Conservative treatment of urinary incontinence in women

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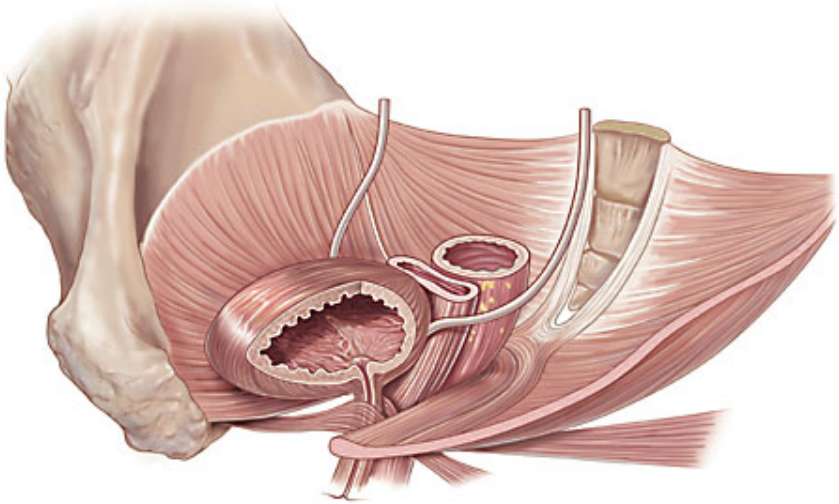
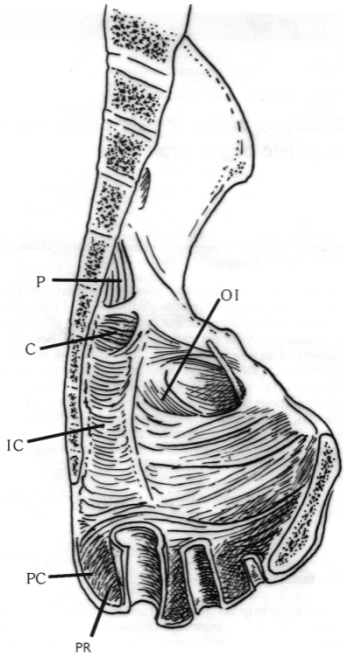
Conservative options

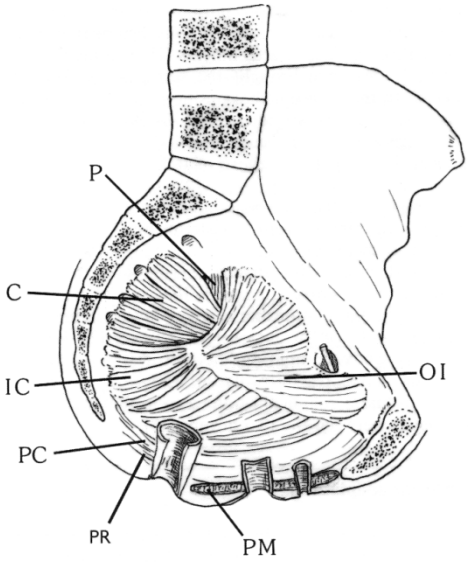
- Rehabilitation & supportive care
- Drinking & voiding behavioural therapy
- Weight loss & smoking cessation
- Pessaries & devices
- Intermittent catheterization
- Pelvic floor muscle training
- Pharmacological therapy

Pelvic floor muscle training (PFMT)



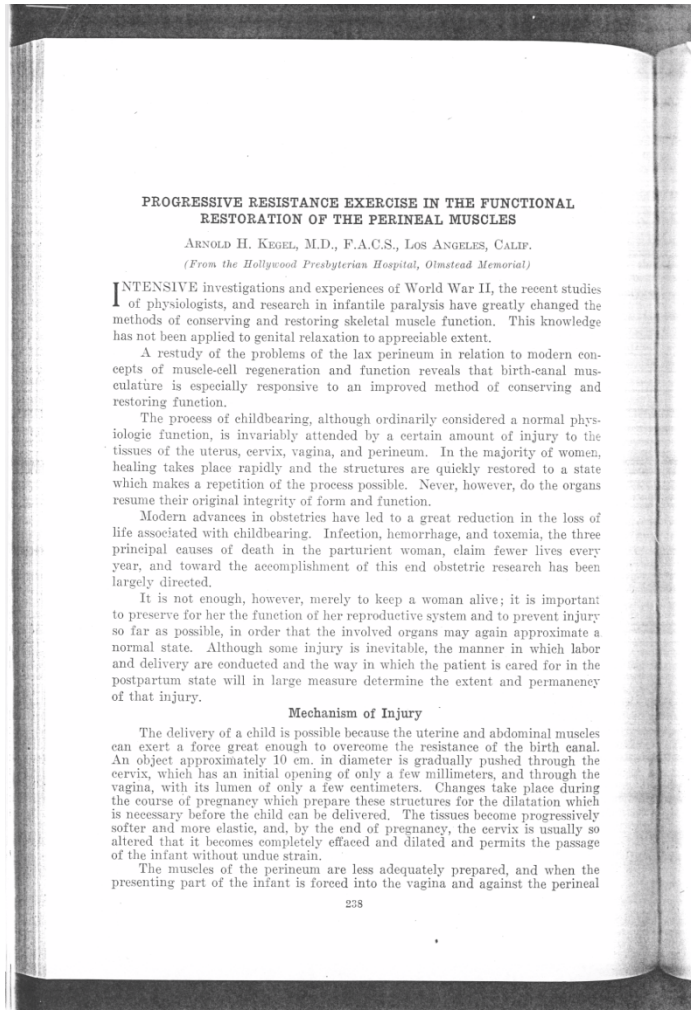
Evolution





Schimpf M, Tulikangas P. Int Urogyn J 2005; 16: 315

Arnold H. Kegel



PROGRESSIVE RESISTANCE EXERCISE IN THE FUNCTIONAL RESTORATION OF THE PERINEAL MUSCLES

ARNOLD H. KEGEL, M.D., F.A.C.S., LOS ANGELES, CALIF.

(From the Hollywood Presbyterian Hospital, Olmstead Memorial)

INTENSIVE investigations and experiences of World War II, the recent studies of physiologists, and research in infantile paralysis have greatly changed the methods of conserving and restoring skeletal muscle function. This knowledge has not been applied to genital relaxation to appreciable extent.

A restudy of the problems of the lax perineum in relation to modern concepts of muscle-cell regeneration and function reveals that birth-canal musculature is especially responsive to an improved method of conserving and restoring function.

The process of childbearing, although ordinarily considered a normal physiologic function, is invariably attended by a certain amount of injury to the tissues of the uterus, cervix, vagina, and perineum. In the majority of women, healing takes place rapidly and the structures are quickly restored to a state which makes a repetition of the process possible. Never, however, do the organs resume their original integrity of form and function.

Modern advances in obstetrics have led to a great reduction in the loss of life associated with childbearing. Infection, hemorrhage, and toxemia, the three principal causes of death in the parturient woman, claim fewer lives every year, and toward the accomplishment of this end obstetric research has been largely directed.

It is not enough, however, merely to keep a woman alive; it is important to preserve for her the function of her reproductive system and to prevent injury so far as possible, in order that the involved organs may again approximate a normal state. Although some injury is inevitable, the manner in which labor and delivery are conducted and the way in which the patient is cared for in the postpartum state will in large measure determine the extent and permanency of that injury.

Mechanism of Injury

The delivery of a child is possible because the uterine and abdominal muscles can exert a force great enough to overcome the resistance of the birth canal. An object approximately 10 cm. in diameter is gradually pushed through the cervix, which has an initial opening of only a few millimeters, and through the vagina, with its lumen of only a few centimeters. Changes take place during the course of pregnancy which prepare these structures for the dilatation which is necessary before the child can be delivered. The tissues become progressively softer and more elastic, and, by the end of pregnancy, the cervix is usually so altered that it becomes completely effaced and dilated and permits the passage of the infant without undue strain.

The muscles of the perineum are less adequately prepared, and when the presenting part of the infant is forced into the vagina and against the perineal

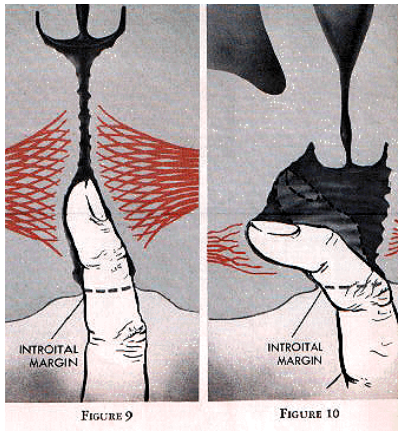
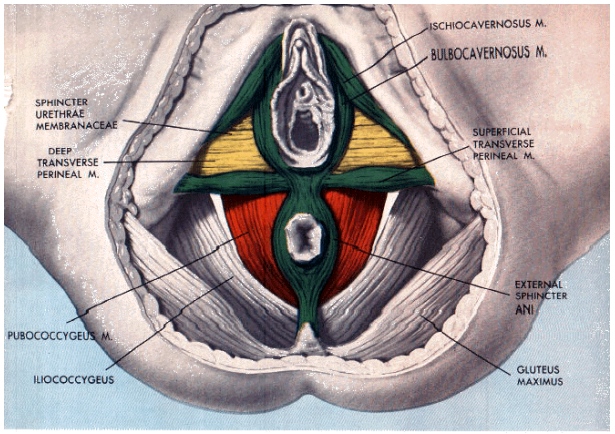
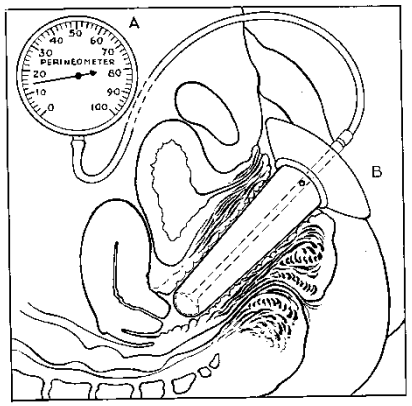


FIGURE 9 FIGURE 10





Kegel AH. AJOG 1948; 56: 1948 | Kegel AH. JAMA 1951: 916
Kegel AH. CIBA Clinical Symposia 1952; 4: 35-52

