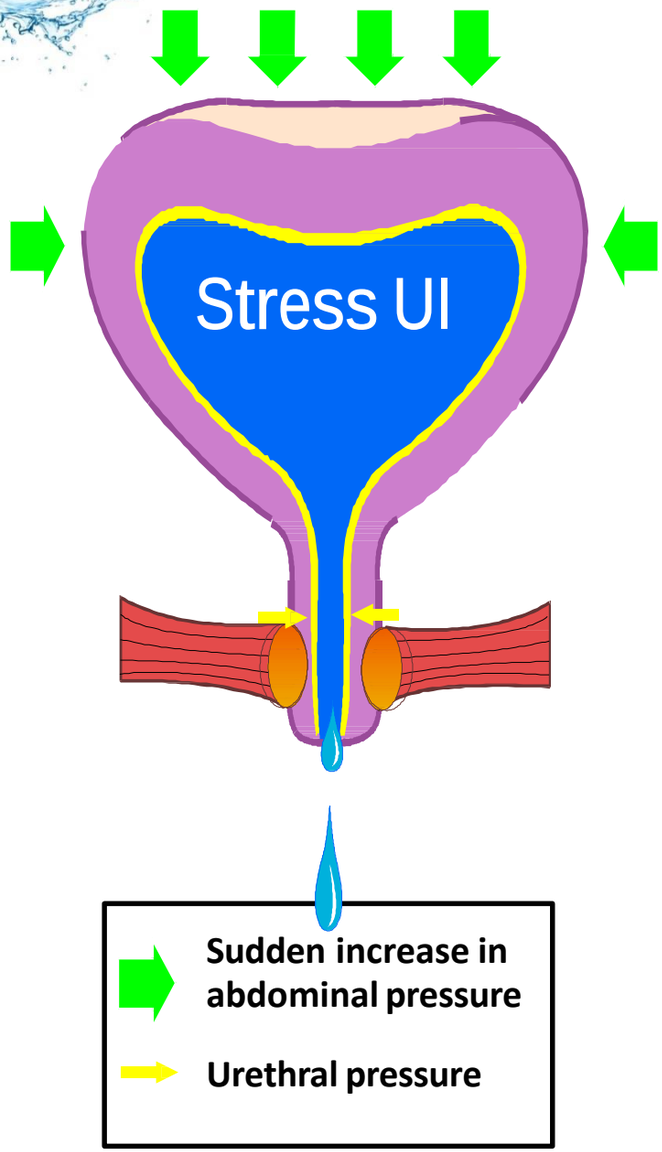
Impact of Urinary Incontinence

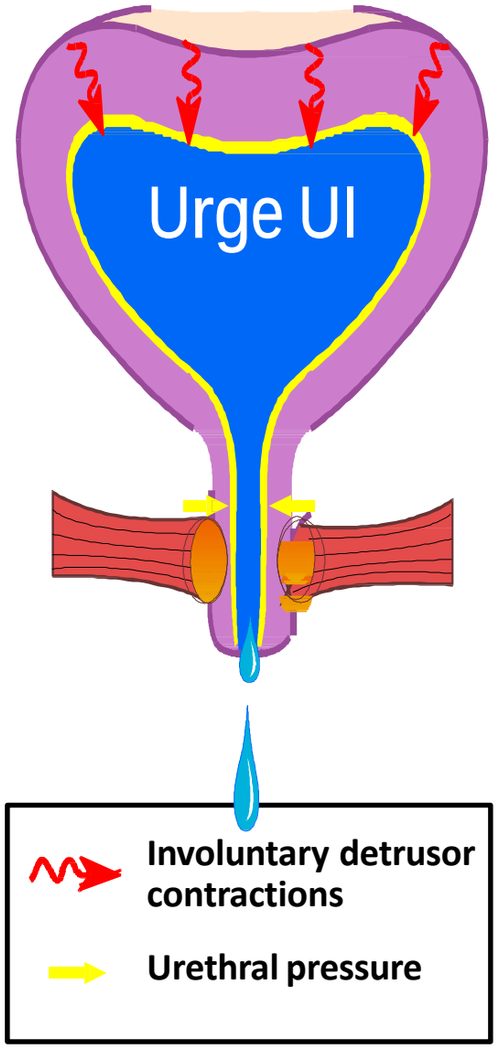


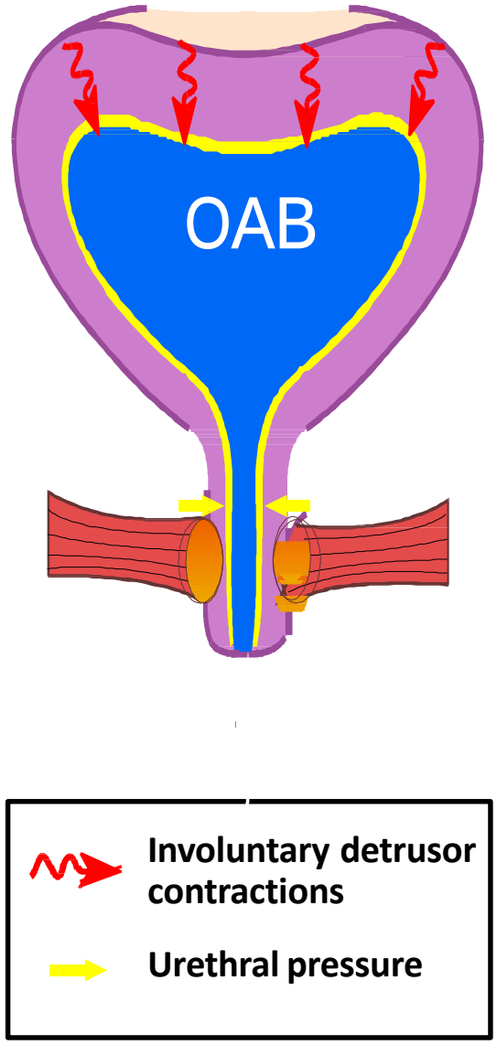
- Symptom distress
- Social isolation
- Decreased quality of life
- Emotional impact
