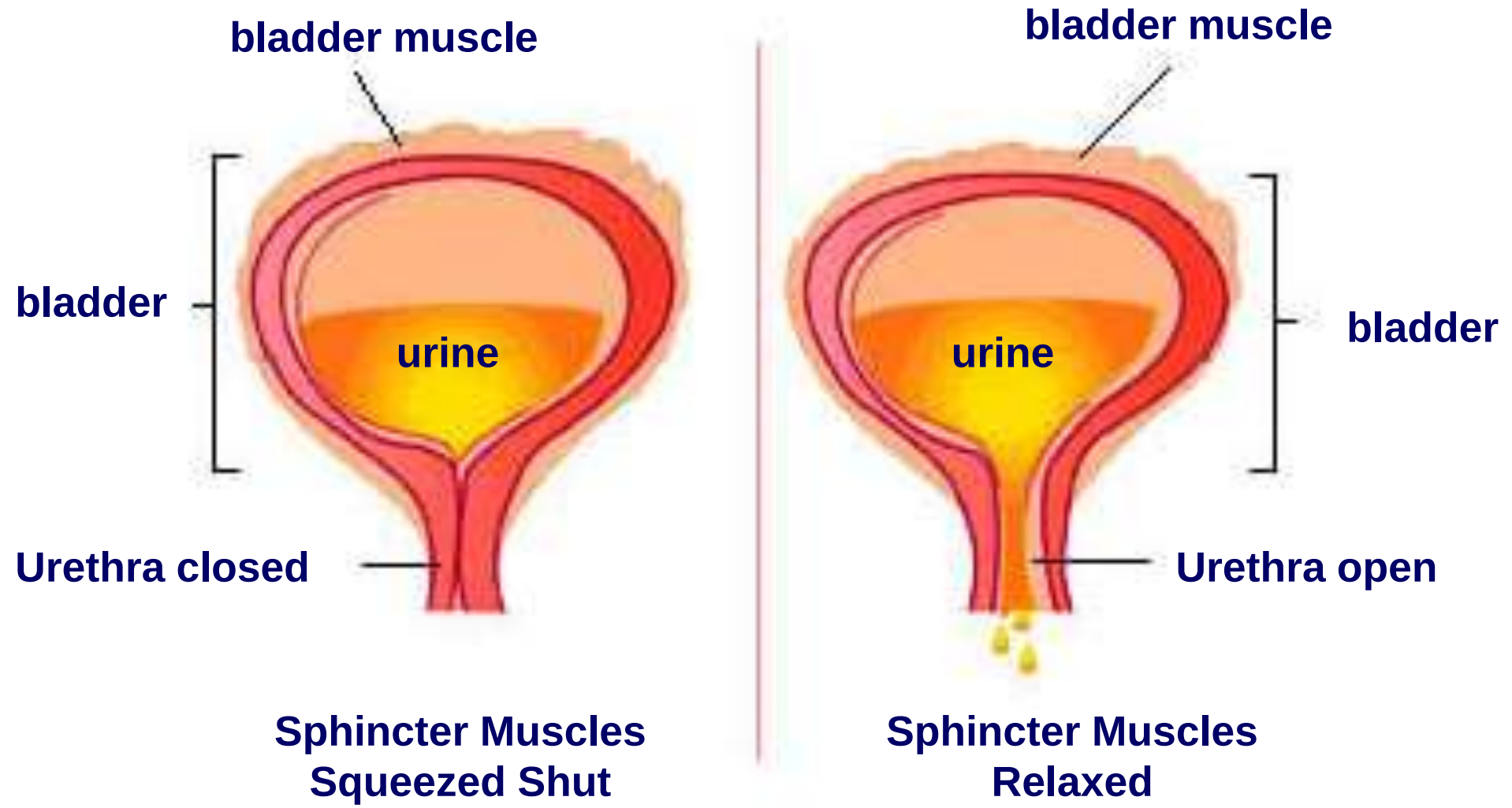
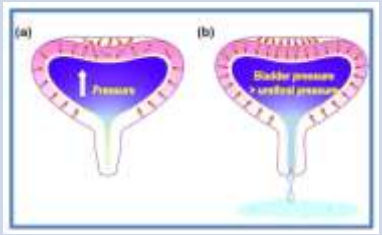
Advances in Medical Treatment for Urinary Incontinence

Dr. BC Tong
Geriatrician, PMH
Hon Treasurer, HKCS

Urinary incontinence

- The complaint of any involuntary leakage of urine (which is objectively demonstrable and is a social or hygiene problem)


bladder muscle
bladder
urine
Urethra closed
Sphincter Muscles
Squeezed Shut
bladder muscle
urine
bladder
Urethra open
Sphincter Muscles
Relaxed

Type	Urge Incontinence	Stress Incontinence	Overflow Incontinence	Functional Incontinence
	 			