The pelvic floor

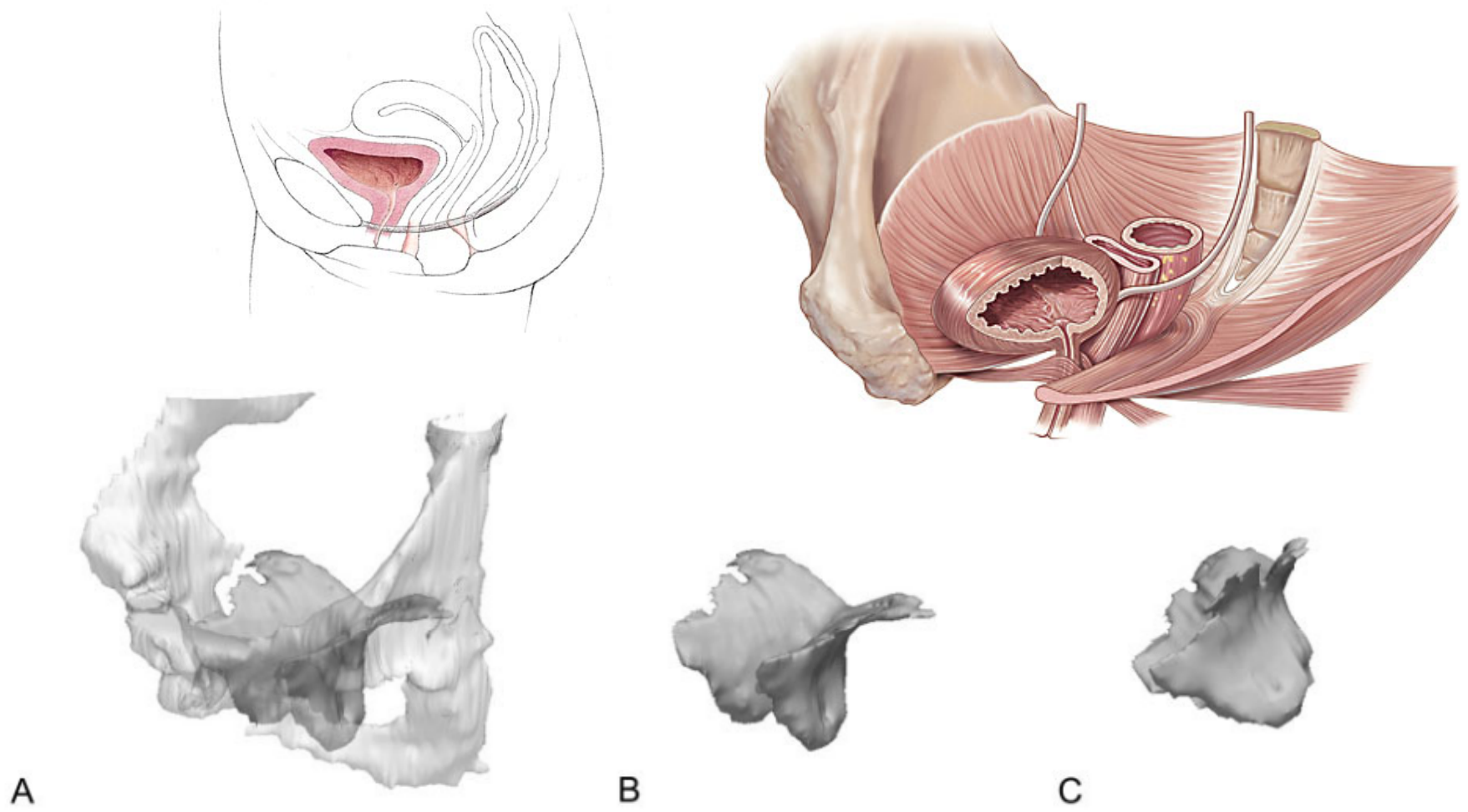
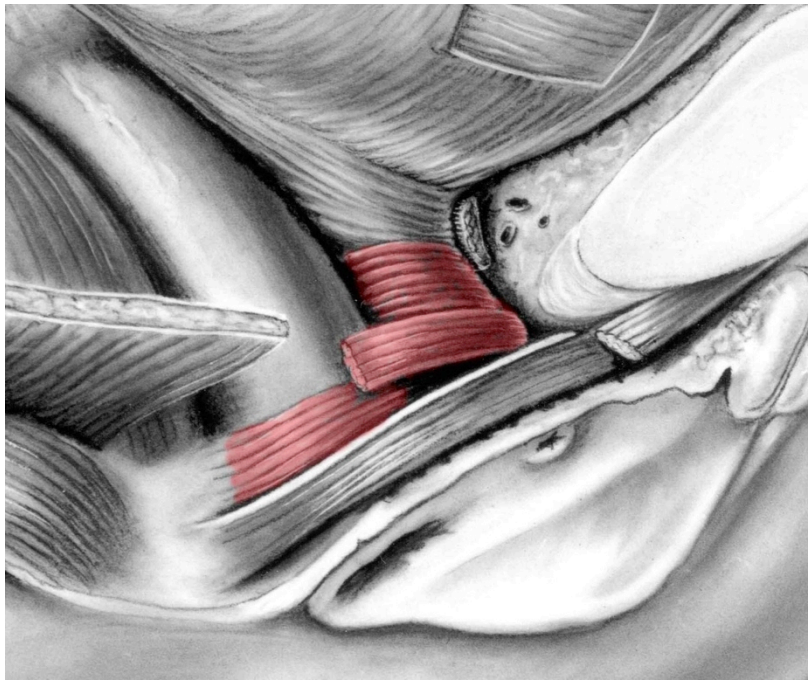
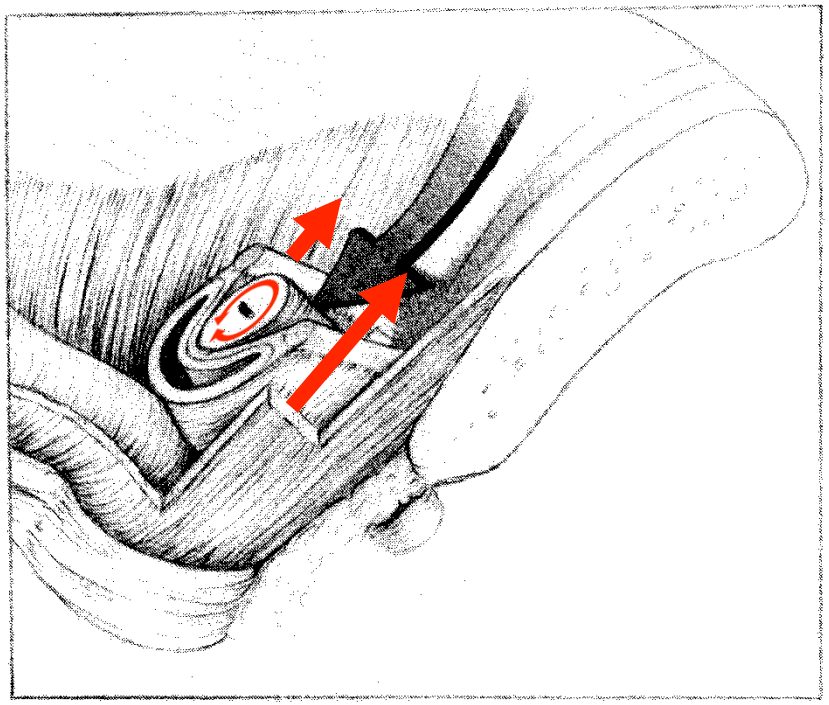


Fig. 2. 3D Slicer models. **A.** Three-fourths view of the levator ani muscle and pubic bone. **B.** Levator ani with pubic bones removed. **C.** Lateral view of muscle. © DeLancey 2006.

The continence mechanism





DeLancey JD et al. AJOG 1994; 170: 1713

Statements

”Pelvic floor muscle training appeared to be an effective treatment for adult women with stress or mixed incontinence”

Hay-Smith EJ et al. Cochrane 2001; CD001407

”The effectiveness of treatment is established”

Bø K. Int Urogynecol J Pelvic Floor Dysfunct 2004; 15: 76-84

”PFMT should be offered, as first line therapy, to all women with stress, urge or mixed urinary incontinence”

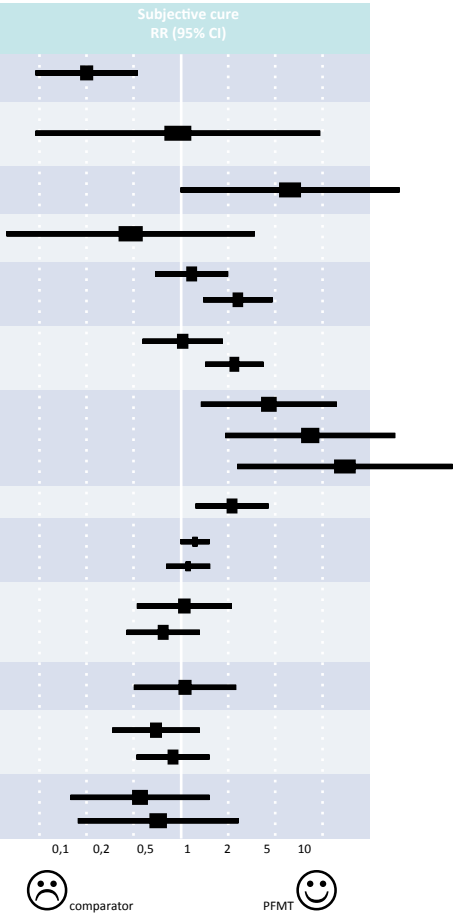
Wilson PD. International Consultation on Incontinence 2005

”Review provides some support for the widespread recommendation that PFMT be included in first-line conservative management programmes for women with stress, urge, or mixed, urinary incontinence”

Hay-Smith EJ, Dumoulin C. Cochrane 2006; CD005654

Subjective cure

Reference	Number randomized	Inclusion criteria	Age	Active intervention	Comparator(s)	Outcomes	Results Intervention	Results Comparator(s)	Comments
Klarskov 1986	**50**	Urodynamic SUI	Median 48 (31-66)	Five or more group sessions with physiotherapist	Burch colposuspension and/or vaginal repair	Self-reported improvement at 12 mo	Subjective cure: 3/24 (13%)	Subjective cure: 16/26 (62%)	RR (95% CI) = 0,20 (0,07-0,61)
Hahn 1991	**20**	Urodynamic SUI	Mean 47.2 (34-64)	Four weekly then 5 monthly visits to physiotherapist plus home exercises	Electrical stimulation	Self-reported improvement at end of treatment	Subjective cure: 1/10 (10%)	Subjective cure: 1/10 (10%)	RR (95% CI) = 1,00 (0,07-13,87)
Burns 1993	**135**	Urodynamic SUI or MUI	Mean 63	Eight weekly visits with nurse plus home exercisers	**No care**	Self-reported urine loss at end of treatment	Subjective cure: 7/43 (16%)	Subjective cure: 1/39 (3%)	RR (95% CI) = 8,78 (1,17-66,04)
Smith 1996	**18**	Urodynamic SUI	(24-82)	Instructions by urologist plus daily home exercises	Electrical stimulation	Self-reported urine loss at end of treatment	Subjective cure: 1/9 (11%)	Subjective cure: 2/9 (22%)	RR (95% CI) = 0,50 (0,05-4,58)
Burgio 1998	**197**	Urge UI or mixed UI with urodynamic DO	Mean 67.7 (55-92)	Four bi-weekly visits with nurse and bio-feedback plus home exercises	Four bi-weekly visits with nurse plus daily oxybutynin or placebo	Self-reported improvement at end of treatment	Subjective cure: 19/63 (30%)	Drug: Subjective cure: 15/65 (23%) Placebo: Subjective cure: 8/62 (13%)	RR (95% CI) = 1,31 (0,73-2,34) RR (95% CI) = 2,34 (1,11-4,94)
Wilson 1998	**192**	Any UI at 3 months post partum	Mean 28.4	Four sessions with physiotherapist at 3, 4, 6 and 9 m pp, using perineometer	Routine care and/or weighted vaginal cones.	Self-reported UI at 12 m pp	Subjective cure: 10/19 (53%)	Cones: Subjective cure 11/21 (52%) Controls: Subjective cure: 22/91 (24%)	RR (95% CI) = 1,00 (0,56-1,81) RR (95% CI) = 2,18 (1,24-3,81)
Bø 1999	**122**	Urodynamic SUI	Mean 49.5	Six months of weekly classes with physiotherapist plus home exercises	Electrical stimulation, vaginal cones or instruction on use of vaginal continence device	Self-reported improvement at end of treatment	Subjective cure: 14/25 (56%)	Electrical stimulation: Subjective cure: 3/25 (12%) Cones: Subjective cure: 2/27 (7%) Controls: Subjective cure: 1/30 (3%)	Electrical stimulation: RR (95% CI) = 4,67 (1,53-14,26) Cones: RR (95% CI) = 7,56 (1,91-29,99) Controls: RR (95% CI)=16,80(2,37-119,05)
Ishiko 2000	**38**	Symptomatic SUI	Mean 54.8	Instructions by gyneco-logist plus home exercises	**β-adrenergic (clenbuterol)**	Self-reported UI at 8-12 w	Subjective cure: 9/19 (47%)	Subjective cure: 3/13 (23%)	RR (95% CI) = 2,05 (0,68-6,17)
Glazener 2001 Glazener 2005	**747**	Any UI 3 months post partum	Mean 29.6	Advice by nurse at 5, 7 and 9 mo pp	Routine care	Self-reported UI at 12 m and 6 y pp	12 m: Subjective cure: 112/279 (40%) 6 y: Subjective cure: 62/263 (24%)	12 m: Subjective cure: 76/245 (31%) 6 y: Subjective cure: 52/253 (21%)	3 m: RR (95% CI) = 1,29 (1,02-1,64) 6 y: RR (95% CI) = 1,15 (0,83-1,59)
Burgio 2002	**222**	Urge UI or MUI, with urodynamic detrusor overactivity	65.4 (55-92)	Four bi-weekly visits with nurse – using biofeedback or digital assessment, plus home exercises	Written self-help program	Self-assessed improvement at end of treatment	Biofeedback: Subjective cure: 14/73 (19%) Digital assessment: Subjective cure: 16/74 (22%)	Subjective cure: 13/75 (17%)	Biofeedback: RR (95% CI) = 1,11 (0,56-2,19) Digital assessment: RR (95% CI) = 0,89 (0,47-1,68)
Goode 2003	**133**	SUI or MUI, with urodynamic SUI	56.2 (40-78)	Four bi-weekly visits with nurse using biofeedback, plus home exercises	Written self-help program	Self-assessed improvement at end of treatment	Subjective cure: 12/66 (18%)	Subjective cure: 11/67 (16%)	RR (95% CI) = 1,11 (0,53-2,33)
Wang 2004	**120**	Overactive bladder syndrome	Mean 53.2	12 weeks of twice weekly visits with physiotherapist using verbal instructions only or biofeedback	Electrical stimulation	Self-reported urinary symptoms at end of treatment	Verbal: Subjective cure: 10/34 (29%) Biofeedback: Subjective cure: 13/34 (38%)	Subjective cure: 14/35 (40%)	Verbal instruction: RR (95% CI) = 0,74 (0,38-1,42) Biofeedback: RR (95% CI) = 0,96 (0,53-1,72)
Williams 2006	**238**	Urodynamic SUI or MUI	56.9	Four biweekly instructions by nurse using digital assessment and perineometry	Vaginal cones or routine care	Self-reported UI at 12 w	Subjective cure: 4/80 (5%)	Cones: Subjective cure: 7/77 (9%) Controls: Subjective cure: 6/79 (8%)	Cones: RR (95% CI) = 0,55 (0,17-1,8) Controls: RR (95% CI) = 0,66 (0,19-2,24)