- Financial impact
- Major indication for nursing home placement

Adapted from Markland

Types of UI

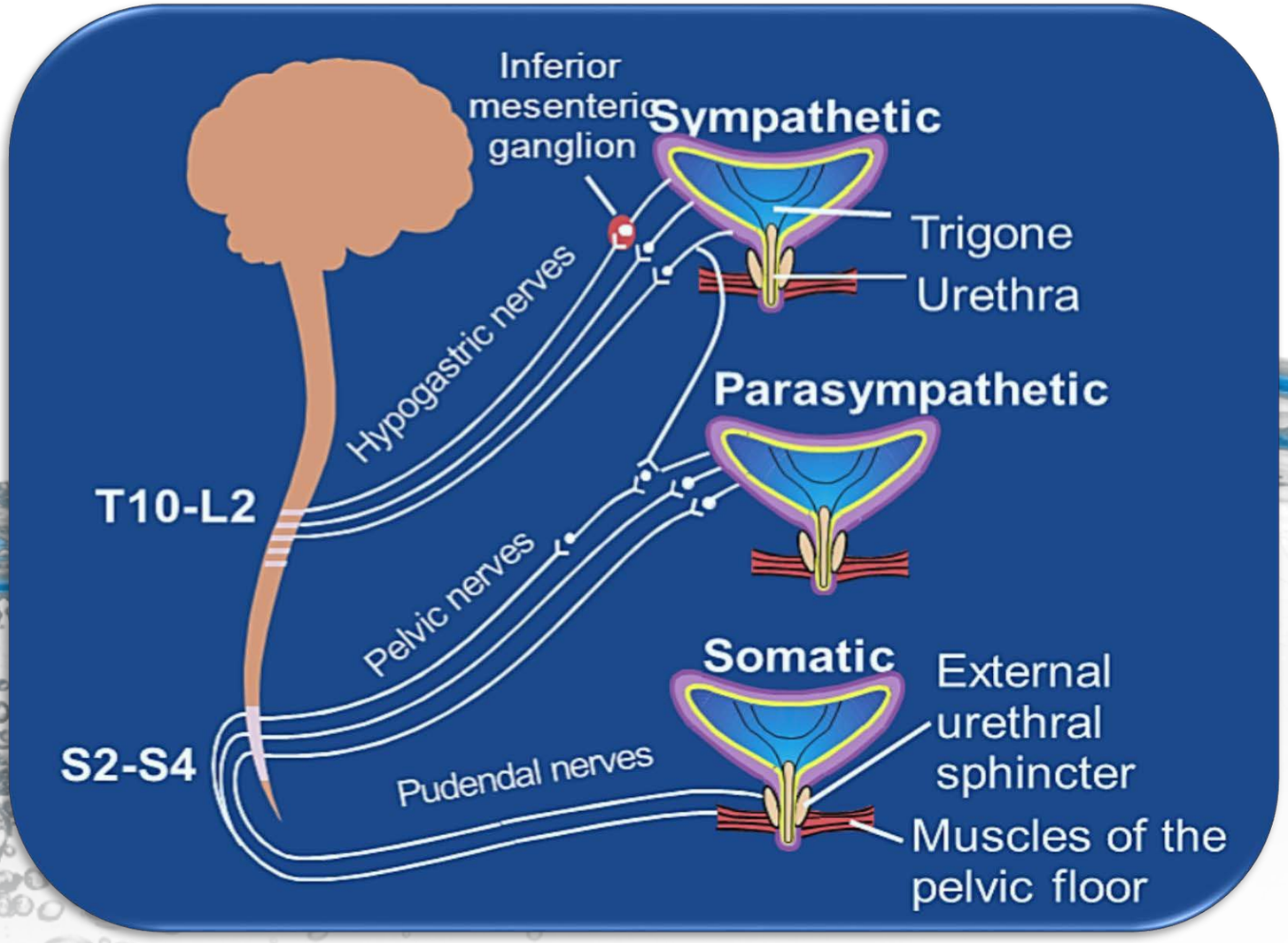






Abrams P et al. *Urology*. 2003;61:37-49.
Ouslander J. *N Engl J Med*. 2004;350(8):786-799.