Cause	**Detrusor overactivity** Uninhibited bladder contraction causing leakage of moderate to large amounts of urine 	**Reduced outlet resistance** Increase in intraabdominal pressure, eg. coughing, sneezing, laughing or other physical activity, causing leakage of small to moderate amount of urine 	**Increased outlet resistance** **Detrusor underactivity** Distension of bladder causing overflow leakage of small amount of urine 	**Unrelated to lower urine tract cause** Inability or unwillingness of a normal continent elderly to go to the toilet 
Etiology	Cystitis Bladder stone/ neoplasm CNS disorder Spinal cord disease Idiopathic	Obesity Estrogen deficiency Childbirth Weakness and laxity of pelvic floor muscles Post-prostatectomy	Prostatic enlargement Urethral stricture Spinal cord disease Faecal impaction Diabetic neuropathy Sacral nerve damage Medication	Musulosketetal disorders Impaired mental status Unfamiliar environment Depression Hostility Sedating medication Use of physical restraints ....
	Mixed incontinence			

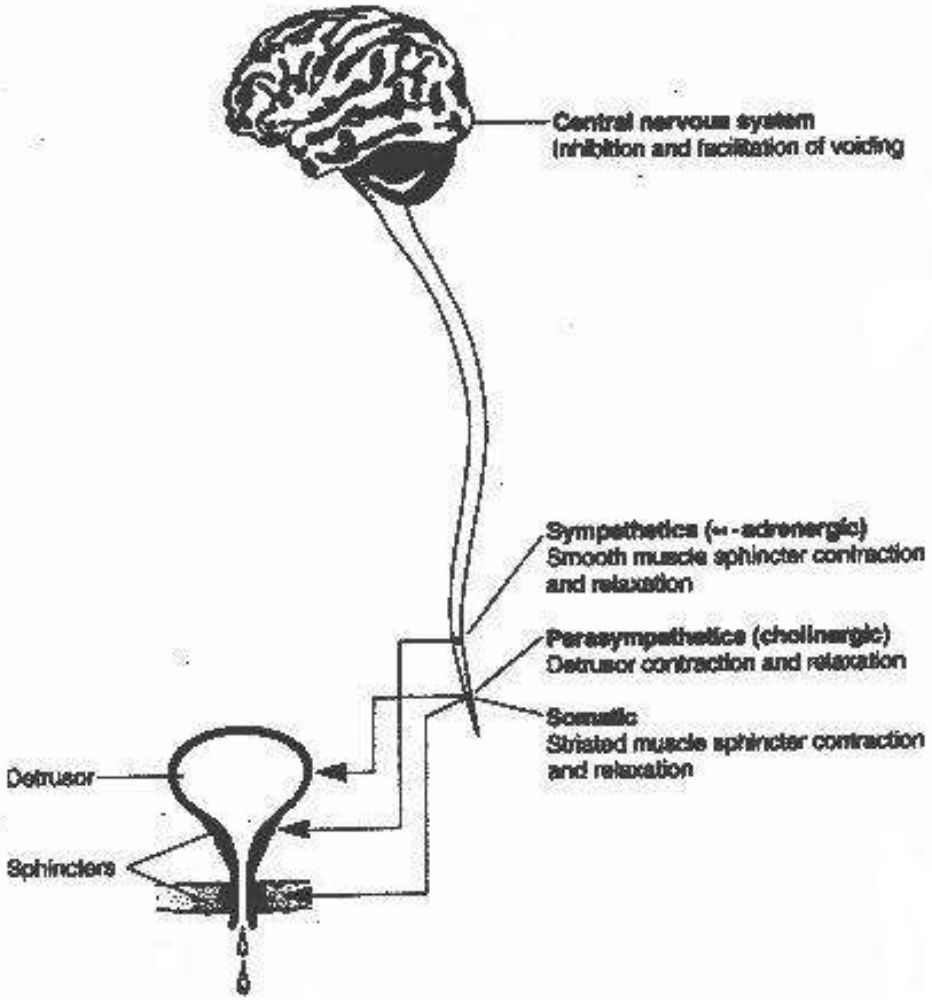
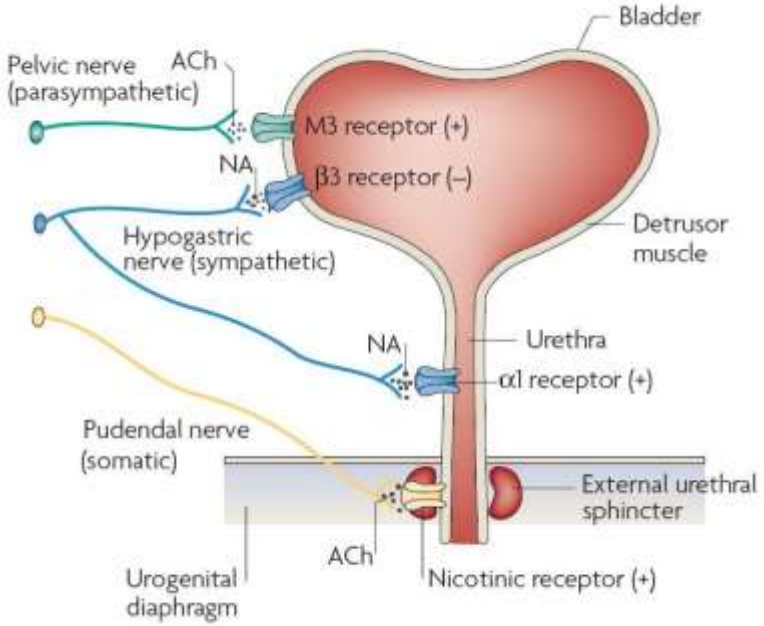
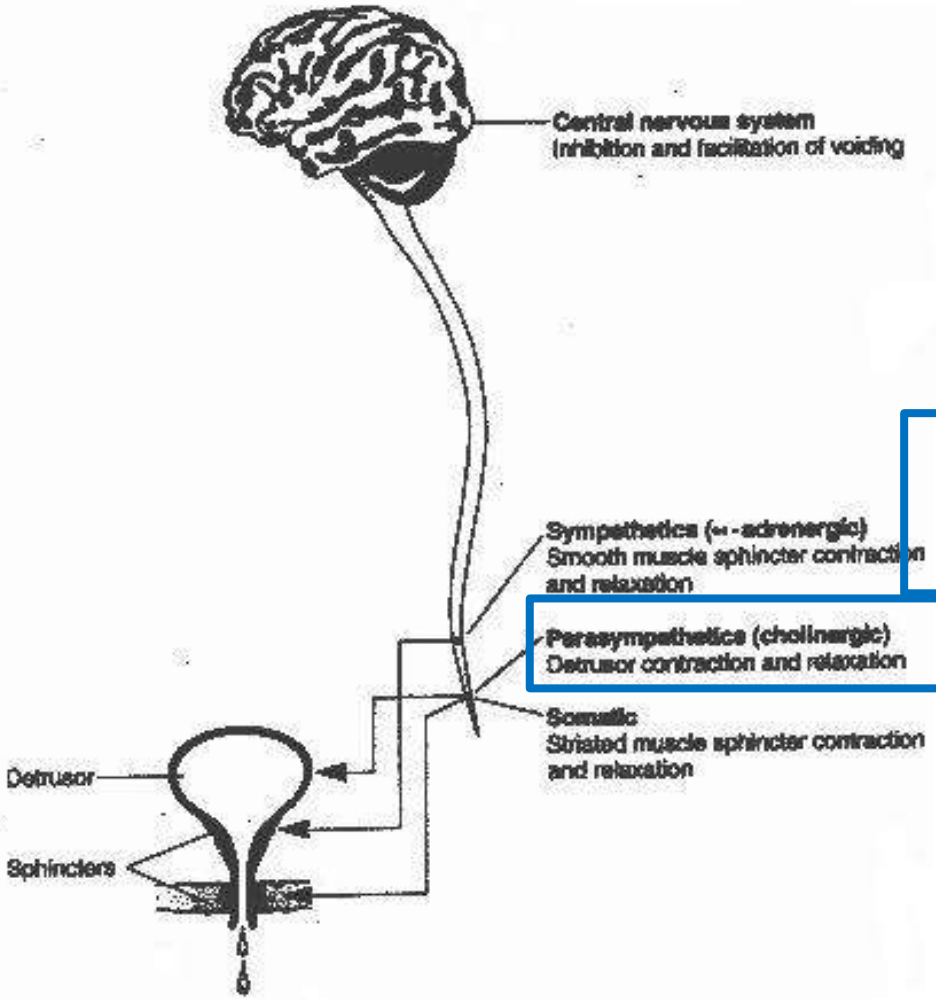