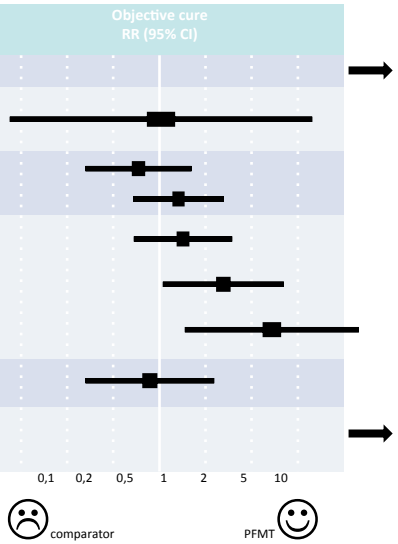


30 studies, 3283 randomized patients, small studies: median 50 (range 18-747)

Brostrøm, Lose. Acta Obstet Gyn Scand 2008; 87: 384-402

Objective cure

Reference	Number randomized	Inclusion criteria	Age	Active intervention	Comparator(s)	Outcomes	Results Intervention	Results Comparator(s)	Comments
Henalla 1990	**26**	Urodynamic SUI	Mean 54 (49-64)	"Pelvic floor re-education"	Vaginal estrogen or control	Unspecified pad-test	Objective improvement: 4/8 (50%)	Objective improvement: 0/18 (0%)	RR = ∞
Hahn 1991	**20**	Urodynamic SUI	Mean 47.2 (34-64)	Four weekly + 5 monthly visits to physiotherapist + home exercises	Electrical stimulation	Pad test at end of treatment	Objective cure: 1/10 (10%)	Objective cure: 1/10 (10%)	RR (95% CI) = 1,00 (0,07-13,87)
Wyman 1998	**137**	Urodynamic SUI and/or detrusor overactivity	Mean 61	6 visits with nurse + biofeedback + 6 phone consults + home exercises	6 visits with nurse + biofeedback + 6 phone consults + home exercises	Weekly frequency of incontinence episodes at end of treatment and after 3 months	End of treatment: Objective cure: 8/64 (13%) 3 m: Objective cure: 13/64 (20%)	End of treatment: Objective cure: 12/68 (18%) 3 m: Objective cure: 10/68 (16%)	RR (95% CI) = 0,71 (0,31-1,62) RR (95% CI) = 1,38 (0,65-2,93)
Bø 1999	**122**	Urodynamic SUI	Mean 49.5	Six months of weekly classes with physiotherapist plus home exercises	Electrical stimulation, vaginal cones or instruction on use of vaginal continence device	Pad test and 3-day bladder diary at end of treatment	Objective cure: 11/25 (44%)	Electrical stimulation: Objective cure: 7/25 (28%) Cones: Objective cure: 4/27 (15%) Controls: Objective cure: 2/30 (7%)	Electrical stimulation: RR (95% CI) = 1,57 (0,73-3,39) Cones: RR (95% CI) = 2,97 (1,09-8,13) Controls: RR (95% CI) = 6,60 (1,61-27,04)
Spruijt 2003	**37**	Any UI	(65-92)	Instructions during gynecological exam + home exercises	Electrical stimulation	48-hours bladder diary and pad test	Objective cure: 7/24 (29%)	Objective cure: 4/11 (36%)	RR (95% CI) = 0,80 (0,3-2,18)
Dumoulin 2004	**41**	Urodynamic SUI > 3 mo pp		8 weekly classes by physio + electrostimulation+ home exercises.	8 weekly sessions of relaxation massage by physiotherapist	20-minute pad test (Objective cure: < 2 g)	Objective cure: 14/20 (70%)	Objective cure: 0/19 (0%)	RR = ∞



Brostrøm, Lose. Acta Obstet Gyn Scand 2008; 87: 384-402

Trends

More effective in stress incontinent women?

More effective in young women?

More effective with intensive programmes?

How effective?

149 stress incontinent
8 weeks PFMT vs. 'sham' (hip abductions) + placebo,
Median reduction of incontinence episodes:
PFMT: 34.7% - 'Sham' 28.9%

Ghoniem et al. J Urol 2005; 173: 1647

133 stress incontinent
8 weeks PFMT vs. 'self-help booklet'
Median reduction of incontinence episodes:
PFMT: 15.1 → 4.5 - 'Booklet' 14.8 → 7.5

Goode et al. JAMA 2003; 290: 345

QOL

101 stress incontinent
3 mo PFMT vs. vaginal weights,
King's Health Questionnaire, statistically significant,
not clinically meaningful level

Laycock et al. Br J Community Nurs 2001; 6: 230

222 urge incontinent
8 weeks PFMT vs. 'self-help booklet', three QOL measures
no significant differences

Burgio et al. JAMA 2002; 288: 2293

120 overactive bladder
12 weeks PFMT vs. electrical stimulation,
King's Health Questionnaire, electrical stimulation better

Wang et al. Urology 2004; 63: 61

PFMT vs. TVT

- Multi-center RCT, Holland, 462 women
- 9-18 weekly sessions PFMT vs. mid-urethral sling
- 4 mo follow-up: 20 of PFMT got sling
- ”Still have SUI”: 83% vs. 14%
- ”Incontinence still severe”: 39% vs. 6%

Labrie. IUGA 2011 # 004

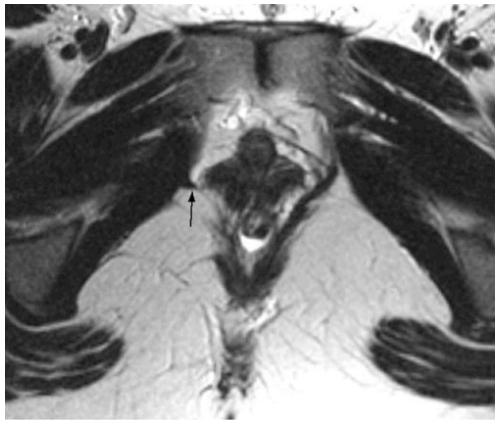
Why it (perhaps) doesn't work

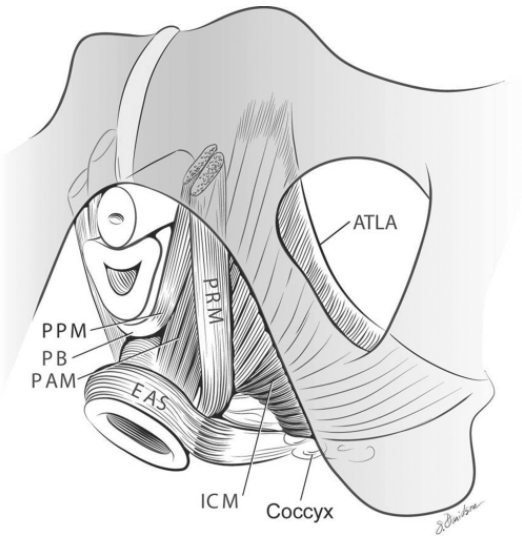
Only 1 in 4 able to contract on
simple verbal instructions

Nerve injuries

Levator avulsions

Urethral muscle fiber loss -65% (15→80 years),
equals 100 → 30 mmHg urethral pressure,
12 weeks muscle exercise = max. +30% strength





Hoyte. Annals N Y Acad Sci 2007; 1101: 361 | Ashton-Miller. Annals N Y Acad Sci 2007; 1101: 266
DeLancey. Obstet Gynecol 2003; 101: 46 | Bump. Am J Obstet Gynecol 1991; 165: 322
Dietz. BJOG 2006; 113: 225 | Perucchini. Am J Obstet Gynecol 2002; 186: 351

Conclusions

'Routine care' is effective!

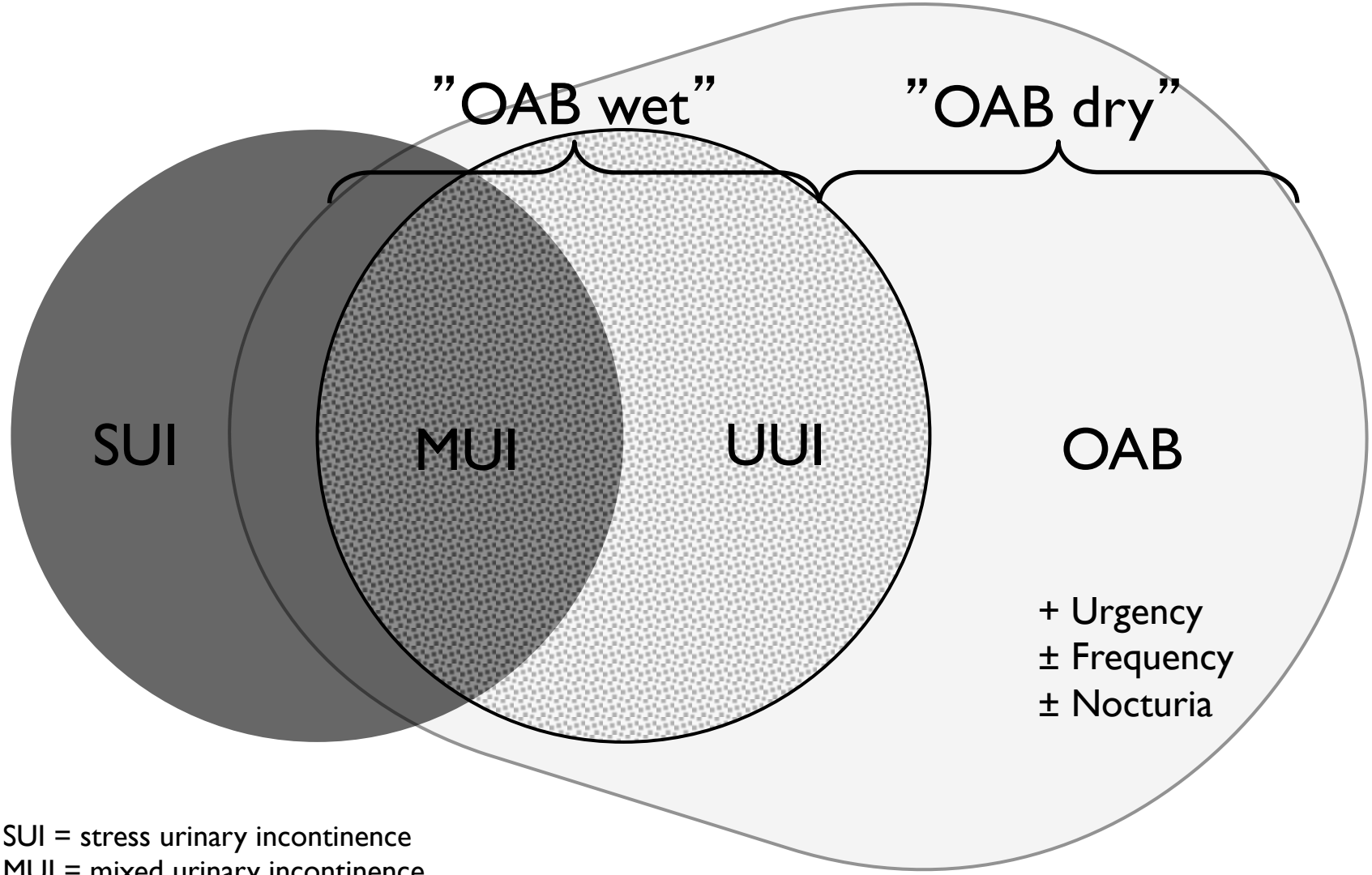
Inherent efficacy of PFMT minimal

No evidence for long term efficacy

Safe

Added benefits on sexual function etc

Pharmacological therapy



SUI = stress urinary incontinence
MUI = mixed urinary incontinence
UUI = urgency urinary incontinence
OAB = overactive bladder syndrome