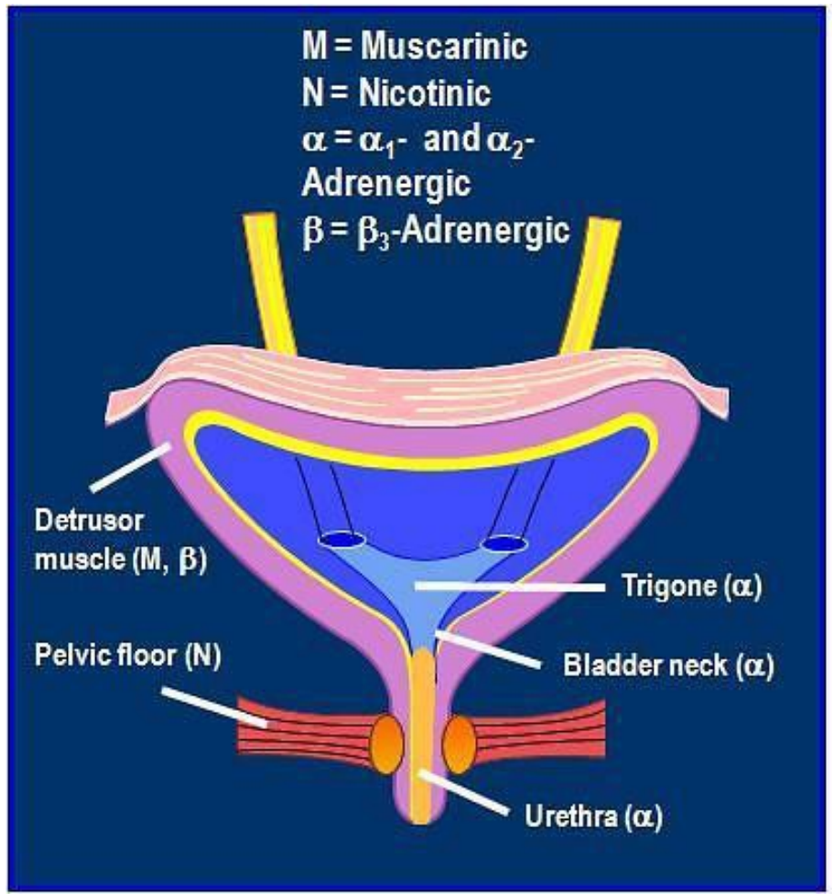
Innervation of the Lower Urinary Tract (LUT)



Abram P et al. *The Overactive Bladder: A Widespread and Treatable Condition*. 1998.

Distribution of Cholinergic and Adrenergic Receptors

- Human bladder smooth muscle contains primarily M2 (66%) and M3 (33%) subtypes.
- Activation of M3 receptors is primary stimulus for bladder contraction.
- β_3 adrenoceptor mediates detrusor muscle relaxation.



Anderson KE. Lancet Neurol. 2004;3:46-53.
Braverman AS et al. Urology. 2002;167:43
Cameron AP. Transl Androl Urol. 2016; 5E51-62..

Screening for UI

During the last 3 months did you leak urine:

- When you were performing some physical activity such as: coughing, sneezing, lifting or exercising? — STRESS INCONTINENCE
- When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough? — URGE INCONTINENCE
- Without any physical activity or without a sense of urgency? — OTHER INCONTINENCE

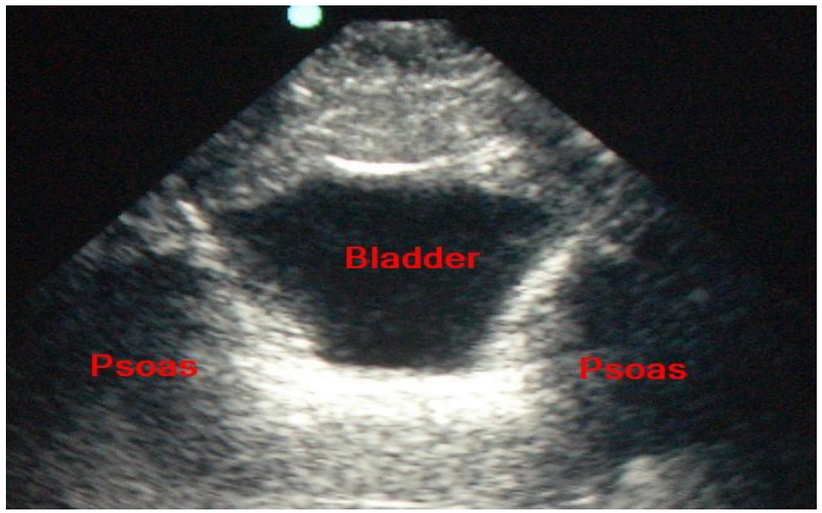
Which one most often?

Brown et al. Ann Intern Med 2006;144.