Fig. 15–1. Normal micturition occurs when bladder contraction is coordinate urethral sphincter relaxation. Four nervous system components are involved: (1) The *central nervous system* inhibits voiding until the appropriate time; it also coordinates and facilitates input from the bladder to start and complete voiding. (2) The *sympathetic system* contracts the smooth muscle sphincter through α-adrenergic fibers from the hypogastric nerve. (3) The *parasympathetic system* contracts the bladder detrusor muscle through cholinergic fibers from the pelvic nerve. (4) The *somatic nervous system* contracts the striated muscle sphincter through cholinergic fibers from the pudendal nerve. (Adapted from DuBeau CE, Resnick NM, with the Massachusetts Department of Health EDUCATE project collaborators. Urinary Incontinence in the Older Adult: An Annotated Speaker/Teacher Kit, 1993; used with permission of the authors.)



Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci. 2008 Jun;9(6):453-66



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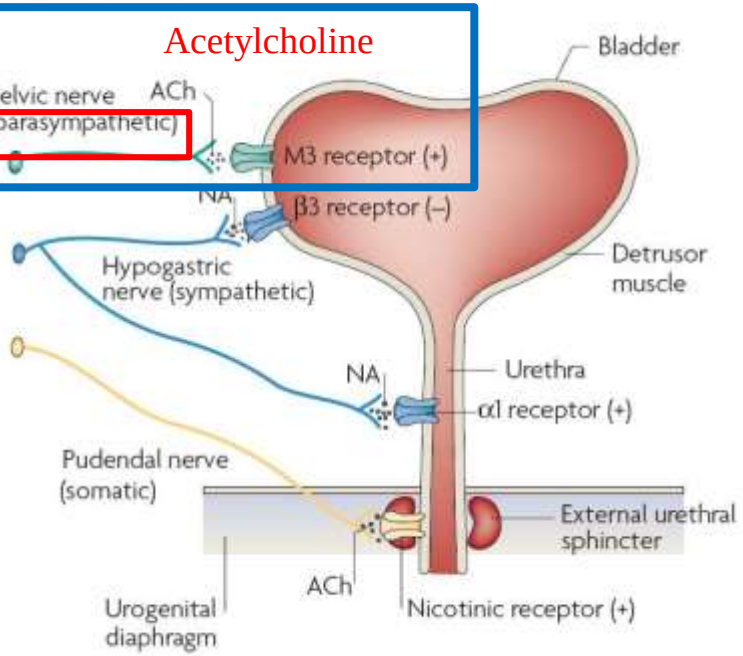
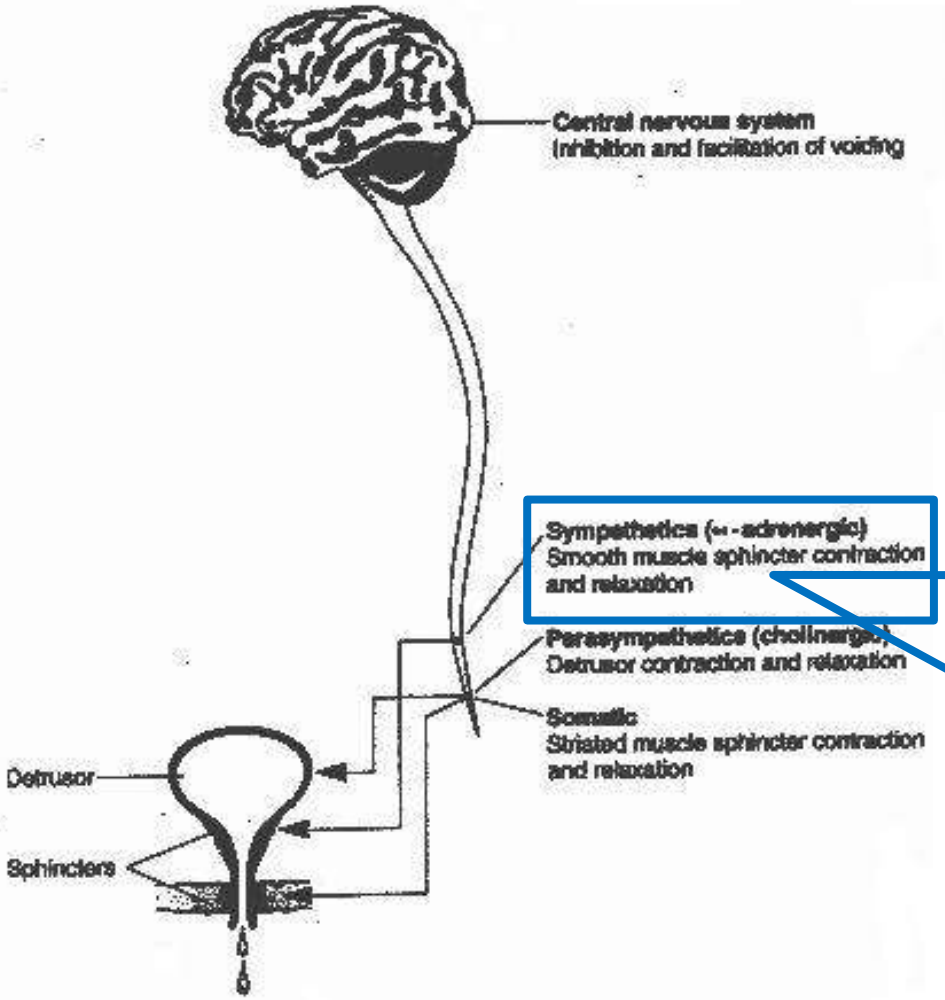


Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci. 2008 Jun;9(6):453-66



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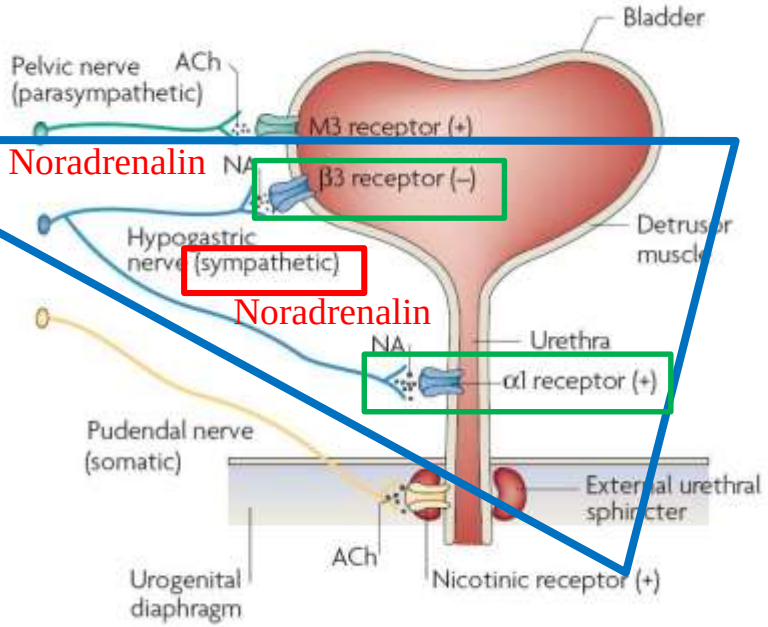
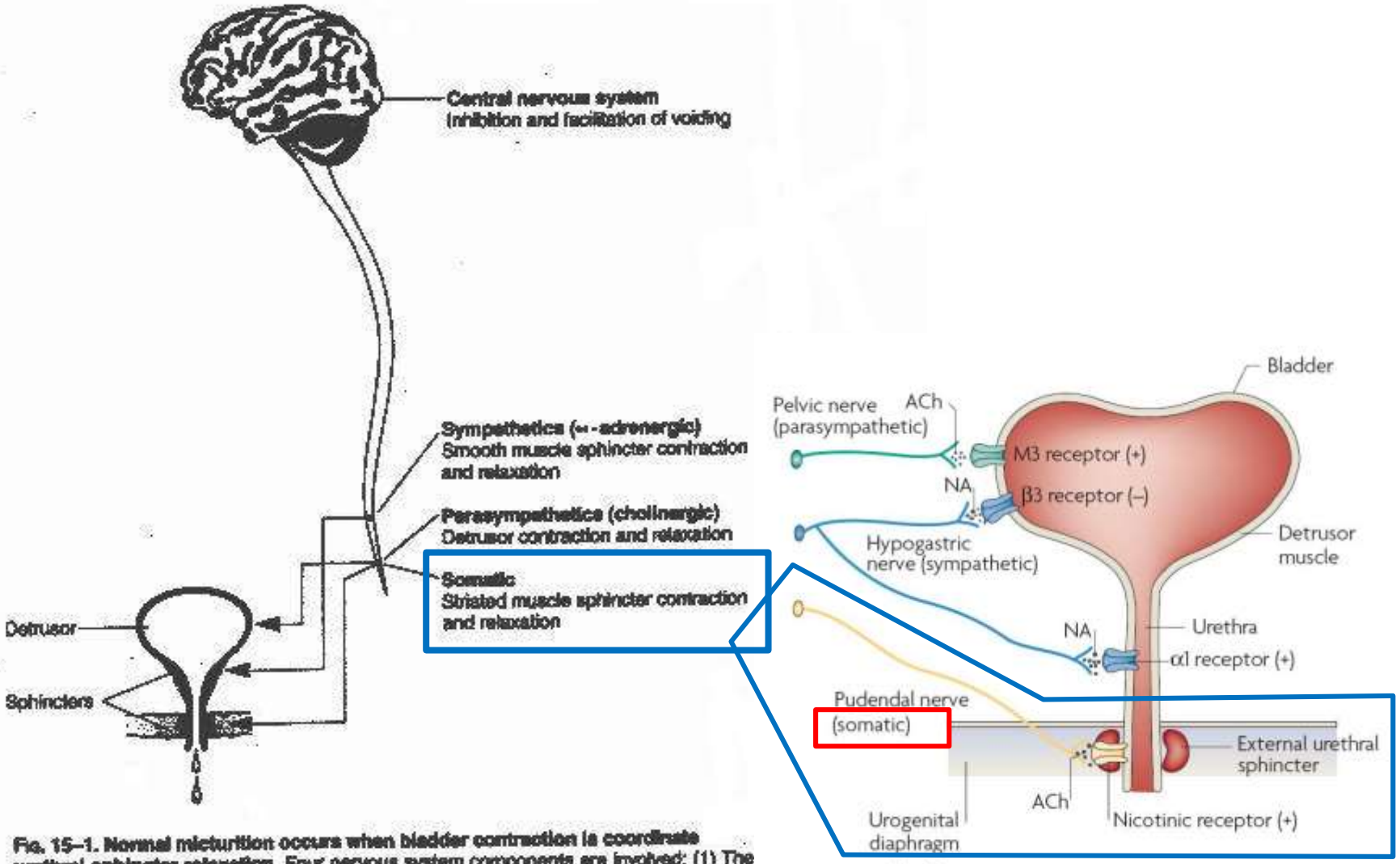


Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci. 2008 Jun;9(6):453-66



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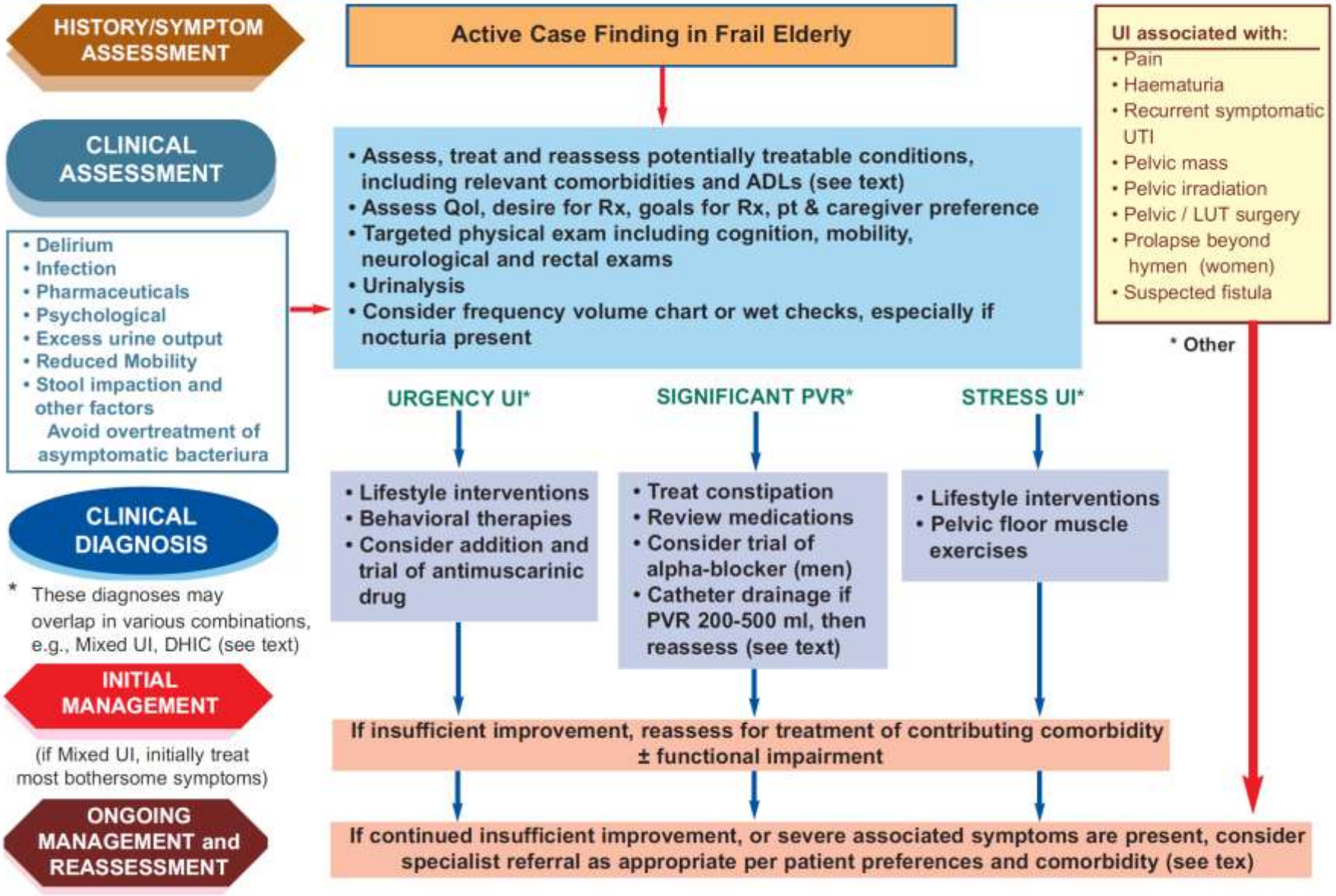
Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci. 2008 Jun;9(6):453-66

Management of urinary incontinence

depends on causes

Management of Urinary Incontinence in Frail Older Persons



4th International Consultation on Incontinence, 2008

CAUSE OF URINARY INCONTINENCE

Transient

Established

Cause of transient incontinence
DI(A)PPERS

Resnick NM 1984

- **D**elirium
- **I**nfection, urinary
- **(A**trophic urethritis/ vaginitis)
- **P**harmaceutical
- **P**sychological
- **E**xcessive urine output
  - Large fluid intake
  - Diuretic agents: caffeinated beverages, alcohol
  - Metabolic caused: sugar, calcium
- **R**estricted mobility
- **S**tool impaction

Iatrogenic Incontinence

Effects	Drug classes
Delirium, sedation	Anticholinergics, antipsychotics, TCA, Anti-parkinsonic drugs, Sedative/hypnotics, nacrotic analgesics, alcohol
Cough	ACEI
Polyuria	Diuretics, alcohol
Bladder stimulation	Caffeinated beverages
Bladder relaxation	Anticholinergics, calcium channel blocker
Sphincter contraction	Alpha-adrenergic agonist
Sphincter relaxation	Alpha-adrenergic blockers
Constipation	Anticholinergics, narcotic analgesics, calcium channel blockers etc

Antihypertensive Drug Class Use and Differential Risk of Urinary Incontinence in Community-Dwelling Older Women

Emily P. Peron,[1] Yan Zheng,[2] Subashan Perera,[2] Anne B. Newman,[2,3] Neil M. Resnick,[2] Ronald I. Shorr,[4] Douglas C. Bauer,[5] Eleanor M. Simonsick,[6,7] Shelly L. Gray,[8] Joseph T. Hanlon,[2,3,9,10] and Christine M. Ruby[2,10] for the Health, Aging, and Body Composition (Health ABC) Study

J Gerontol A Biol Sci Med Sci. 2012 December;67(12):1373–1378

Table 3. Logistic Regression of Urinary Incontinence and Antihypertensive Drug Class Use in Older Women (n = 959)