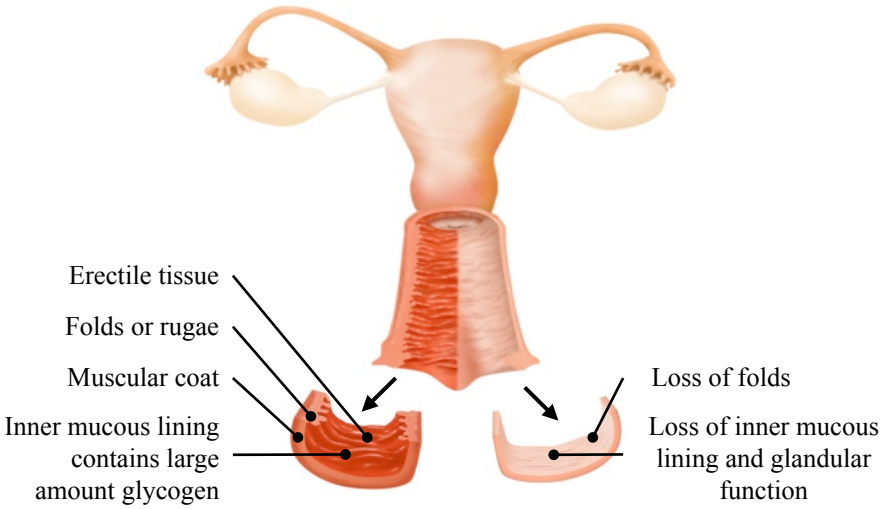
Haylen. Neurourol Urodyn 2010; 29: 4

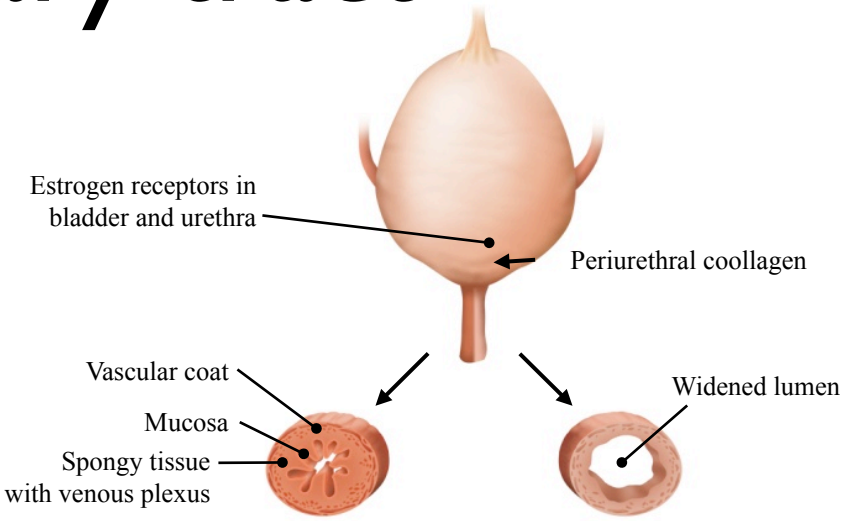
Pharmacological options

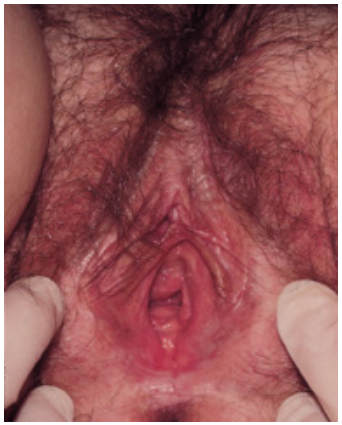
- **Estrogens**
- **Duloxetine**
- **Antimuscarinics**
- **Botulinum toxin**
- **Desmopressin**

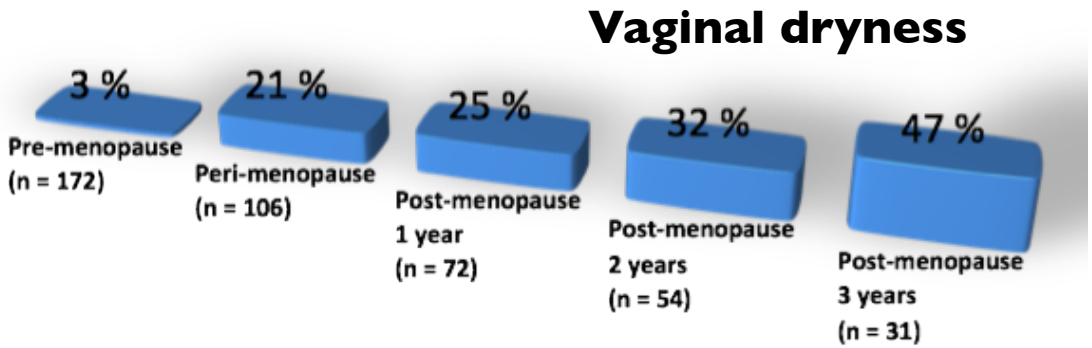
Estrogens

Menopause and lower urinary tract









Samsioe. A profile of the Menopause, 1995; 49 | Falconer. Maturitas 1996; 24: 197
Jackson. BJOG 2002; 109: 339 | Iosif. AJOG 1981; 141: 817
Batra. J Urol 1987; 138: 130 | Iosif. Acta Obst Gyn Scand 1984; 63: 257
Dennerstein. Obstet Gynecol 2000; 96: 351

Estrogen & incontinence

Postmenopausal women. Systemic HRT. RCT vs. placebo. Probability of improvement.

Reference	N =	Type UI	Therapy	Duration and outcome	Comparison
Walter. Urol Int 1978; 33: 135	29	Stress/mixed UI	Estradiol 2 mg/day + estriol 1 mg/day	4 months, subjective cure	6.36 (0.94-43.07) RR (95% CI)
Jackson. BJOG 1999; 106: 711	67	Stress UI	Estradiol 2 mg	6 months, subjective cure	5.50 (0.27-110.01) RR (95% CI)
Cardozo. Maturitas 1993; 18: 47	64	Urge UI Stress UI	Estriol 3 mg/day	3 months, subjective cure	1.45 (0.68-3.09) 0.91 (0.43-1.90) RR (95% CI)
Rufford. Int Urogyn J 2003; 14: 78	40	Urge UI Stress UI	17β-estradiol 25 mg subcutaneously	6 months, subjective cure	1.63 (0.61-4.39) 1.05 (0.61-2.31) RR (95% CI)
Grady. Obst Gyn 2001; 97: 116.	1525	Any UI	CEE 0.625 mg/day + MPA 2.5 mg/day	4 years, incontinence frequency	0.66 (0.55-0.79) OR (95% CI)
Hendrix. JAMA 2005; 293: 935.	15041	Any UI	- CEE + MPA - CEE alone	1 year, incontinence frequency	0.72 (0.67-0.78) 0.68 (0.62-0.74) RR (95% CI)

OAB and local estrogens

RCT, estriol 1 or 3 mg/day, 12 weeks, N= 40
- No reduction of voiding frequency

Enzelsberger. Geburtshilfe Frauenheilkunde 1991; 51: 834

RCT, 17β-estradiol 25 µg vaginal tablet, 12 weeks, N= 164
- Reduction of frequency, urgency etc.

Eriksen. Eur J Obst Gyn 1992; 44: 137

RCT, 17β-estradiol 25 µg vaginal tablet, 12 weeks, N= 104
- Reduction of sensory urgency only

Cardozo. J Obst Gyn 2001; 21: 383

RCT, tolterodine 2 mg BID +/- CEE 0.625 mg, 11 months, N=80
- Additional reduction of frequency, no effect on incontinence

Tseng. Neurourol Urodyn 2009; 28: 47

Conclusion: Local estrogens works for OAB <u>dry</u>

Conclusions

Local oestrogen treatment may improve ... incontinence

Systemic use... appears not to improve incontinence and may in fact make incontinence worse

Cody. Cochrane 2010: CD00140

Estrogen therapy may be of benefit for the irritative symptoms of urinary urgency, frequency and urge urinary incontinence ... due to reversal of urogenital atrophy rather than a direct action on the lower urinary tract

International Consultation on Incontinence 2005

Local estrogens

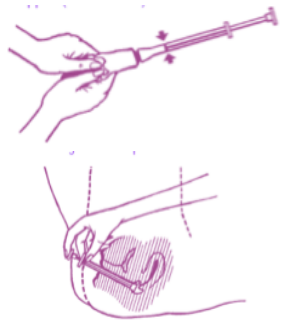



Creme

Ovesterin®
Estriol 1 mg/g

Daily 2 weeks
then 2 x / week

1,65 kr/d



Vaginal ring

Oestring®
17β-estradiol 7,5µg/d

Change every
three months

4,54 kr/d

Vaginal suppositories

Ovesterin®
Estriol 0,5 mg

Daily 2 weeks
then 2 x / week

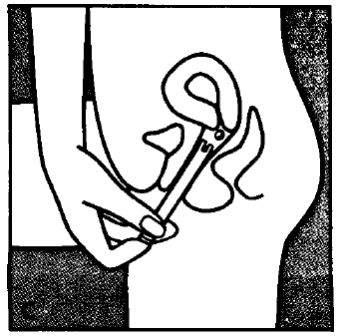
1,10 kr/d

Vaginal tablets

Vagifem®
17β-estradiol 10/25 µg

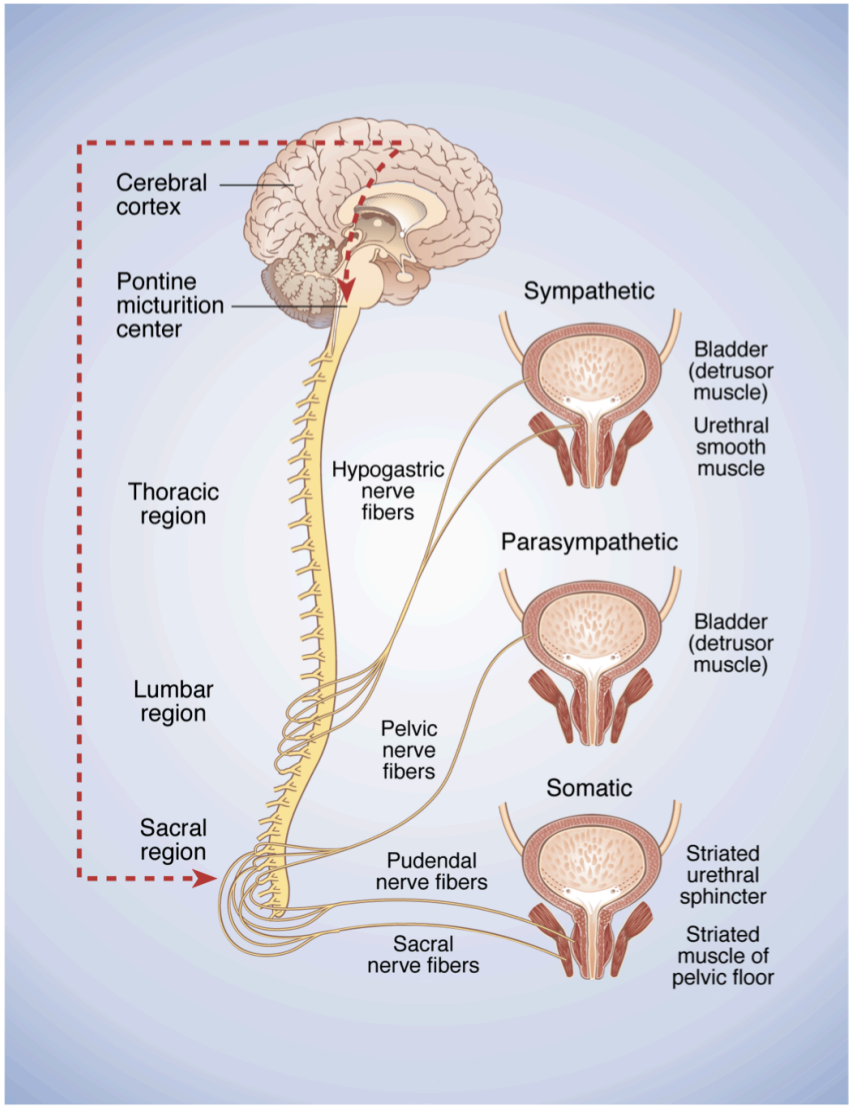
Daily 2 weeks
then 2 x / week

3,38 kr/d

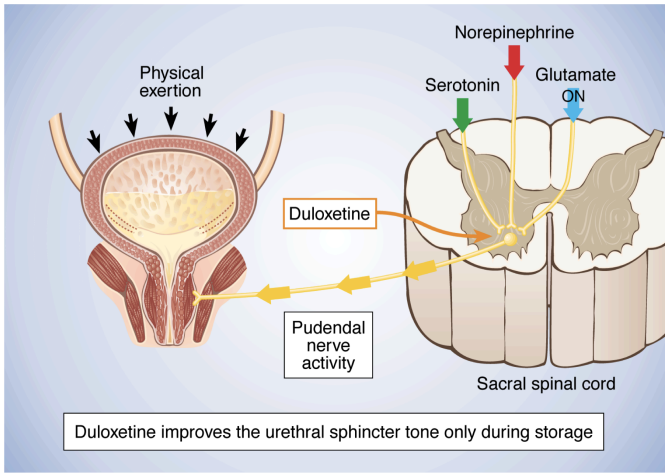


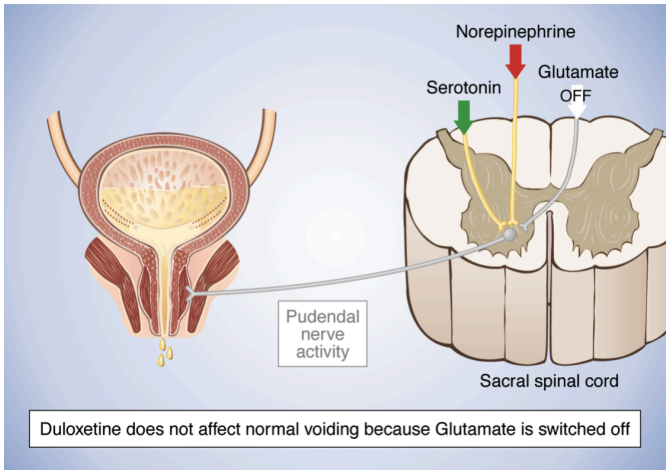
fass.se 28/4/11

Stress urinary incontinence


Cerebral cortex
Pontine micturition center
Thoracic region
Lumbar region
Sacral region
Hypogastric nerve fibers
Pelvic nerve fibers
Pudendal nerve fibers
Sacral nerve fibers
Sympathetic
Bladder (detrusor muscle)
Urethral smooth muscle
Parasympathetic
Bladder (detrusor muscle)
Somatic
Striated urethral sphincter
Striated muscle of pelvic floor