Evaluation of UI

- History: Bladder diary
- Physical examination, especially Genitourinary and Neurological
- Bladder stress test
- Postvoid residual volume
- Urinalysis, urine culture if indicated
- BUN, creatinine, fasting glucose

24 Hour Bladder Diary			Date 12/03/14		
Time	Drinks		Urine		Pads
	Amount (ml)	Type	Amount (ml)	Bladder Sensation	
6am *WOKE*			500	2	
7 am	300	Water			
8 am			✔	2	
9 am					
10 am	Cup	Tea	LEAK	3	✔
11 am					
Midday					



http://www.erpocketbooks.com/er-ultrasounds/trauma-ultrasounds-from-the-ed/

Potentially Reversible Factors

Delirium/**D**rugs

Infection – UTI vs. asymptomatic bacteriuria

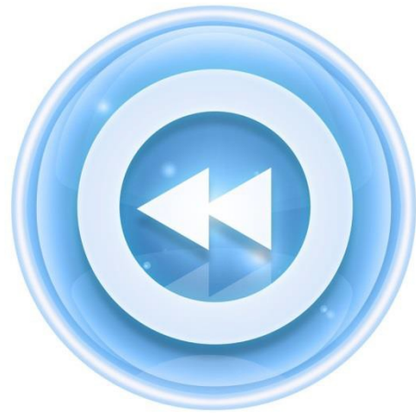
Atrophic Urethritis

Psychological - Depression, Dementia

Endocrine – Diabetes

Restricted Mobility

Stool Impaction (Constipation)



Neil M. Resnick, M.D., and Subbarao V. Yalla, M.D.
N Engl J Med 1985; 313:800-805

Drugs Potentially Contributing to UI

ACE inhibitors

Antipsychotics

Alcohol

Alpha Blockers

Anticholinergics

Caffeine

Calcium Channel Blockers

Diuretics

Narcotics

Sedatives

Case 1: Mrs. G

78 y/o with worsening UI. Symptoms of urgency and large volume loss, also loss with laughing and sneezing. HTN, Diabetes Type 2, Insomnia and worsening UI Symptoms, no Dysuria or Hematuria.

Habits: 3 cups coffee daily

2 glasses of wine at dinner

Meds:

HCTZ

Metoprolol

Glipizide

Benadryl

Case 1: Mrs. G

Exam:

mild atrophy

mild cystocele

weak pelvic squeeze

Urinalysis:

1+ glucose

4 WBC

8 epithelial cells

Glucose: 185

PVR: 90 mL

www.saludtoday.com

Treatment Options for UI

- Behavioral
- Pharmacological
- Neuromodulation
- Surgery

www.sangay.com/
www.funnynamesblog.com/

What should you prescribe first?

A. Stop Caffeine

B. Stop HCTZ

C. Stop Wine

D. Stop Benadryl

E. All of the Above

What should you prescribe next?

A. Pelvic floor exercises

B. Scheduled voiding

C. Anticholinergic drug

D. Botox Injection

Weight Loss

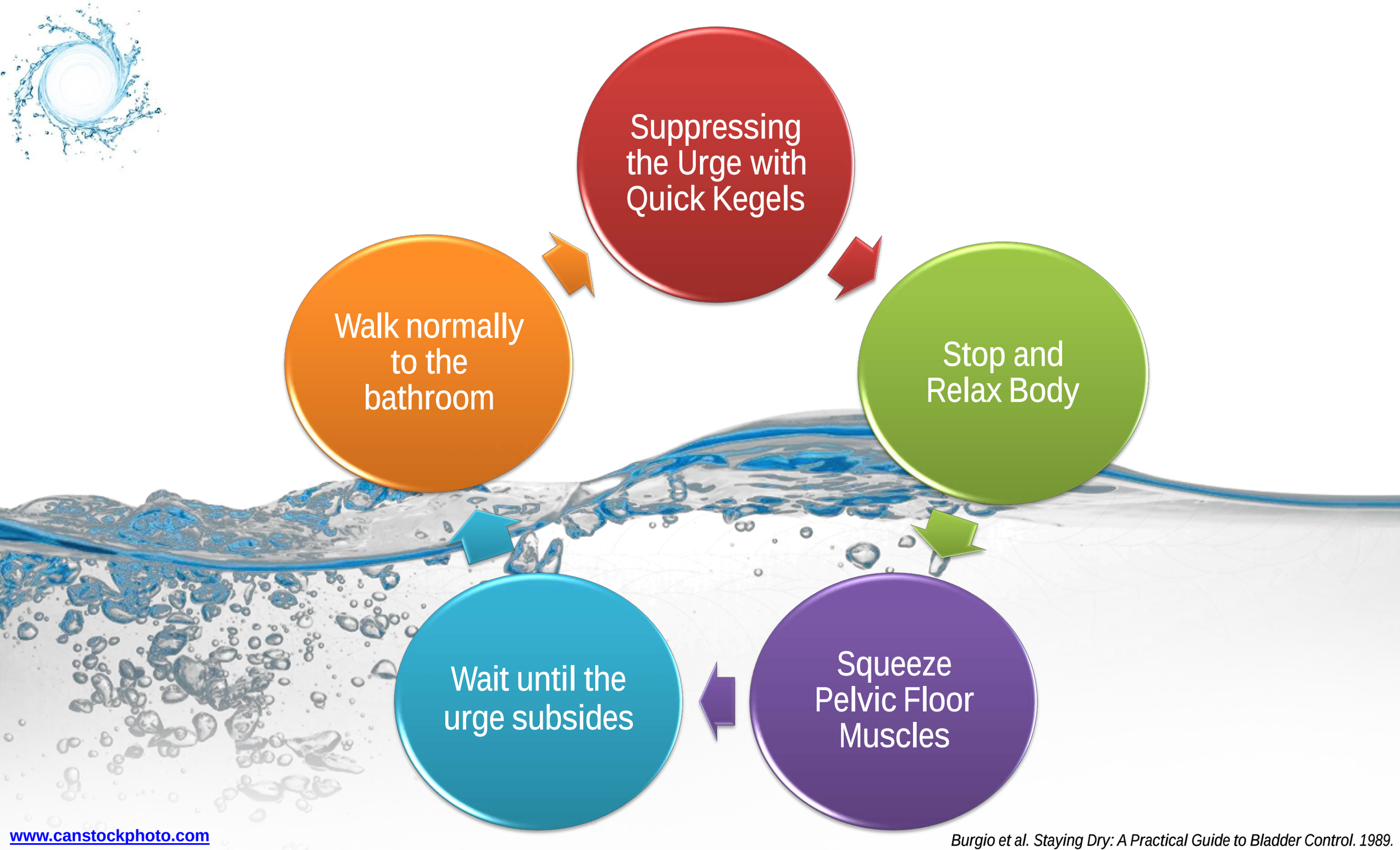
- Randomized trial of 338 women, mean BMI 36 kg/m²
- 6 month weight loss vs. education
- Weight loss 8% vs. 1.6%
- 47% vs. 28% in stress but not urge UI