Medication Use at Year 3	UI (n = 197), n (%)	No UI (n = 762), n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*,†
Antihypertensive drug classes				
Beta blockers	27 (13.71)	131 (17.19)	0.77 (0.49–1.20)	0.72 (0.45–1.16)
Peripheral alpha blockers	11 (5.58)	11 (1.44)	4.04 (1.72–9.46)	4.47 (1.79–11.21)
Central alpha blockers‡	7 (3.55)	23 (3.02)	1.18 (0.50–2.80)	1.25 (0.50–3.11)
Loop diuretics	17 (8.63)	61 (8.01)	1.09 (0.62–1.90)	0.96 (0.51–1.81)
Thiazide diuretics	50 (25.38)	183 (24.02)	1.08 (0.75–1.55)	0.91 (0.57–1.45)
Potassium-sparing diuretics	24 (12.18)	70 (9.19)	1.37 (0.84–2.25)	1.48 (0.79–2.76)
Calcium channel blockers	44 (22.34)	196 (25.72)	0.83 (0.57–1.21)	0.76 (0.51–1.14)
ACE inhibitors	35 (17.77)	128 (16.80)	1.07 (0.71–1.62)	1.10 (0.70–1.71)
ARBs and vasodilators	12 (6.09)	51 (6.69)	0.90 (0.47–1.73)	0.88 (0.44–1.76)

Note. ACE = angiotensin-converting enzyme; ARBs = angiotensin-II receptor blockers; CI = confidence interval; OR = odds ratio; UI = urinary incontinence.

*Adjusted for site, race, age, education, anxiety, knee osteoarthritis, persistent lower extremity limitation, visual acuity, drinking status, smoking status, and estrogen use.

†Assumptions of the logistic regression model were met according to the Hosmer–Lemeshow goodness-of-fit test (x^2 = 3.21, df = 8, p = .92) (34,35).

‡Includes methyldopa, reserpine, clonidine, guanfacine, guanabenz, and guanethidine.

Post hoc analyses identified an even greater likelihood of UI with peripheral alpha blockers when taken in combination with loop diuretics (AR = 8.81; 95% CI = 1.78–43.53; p = .0076)