Yentreve® (duloxetin 40 mg BID) 16 kr/d



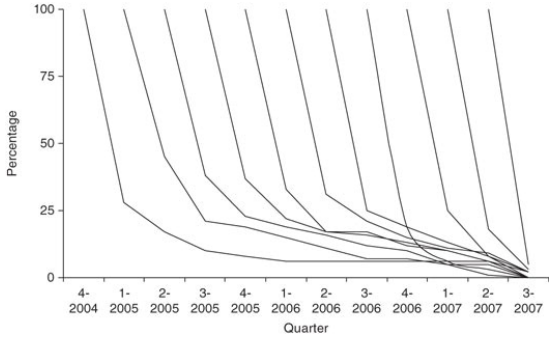


Review: Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults
Comparison: 1 A SNRI is better than placebo or no treatment
Outcome: 1 Numbers not cured during treatment

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Duloxetine 80 mg daily					
Dmochowski 2003	308/344	319/339		49.9 %	0.95 [0.91, 1.00]
Millard 2003	211/227	217/231		33.4 %	0.99 [0.94, 1.04]
Norton 2002	100/123	112/132		16.8 %	0.96 [0.86, 1.07]
Subtotal (95% CI)	**694**	**702**		**100.0 %**	**0.97 [0.93, 1.00]**

Review: Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults
Comparison: 1 A SNRI is better than placebo or no treatment
Outcome: 3 Numbers not improved during treatment

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Duloxetine 80 mg daily					
Cardozo 2004	16/46	45/52		7.9 %	0.40 [0.27, 0.61]
Dmochowski 2003	167/344	225/339		42.6 %	0.73 [0.64, 0.84]
Millard 2003	92/227	100/231		18.6 %	0.94 [0.75, 1.16]
Van Kerrebroeck 2004	119/247	164/247		30.8 %	0.73 [0.62, 0.85]
Subtotal (95% CI)	**864**	**869**		**100.0 %**	**0.74 [0.68, 0.81]**



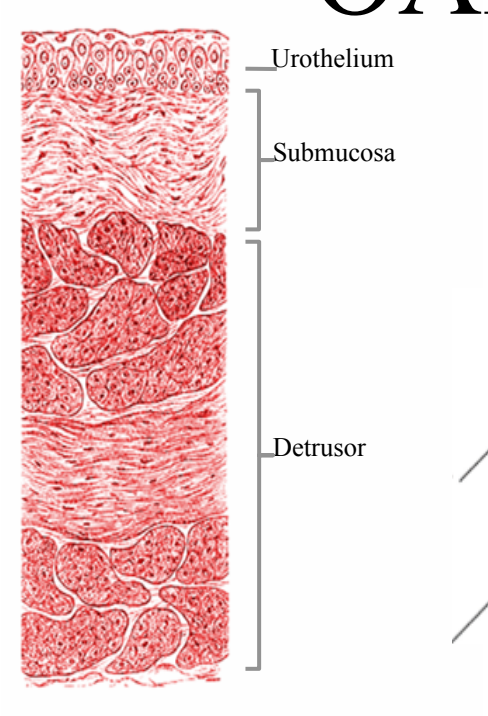
Percentage of users of duloxetine by quarters after the first purchase of the drug.

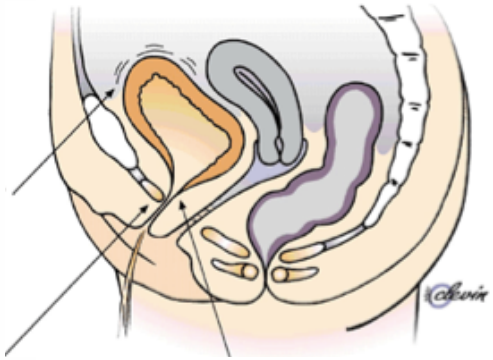
Nausea 23-25%
(side)effects seen week 1-4

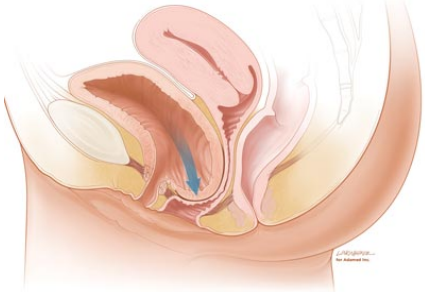
Mariappan. Cochrane 2009; CD004742
Hunskaar. Acta Obst Gyn Scand 2010; 89: 217

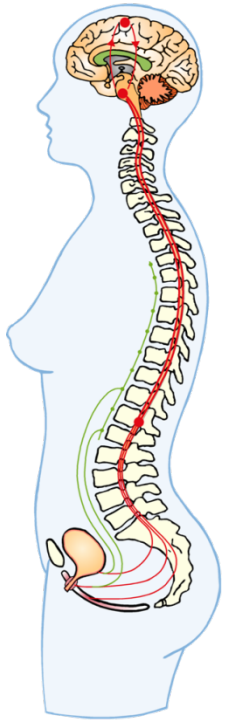
Overactive bladder syndrome

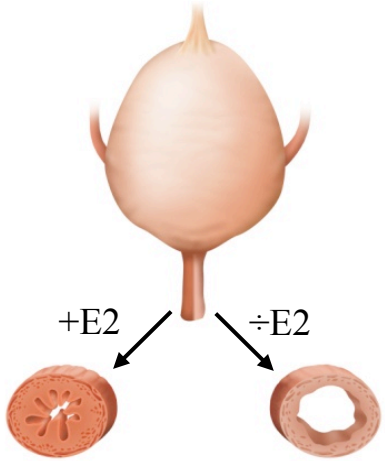
OAB pathophysiology ?

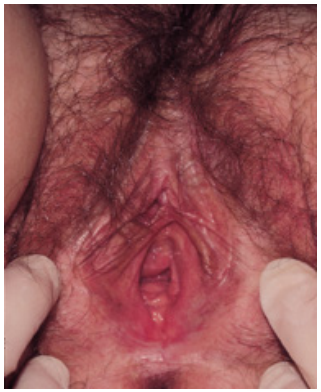


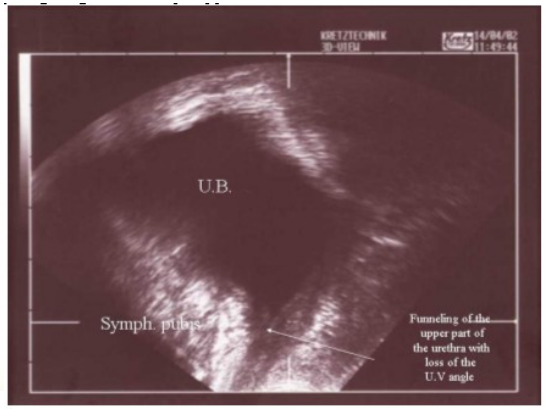








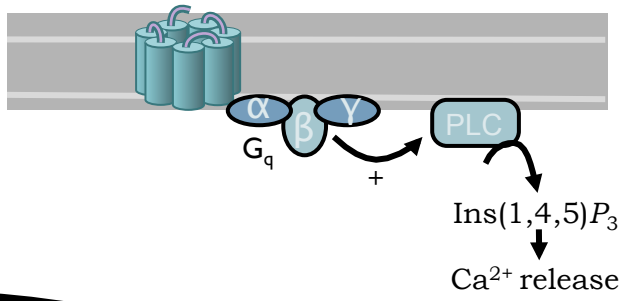


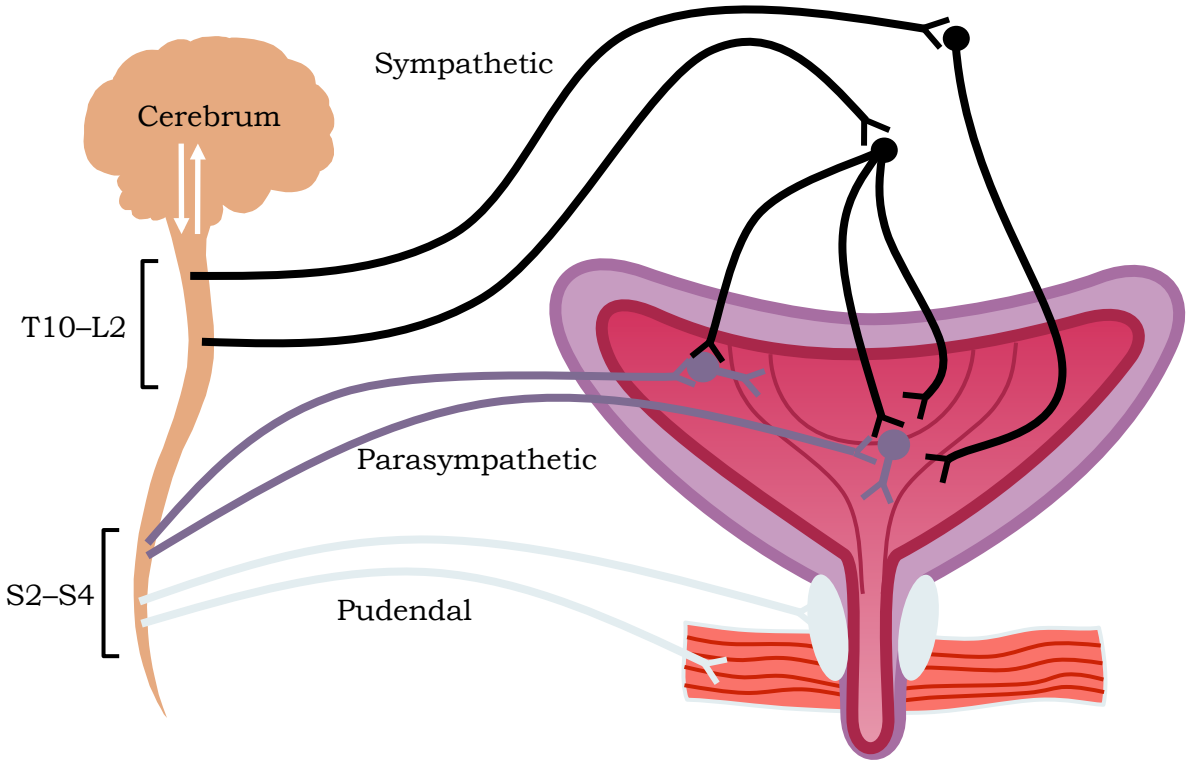


History

- 1953 – anticholinergics for neurogenic bladder
- 1965 – oxybutynin
- 1968 – flavoxate
- 1980 – trospium chloride
- 1995 – tolterodine
  - ← bladder selectivity
  - ← extended release
- 1997 – darifenacin
  - ← receptor selectivity
  - ← focus on CNS
- 2000 – solifenacin
  - ← receptor selectivity
  - ← dose titration
- 2002 – fesoterodine
  - ← serum metabolism

Muscarinic receptors





Antimuscarinics

Trospium chloride
(Spasmo-Lyt®, Sanctura® etc)

Oxybutynin IR/ER
(Ditropan®, Cystrin® etc)

Oxybutynin TDS
(Kentera®)

Tolterodine ER
(Detrusitol®)