NEJM 2009; 360:481

Pelvic Muscle Exercises (Kegels)

- Isolation of the pelvic muscles during pelvic exam using biofeedback
- Avoidance of abdominal, buttock or thigh muscle contractions
- Ability to hold contraction 2 seconds, increase up to 10 seconds
  - repeat in groups of 10-30 TID
- 3 sets of 8 to 12 slow velocity contractions sustained for up to 10 seconds
  - 3-4 times weekly for at least 4 to 6 months

Obstet Gynecol Survey 1992; 47:322.



Burgio et al. Staying Dry: A Practical Guide to Bladder Control. 1989.

Behavioral Treatments

Behavioral strategies and PFMF are effective:

- Outcomes are similar to anticholinergic medication therapy.
- Clinical guidelines support as first line treatment
- Minimal adverse effects

Obstet Gynecol Survey 1992; 47:322.

www.canstockphoto.com

Randomized Trials of Behavioral Treatment for Stress UI

- 24 RCTs, but only 11 of high quality
- Pelvic floor exercises were effective (up to 75%) in reducing symptoms of stress UI
- Limited evidence for high vs low intensity
- Benefits of adding biofeedback (BFB) unclear

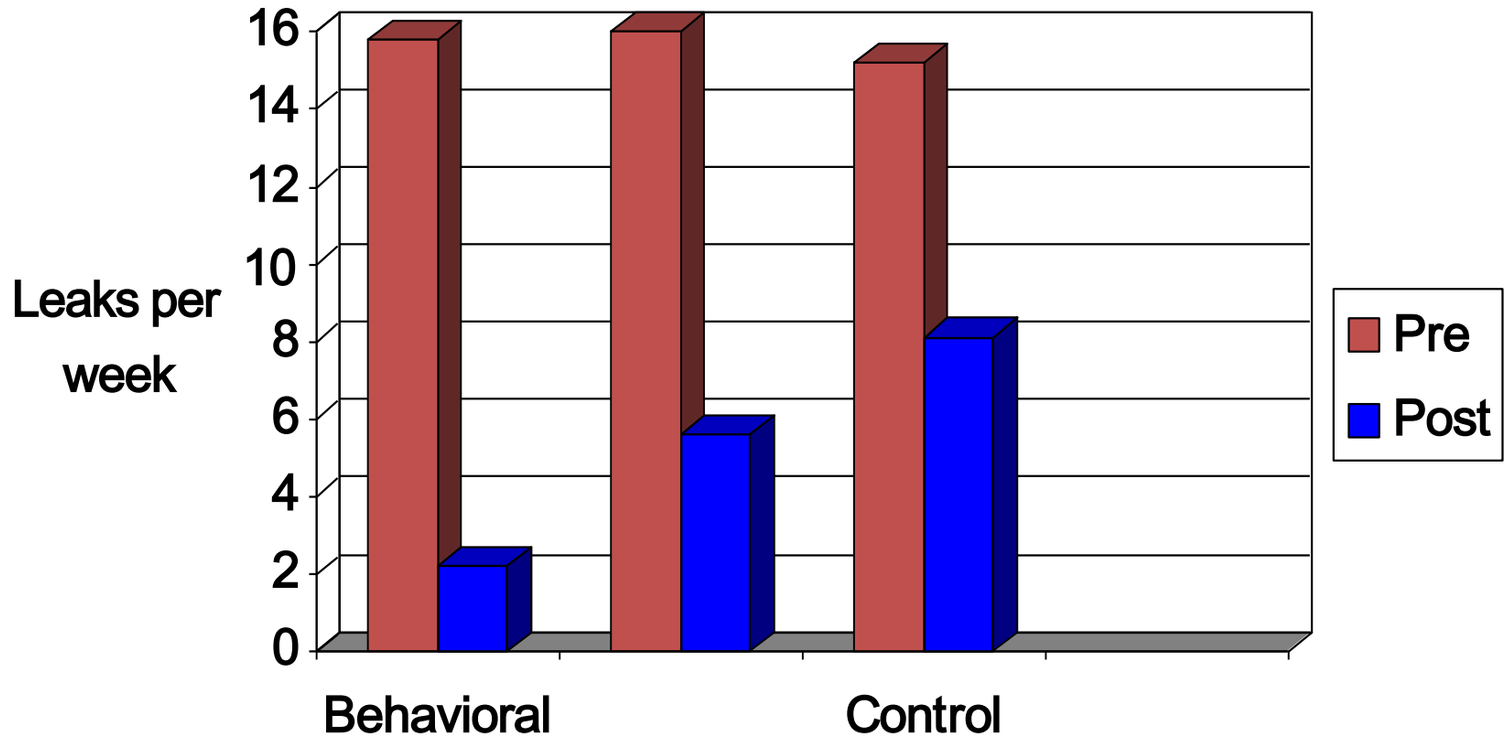
Berghmans et al. Br J Urol 1998; 82:181-191
Cochrane Collaboration 2011