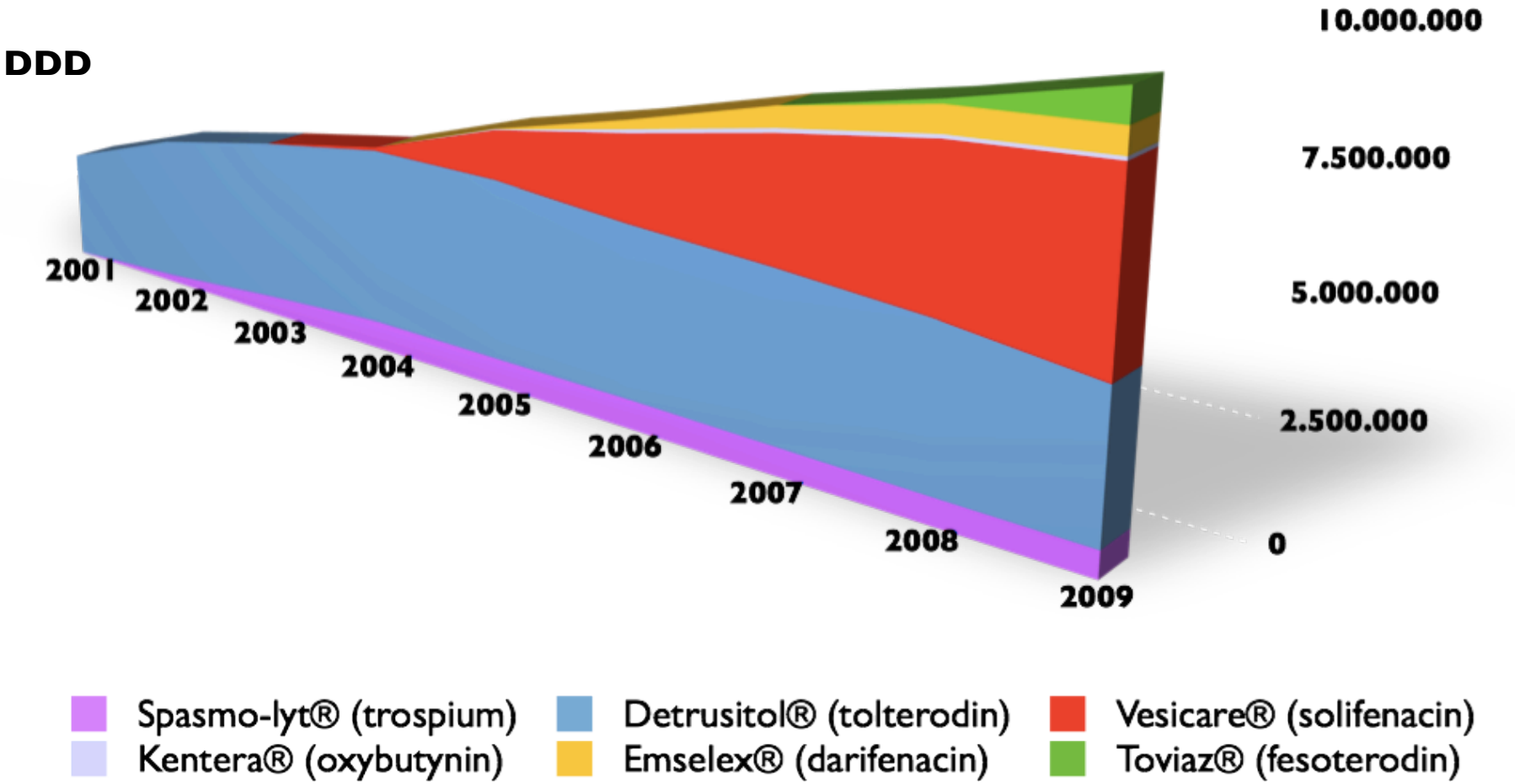
Solifenacin
(Vesicare®)

Darifenacin
(Emselex®)

Fesoterodine
(Toviaz®)

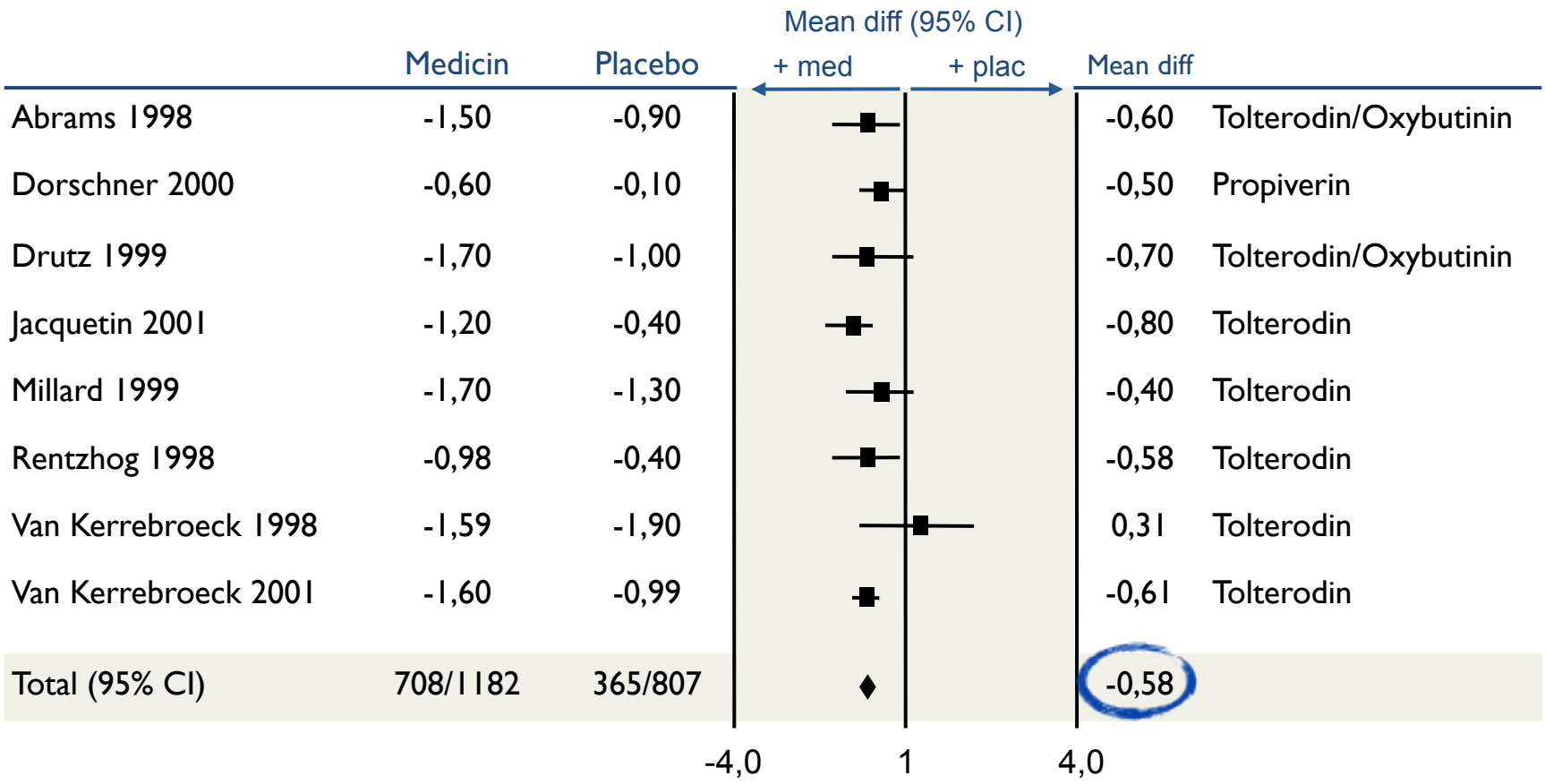
grade A
recommended

The Danish market



www.medstat.dk

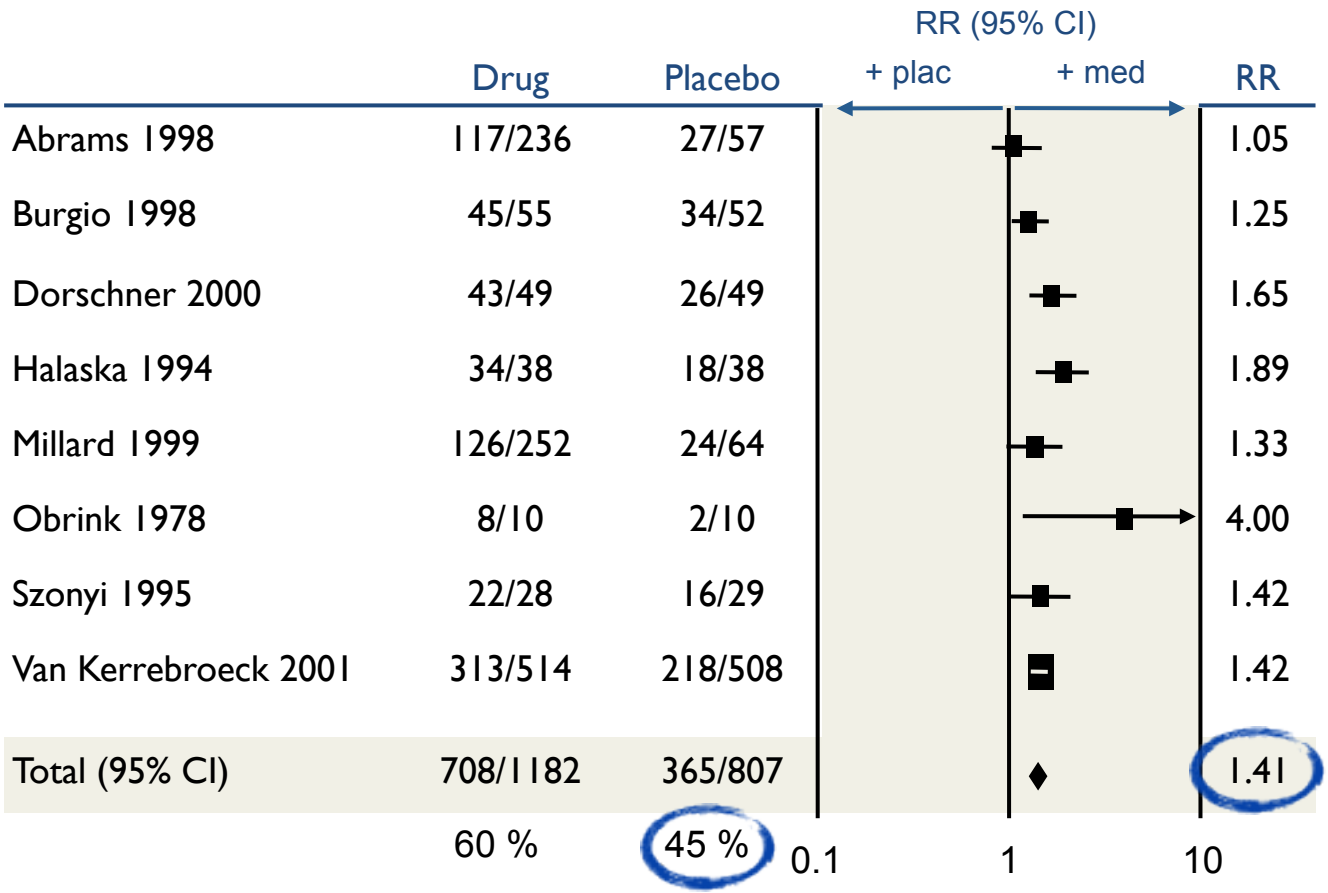
Incontinence episodes



Herbison. BMJ 2003; 326: 841

See also: Nabi. Cochrane 2006; CD003781 | Chapple. Eur Urol 2005; 48: 5
Chapple Eur Urol 2008; 54: 543 | Novara. Eur Urol 2008; 54: 740

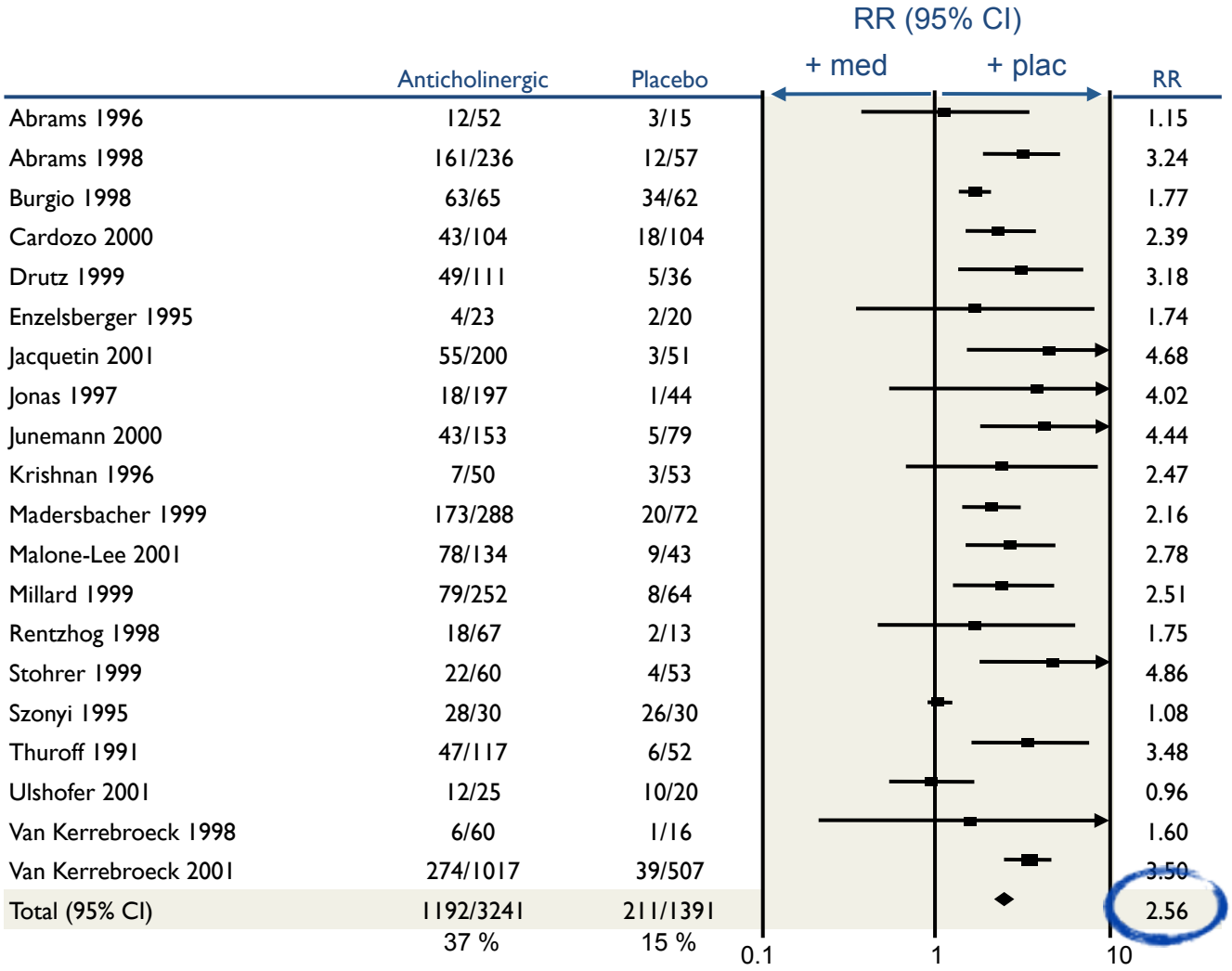
Cured/improved



Herbison. BMJ 2003; 326: 841

See also: Nabi. Cochrane 2006; CD003781 | Chapple. Eur Urol 2005; 48: 5
Chapple Eur Urol 2008; 54: 543 | Novara. Eur Urol 2008; 54: 740