Behavioral vs. Drug Rx for Urge UI in Older Women

- Randomized, controlled trial of 197 women aged 55-92
- 8 weeks of BFB, 8 weeks of oxybutynin
- 2.5 to 5 mg qd to tid, or placebo control
- All 3 groups reduced UI frequency
- Effectiveness: BFB>drug>placebo

Burgio et .al. JAMA 1998; 280; 1995-2000

Oxybutynin vs Behavioral Treatment for Urge UI



Burgio et al JAMA 1998; 280:1995-2000

Pharmacotherapy of Urge Incontinence

Anticholinergics

- Oxybutynin
- Tolterodine
- Fesoterodine
- Darifenacin
- Solifenacin
- Trospium

β_3 Receptor agonist

Mirabegron

Alpha blocker

- Tamsulosin
- Doxazosin

5 α Reductase Inhibitor

- Finasteride
- Dutasteride

Muscarinic Receptor Subtypes

Subtype	Distribution	Role
M1	Brain (cortex, hippocampus), Salivary gland	Cognitive function, memory; saliva secretion
M2	Heart, brain, smooth muscle	Regulation of heart rate & HR variability; behavioral flexibility
M3	Smooth muscle, glands, eye	Smooth muscle contraction, iris contraction, gland secretion
M4	Brain (forebrain, striatum)	Dopamine dependent behaviors
M5	Brain (substantia nigra), eye	Regulation of striatal dopamine release

Anticholinergics

Antimuscarinics & M3 Receptor Selectivity

Ratio of affinity	Muscarinic receptor subtype			
	M_3 vs. M_1	M_3 vs. M_2	M_3 vs. M_4	M_3 vs. M_5
Darifenacin	16.0	53.0	26.0	4.1
Fesoterodine	0.2	0.5	1.3	0.8
Oxybutynin	1.8	6.2	1.9	5.3
Solifenacin	2.2	15.0	9.1	2.6
Tolterodine	0.6	0.95	1.5	0.6
Trospium	1.5	1.3	2.0	4.6

[a]Relative mean affiliates calculated as the ration of K, values as reported by [16]

[b]Relative mean affiliates calculated as the ration of K, values determined from the antilog of pK, values as reported by [17]

[c]Relative mean affiliates calculated as the ration of K, values as reported by [18]

Borawski, et al. Neurourol Urodynamics 26(1): 2007.

Doses and Side Effects

Table 1: Common Pharmacologic Therapies: Doses and Side Effect Rates*					
Antimuscarinics/Anticholinergics	**Dry mouth**	**Constipation**	**Dry Eyes**	**Dyspepsia**	**Dizziness**
Oxybutynin ER (5–30 mg o.d.)	60.8%	13.1%	6.1%	6.8%	6.3%
Oxybutynin CR (5–20 mg o.d.)	64.0%	5.1%	2.5%	5.1%	6.4%
Oxybutynin patch	4.1%	3.3%	n/a	n/a	n/a
Tolterodine ER (4 mg o.d.)	23.4%	5.9%	< 5%	< 5%	< 5%
Solifenacin (5–10 mg o.d.)	10.9%	5.4%	0.3%	1.4%	1.9%
Trospium chloride (20 mg b.i.d.)	20.1%	9.6%	1.2%	1.2%	n/a
Darifenacin (7.5–15 mg)	20.2%	14.8%	2.1%	2.7%	0.9%
β_3-Adrenoreceptor Agonists	**Headache**	**Constipation**	**Dry Eyes**	**Hypertension**	**Dizziness**
Mirabegron (25–50 mg o.d.)**	0.6%	0.9%	0.4%	0.5%	0.5%

* Side effect rates taken from the products' respective product monographs

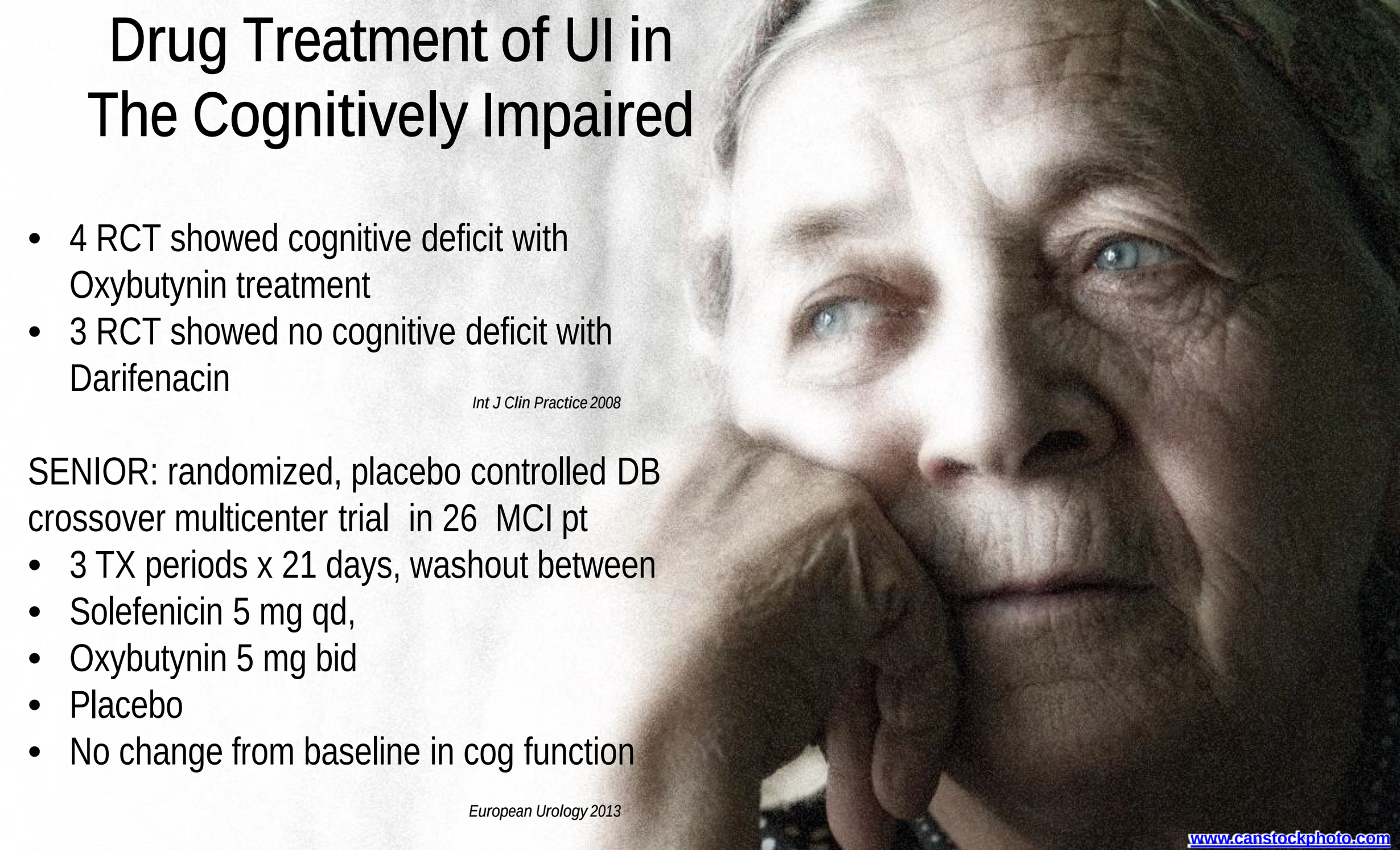
** The side effect rates listed for mirabegron reflect the rates of adverse reactions leading to discontinuation reported by more than two patients and at a rate greater than active control in study 178-CL-049 (as reported by the mirabegron product monograph). These rates do not reflect overall side effect rates for this drug.

Brennand EA, Canadian Journal of CME 02/2015; 27(2):35-37..

Contraindications for Anticholinergics

- Urinary retention
- Gastric retention
- Narrow angle glaucoma
- Bladder outlet obstruction
- Cardiac arrhythmias

Drug Treatment of UI in The Cognitively Impaired



- 4 RCT showed cognitive deficit with Oxybutynin treatment
- 3 RCT showed no cognitive deficit with Darifenacin

Int J Clin Practice 2008

SENIOR: randomized, placebo controlled DB crossover multicenter trial in 26 MCI pt

- 3 TX periods x 21 days, washout between
- Solefenicin 5 mg qd,
- Oxybutynin 5 mg bid
- Placebo
- No change from baseline in cog function

European Urology 2013

Case 2: Mr. D

65 y/o man with mild BPH, COPD and Osteoarthritis of the knees. He has increasingly bothersome nocturia x3

Habits: Former smoker
4 cans of beer over the weekend

Meds: ASA
Metoprolol
Autaminophen
Albuterol inhaler

Case 2: **Mr. D**

Exam:	slightly enlarged prostate gland no nodules
Urinalysis:	negative
PVR:	120 cc

What initial prescription is most appropriate?