Dry mouth

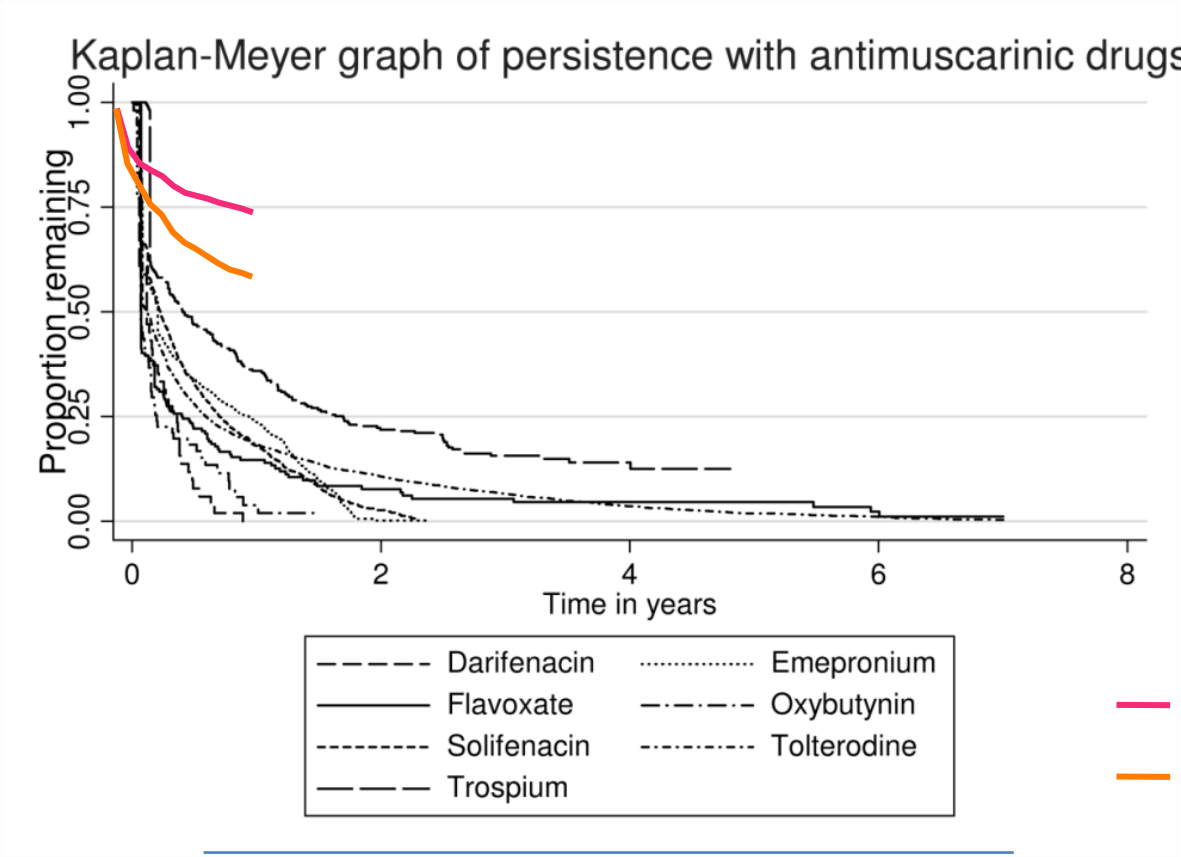


	Anticholinergic	Placebo	RR
Abrams 1996	12/52	3/15	1.15
Abrams 1998	161/236	12/57	3.24
Burgio 1998	63/65	34/62	1.77
Cardozo 2000	43/104	18/104	2.39
Drutz 1999	49/111	5/36	3.18
Enzelsberger 1995	4/23	2/20	1.74
Jacquetin 2001	55/200	3/51	4.68
Jonas 1997	18/197	1/44	4.02
Junemann 2000	43/153	5/79	4.44
Krishnan 1996	7/50	3/53	2.47
Madersbacher 1999	173/288	20/72	2.16
Malone-Lee 2001	78/134	9/43	2.78
Millard 1999	79/252	8/64	2.51
Rentzhog 1998	18/67	2/13	1.75
Stohrer 1999	22/60	4/53	4.86
Szonyi 1995	28/30	26/30	1.08
Thuroff 1991	47/117	6/52	3.48
Ulshofer 2001	12/25	10/20	0.96
Van Kerrebroeck 1998	6/60	1/16	1.60
Van Kerrebroeck 2001	274/1017	39/507	3.50
Total (95% CI)	1192/3241	211/1391	2.56
	37 %	15 %	

Herbison. BMJ 2003; 326: 841

See also: Nabi. Cochrane 2006; CD003781 | Chapple. Eur Urol 2005; 48: 5
Chapple Eur Urol 2008; 54: 543 | Novara. Eur Urol 2008; 54: 740

Persistence of therapy



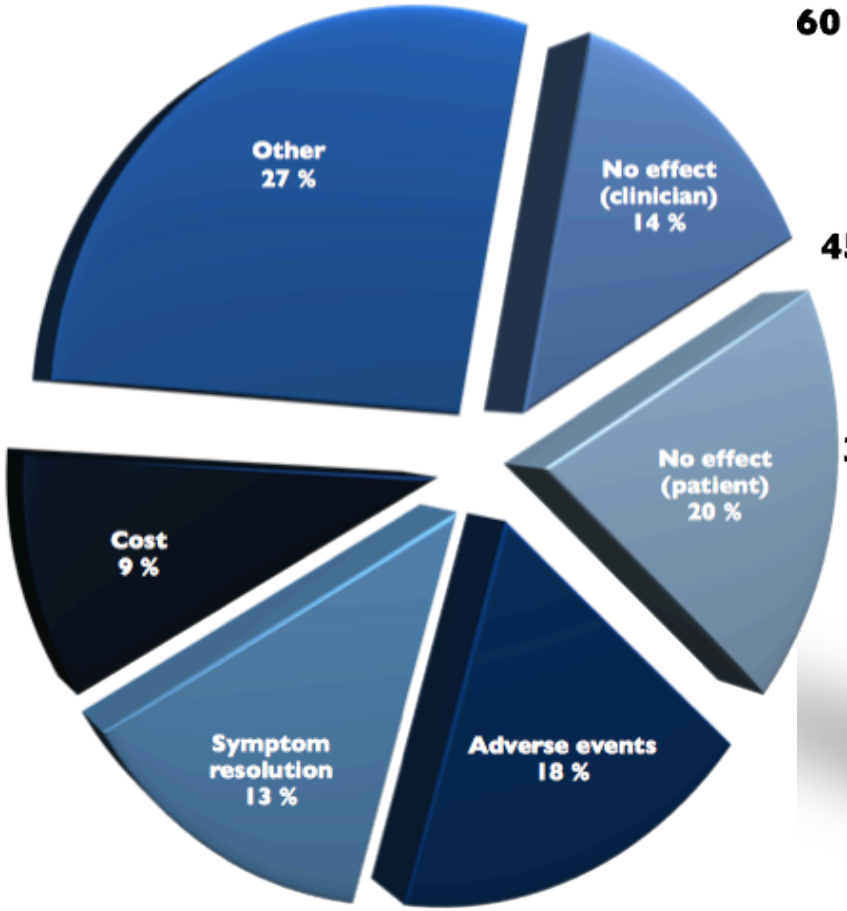
AIIA

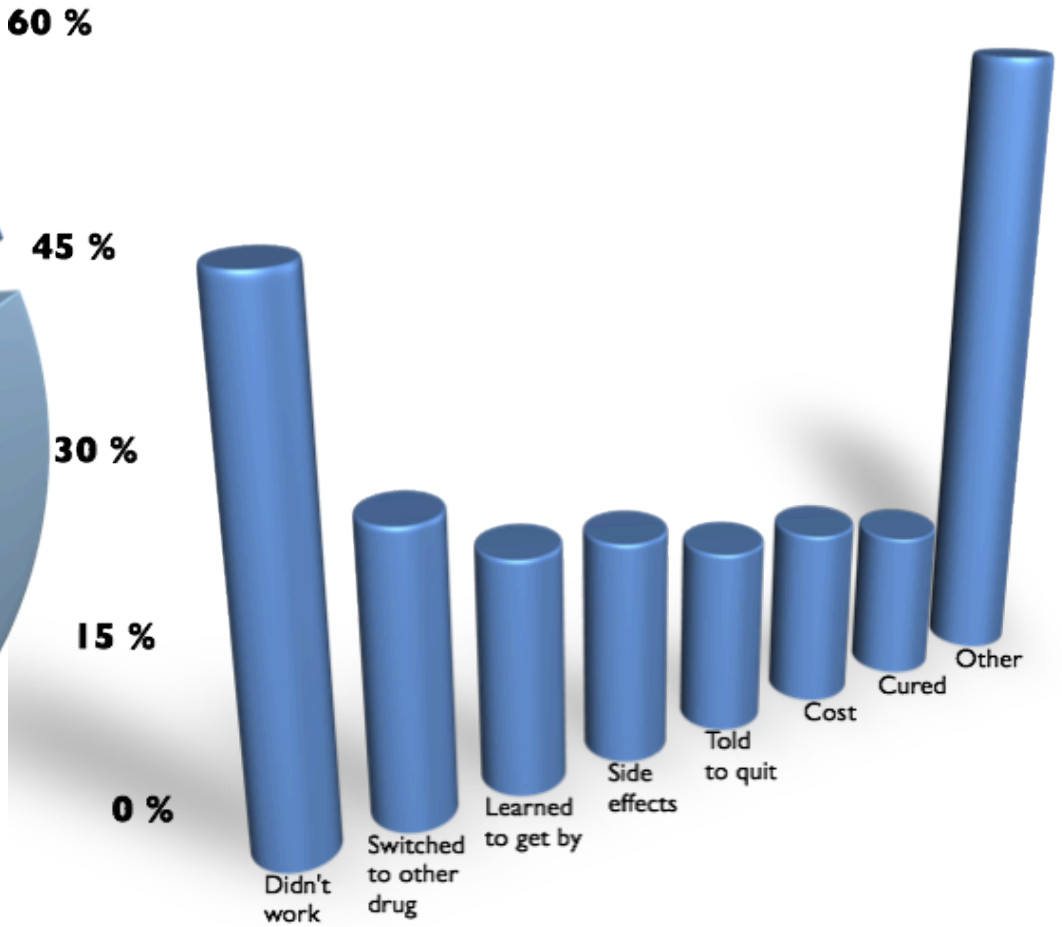
Statins

Continuation rates			
	6 months	1 year	2 years
All except trospium	< 40 %	< 25 %	< 10 %
Trospium	46 %	36 %	22 %

Brostrøm & Hallas. Eur J Clin Pharmacol 2009; 65: 309

Why do patients stop?

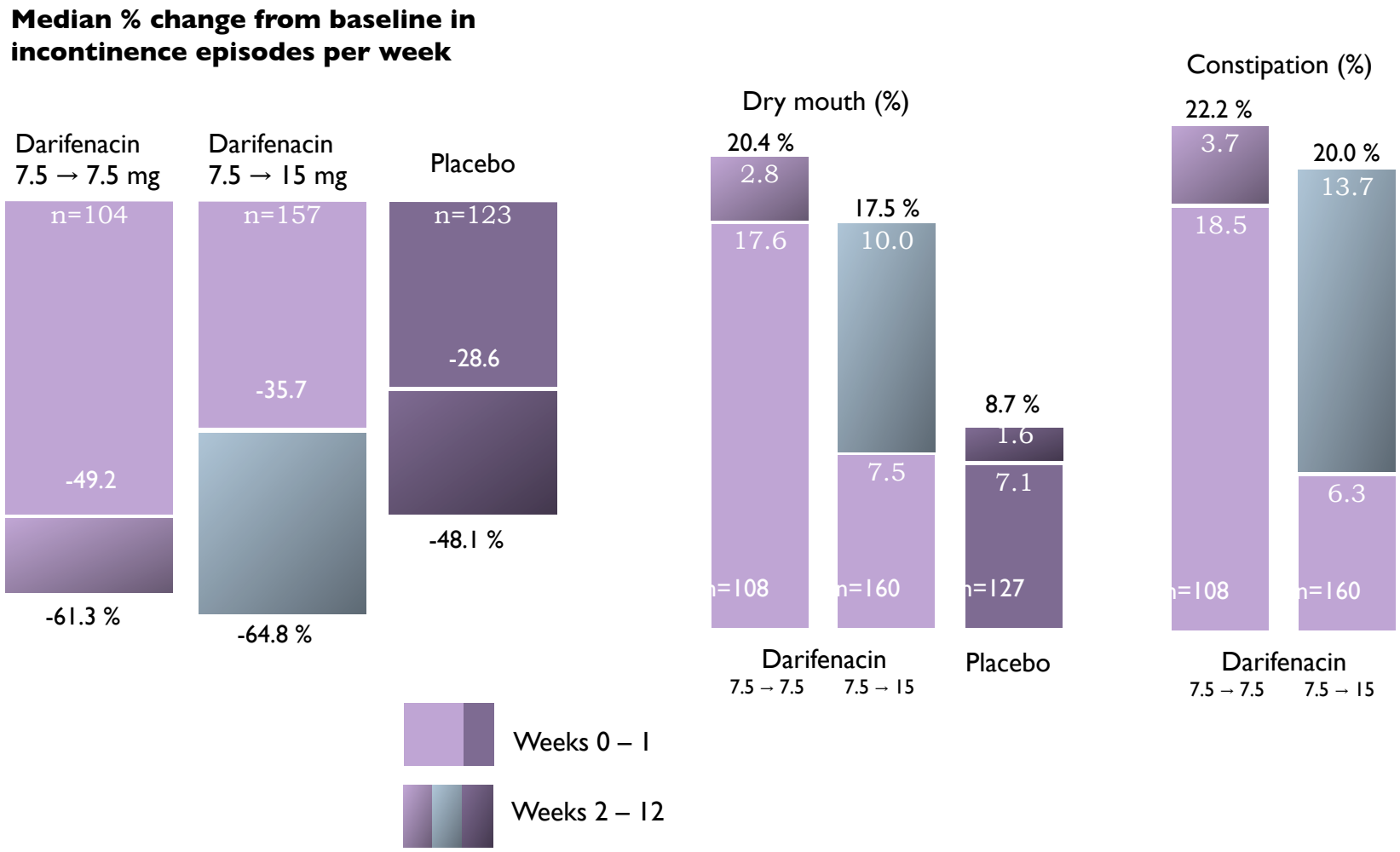




Pesce. ICS 2003. Abstract 304.

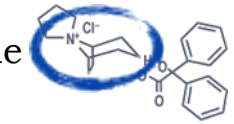
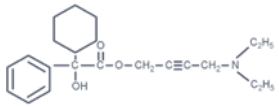
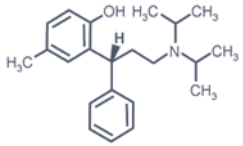
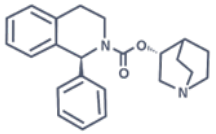
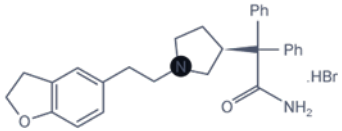
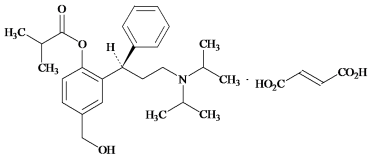
Brubaker. ICS 2006. Abstract 86.

Dose titration



Steers. BJU Int 2005; 95: 580

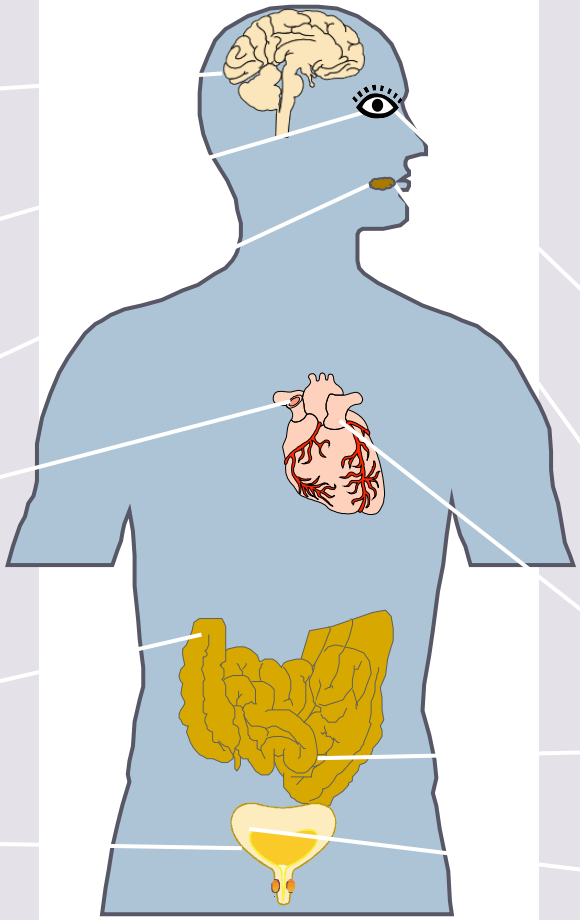
Pharmacology

		Size	M3 vs M1	Metabolism	Formulation	Kinetics
Trospium chloride (Spasmo-Lyt®)		428	1,5	None	Immediate release x 2	C_{max}: 4-6 t $T_{½}$: 12-18 t
Oxybutynin (Kentera®)		357	1,5	CYP3A4	Transdermal	C_{max}: 24-48 t $T_{½}$: 7-8 t (IR: 2-3 t)
Tolterodine (Detrusitol®)		476	0,6	CYP3A4 CYP2D6	ER capsules (coated-bead)	C_{max}: 2-6 t $T_{½}$: 8-9 t (IR: 2-3 t)
Solifenacin (Vesicare®)		481	2,5	CYP3A4	Immediate release x 1	C_{max}: 3-8 t $T_{½}$: 45-68 t
Darifenacin (Emselex®)		508	9,3	CYP3A4 CYP2D6	Matrix tablet (controlled-release)	C_{max}: 6 t $T_{½}$: 12 t
Fesoterodine (Toviaz®)		528	1,1	Serum esterases 5HMT: CYP3A4 CYP2D6	Tablet (prolonged-release)	5HMT: C_{max}: 5 t $T_{½}$: 7-9 t

Muscarinic receptors

Tissue distribution

- Brain
  M1 + M3
- Eye
  M3
- Salivary glands
  M3
- Heart
  M2 + M3
- Intestine
  M2 + M3
- Bladder
  M2 + M3



Potential adverse events

- Cognitive impair
  Memory loss
  Sleep disturbance
- ↓ lacrimation
  ↓ accommodation
- Xerostomia
  (dry mouth)
- Cardiovascular
- Constipation
- Urinary retention

Focus on CNS

Case reports: confusion, hallucinations and 'night terror' with oxybutynin

Choulot. Ann Pediatr (Paris) 1989; 36: 714 | Banerjee. Hum Exp Toxicol 1991; 10: 225
Donnellan. BMJ 1997; 315: 1363 | Katz. J Am Geriatr Soc 1998; 46: 8
Valsecia. Ann Pharmacother 1998; 32: 506

Significant EEG changes with oxybutynin, but with neither trospium, tolterodine nor darifenacin (young healthy volunteers)

Pietzko. Clin Pharmacol 1994; 47: 337
Todorova. J Clin Pharm 2001; 41: 636
Kay. BJUI 2005; 96: 1055

Reduced REM sleep with oxybutynin and tolterodine,
but not with trospium (healthy volunteers 22-36 and > 50 years old)

Diefenbach. Clin Drug Invest 2003; 23: 395
Diefenbach. BJU Int 2005; 95: 346

Cognitive impairment (16 years of 'brain aging') with oxybutynin,
but not with darifenacin. No difference in self-perceived memory loss
(healthy volunteers ≥ 60 years old)

Kay. Eur Urol 2006; 50: 317
Katz. J Am Geriatr Soc 1998; 46: 8
Kay. BJUI 2005; 96: 1055
Lipton. J Urol 2005; 173: 493

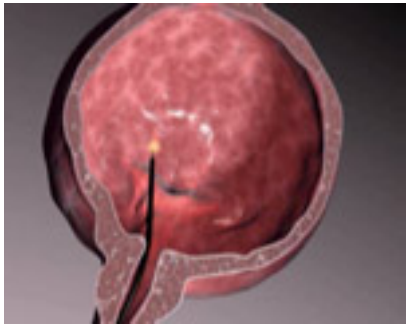
Pros & cons

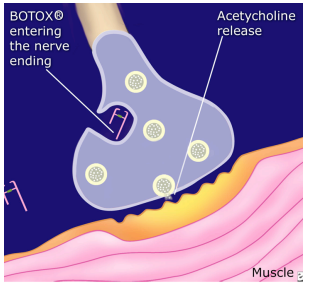
	CNS	Dry mouth	Constipation	Persistence	Interactions	Dose titration	FASS.se 28 april 2011
Trospium chloride (Spasmo-Lyt® 20 mg IR 60 mg ER + generics)	☺			☺	☺		☺
Oxybutynin IR/ER (Ditropan® 5 mg)	☹						4,30 kr/d
Oxybutynin TDS (Kentera® 3.9 mg/d)	☹	☺	☺	☹			13,55 kr/d
Tolterodine ER (Detrusitol® 4 mg)							13,23 kr/d
Solifenacin (Vesicare® 5/10 mg)						☺	12,33 kr/d 14,92 kr/d
Darifenacin (Emselex® 7.5/15 mg)	☺		☹			☺	11,39 kr/d 12,21 kr/d
Fesoterodine (Toviaz® 4 / 8 mg)						☺	12,42 kr/d 15,02 kr/d

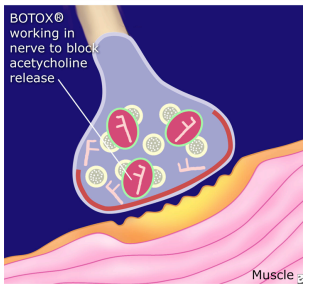
– Hvis dette ikke hjælper, kan De komme igen – så skal De få noget andet.
– Kunne jeg så ikke lige så godt få det andet med det samme!

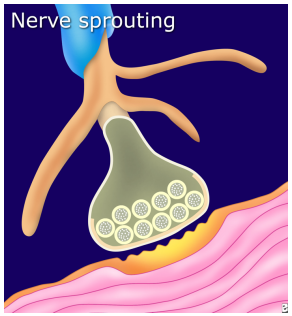
Botulinum toxin

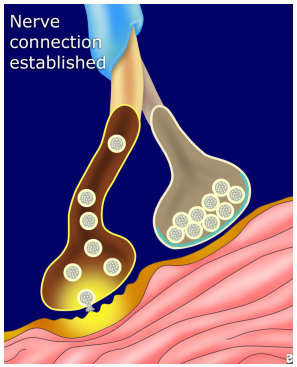
Idiopathic DOI - 12 w	**Placebo**	**Botox® 100 IE**
Urgency continence	16 %	37 %
Micturitions	-1,2	-3,1
Urgency episodes	-2,0	-4,4
PVR > 200 ml	2 %	18 %
UTI	16 %	36 %
Improvements seen week 2-36 100 IE Botox = 1955 SEK		











Brubaker. IUGA 2009 # 140
Duthie. Cochrane 2009: CD005493

Nocturia

Antidiuretic therapy

- Desmopressin = synthetic ADH
- Minirin® 60 µg = Nocutil® 0,1 mg = 6 kr/d
- Increases H_2O reabsorption in collecting tubule, no BP effect
- Verify: nocturnal polyuria > 30%
- Exclude: polydipsia, congestive heart failure
- Try: water restriction, afternoon diuretic, compressive stockings
- Restrict water-intake -1 to + 8 h
- Monitor: P-Na & weight @ + 3 d, + 7 d, + 3 w
- Stop immediately if Na ↓, weight ↑, CNS
- Hyponatremia ~ 8 %
- Risks: > 80 years, > 30 ml/kg

Time	Liquid intake	Voided volume	Leaks	Notes
7 - 8		350		waking
8 - 9	300			coffee
9 - 10		100		
10 - 11	300			coffee
11 - 12		175		
12 - 13	350			
13 - 14	100	100		
14 - 15	225			
15 - 16	250	175		
16 - 17		275		
17 - 18				
18 - 19	250	100		
19 - 20				
20 - 21	200	100		
21 - 22	325	200		coffee
22 - 23				
23 - 24		100		
24 - 1				in bed
1 - 2				
2 - 3		275		
3 - 4			X	pad 100 g
4 - 5		125		
5 - 6		200		
6 - 7				
IALT	2300	2275		

350+275+100+125+200 = 1050
1050/2275 = 46 %

soren@brostrom.dk