A. Pelvic floor exercises

B. Tamsulosin
(alpha-adrenergic blocker)

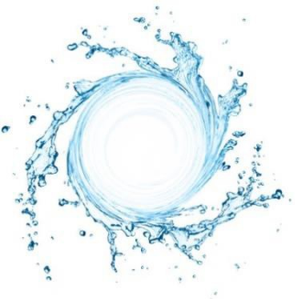
A. Oxybutynin
(anticholinergic)

A. Finasteride
(5 alpha reductase inhibitor)

Myrbetriq (Mirabegron)

Phase 3 randomized, double blind placebo controlled trial (Nitti)

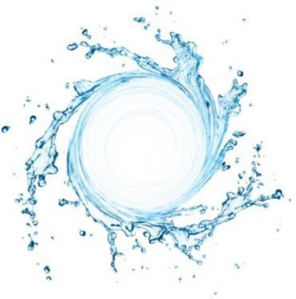
- 1338 patients mean age 60 with OAB >8 voids/24 hr and >3 urgency episodes/72 hr
- Placebo vs 50 mg vs 100 mg x 12 weeks
- Mean # UI episodes/24 hr and voids/24 hr statistically significant improvement at week 4, no diff in adverse events
- Side effects: Hypertension (1.2 mm HG at 100 mg; 2.4 mm HG at 200 mg), increase in HR (1.6 BPM at 100mg, 4.1 BPM at 200 mg), headache, nasopharyngitis



Drug Treatment of Mild BPH

Alpha adrenergic antagonists

- Relaxes prostate smooth muscle of prostate and bladder neck
  - Tamsulosin (Flomax) 0.4 -0.8mg daily
  - Doxazosin (Cardura) 1-2 mg then up to 8 mg daily IR, 4-8 mg ER
- Tamsulosin trials: 53 weeks, 31% and 36% improvement in maximal flow rate with 0.4 mg and 0.8 mg/day vs. 21% placebo
- Adverse effects: orthostatic hypotension and dizziness, floppy iris syndrome in cataract surgery patients



Drug Treatment of Mild BPH

- Dose:
  - Finasteride (Proscar) 5 mg daily
  - Dutasteride (Avodart) 0.5 mg daily
- Type II 5 alpha reductase inhibitor
  - Results in atrophy of the prostatic glandular epithelium due to decreased synthesis of dihydrotestosterone
  - Slow onset, 20% - 30% reduction in prostate volume and LUTS over time
  - Side effects: Ejaculatory dysfunction (8%), loss of libido (10%), erectile dysfunction (16%)
  - Trend for increased risk of more aggressive prostate cancer
  - Rare reports of breast cancer in men taking finasteride either 1 mg or 5 mg

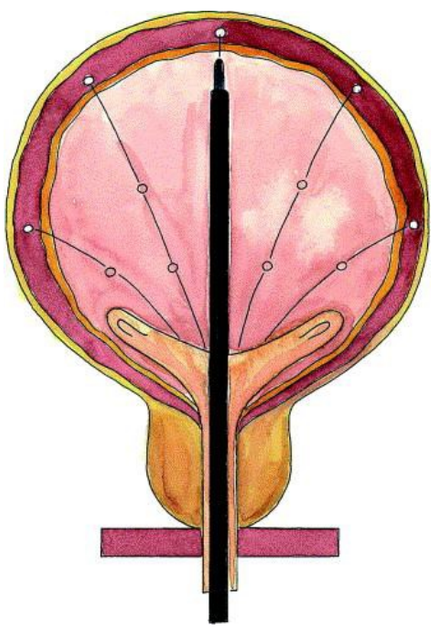
Treatment of Urge UI in Men

- Start with alpha blocker
- May add low dose antimuscarinic
- One randomized trial of tamsulosin plus tolterodine more effective in reducing urge UI than placebo

http://phd7.idaho.gov/health%20promotion/Fit%20and%20Fall/fit&fallmain.html

Botulinum Toxin

- 100 U (US) injected directly into detrusor later and posterior bladder wall, trigone avoided
- 2005 first randomized placebo controlled study of 59 patients, 200 U, 300 U or placebo over 24 wks
- Mean decrease in UI 50% vs 0; p<.05
- RELAX RCT study: 8 UK centers enrolled 240 women, 200 U vs placebo; primary outcome voiding frequency/24 hr; at 6 mo, median leaks 1.67 vs 6.0; continence 31% vs 12%, daily urgency 3.83 vs 6.33; UTIs 16% vs 4%
- Major side effects: urinary retention, UTIs, pain, hematuria



doi:10.1016/S0302-2838(03)00250-1

Key Points

- Identify and treat reversible causes of UI.
- Behavioral therapy is first-line treatment for stress and urge UI, and OAB.
- Anticholinergic medications are effective second-line treatment for urge UI and OAB.
- M3 selective drugs have fewer side effects.
- Mirabegron is a new β_3 agonist effective for urge UI and OAB.

Alpha adrenergic blockers are effective treatment for urge UI due to BPH.

- Botulinum A can be effective for refractory OAB.

Referral Criteria

- ✓ Recurrent urinary tract infections
- ✓ Hematuria not related to UTI
- ✓ Elevated postvoid residual or other evidence of possible obstruction
- ✓ Recent gynecological or urological surgery or pelvic radiation
- ✓ Failed treatment of stress or urge UI