Drugs Use in Urinary Incontinence

Drugs for overactive detrusor

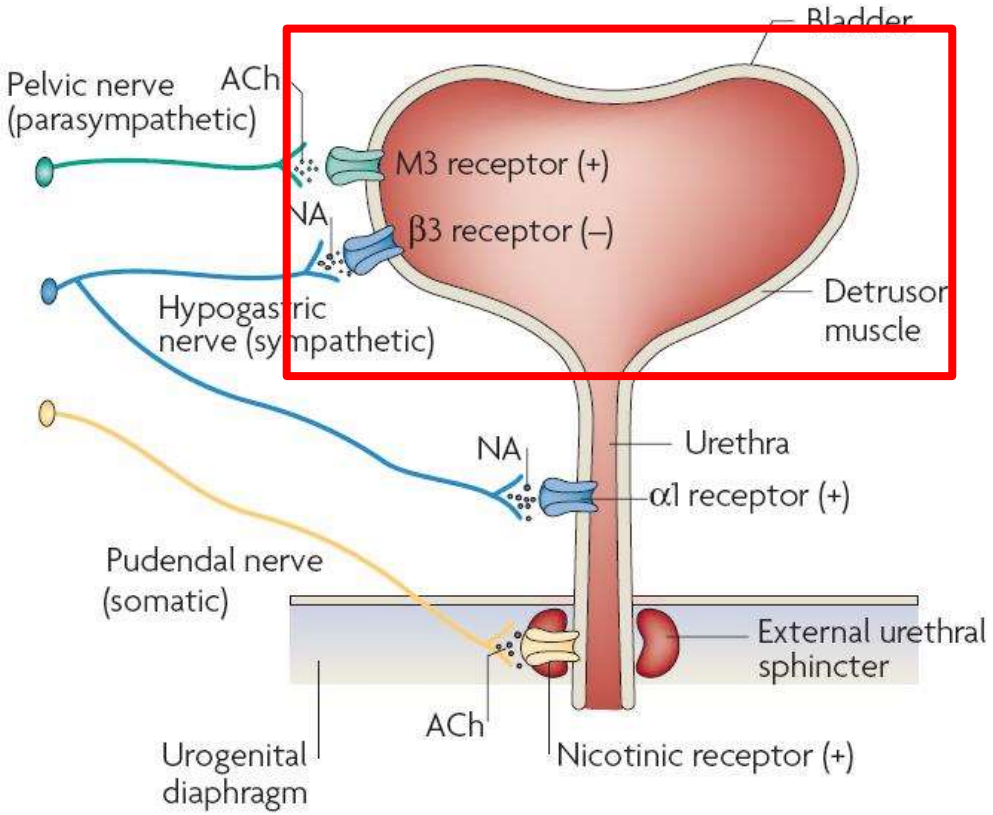


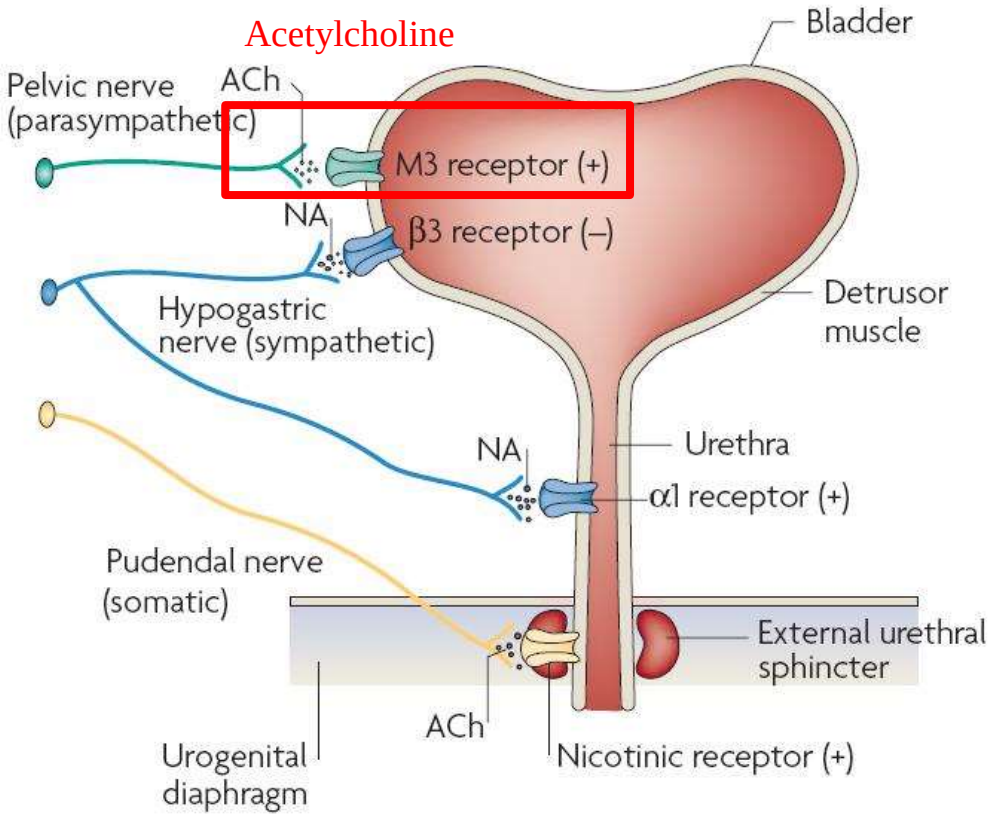
Table 2 Drugs used in the treatment of overactive bladder/ detrusor overactivity

	Level of evidence	Grade of recommendation
Antimuscarinic drugs		
Tolterodine	1	A
Trospium	1	A
Solifenacin	1	A
Darifenacin	1	A
Propantheline	2	B
Atropine, hyoscyamine	3	C
Drugs acting on membrane channels		
Calcium antagonists	2	D
K-Channel openers	2	D
Drugs with mixed actions		
Oxybutynin	1	A
Propiverine	1	A
Dicyclomine	3	C
Flavoxate	2	D
Antidepressants		
Imipramine	3	C
Duloxetine	2	C
α-Adrenoceptor antagonists		
Alfuzosin	3	C
Doxazosin	3	C
Prazosin	3	C
Terazosin	3	C
Tamsulosin	3	C
β-Adrenoceptor antagonists		
Terbutaline (β-2)	3	C
Salbutamol (β-2)	3	C
Mirabegron (β-3)	2	B
PDE-5 inhibitors[a]		
(sildenafil, taladafil, vardenafil)	2	B
COX inhibitors		
Indomethacin	2	C
Flurbiprofen	2	C
Toxins		
Botulinum toxin (neurogenic)[d]	2	A
Botulinum toxin (idiopathic)[d]	3	B
Capsaicin (neurogenic)[c]	2	C
Resiniferatoxin (neurogenic)[c]	2	C
Other drugs		
Baclofen[b]	3	C
Hormones		
Estrogen	2	C
Desmopressin[e]	1	A

Assessments according to the Oxford system (modified).
COX, cyclooxygenase; LUTS, lower urinary tract symptom; OAB, overactive bladder; PDE, phosphodiesterase.
[a] (male LUTS/OAB).
[b] Intrathecal.
[c] Intravesical.
[d] Bladder wall.
[e] Nocturia (nocturnal polyuria), caution hyponatremia, especially in the elderly.

Andersson KE,. Chapple CR,et al.
Pharmacological treatment of overactive bladder: report from the International Consultation on Incontinence
Current Opinion in Urology 2009, 19:380–394

Anticholinergic/ anti-muscarinic agents



- The use of anticholinergic drugs in the management of overactive bladder syndrome is well established when compared to placebo treatment.
- During initial treatment of overactive bladder syndrome there was more symptomatic improvement when

  (a) anticholinergics were compared with bladder training alone, and

  (b) anticholinergics combined with bladder training were compared with bladder training alone

Rai BP, Cody JD, Alhasso A, Stewart L.
Anticholinergic drugs versus non-drug active therapies for non-neurogenic overactive bladder syndrome in adults.
Cochrane Database Syst Rev. 2012 Dec 12;12:CD003193

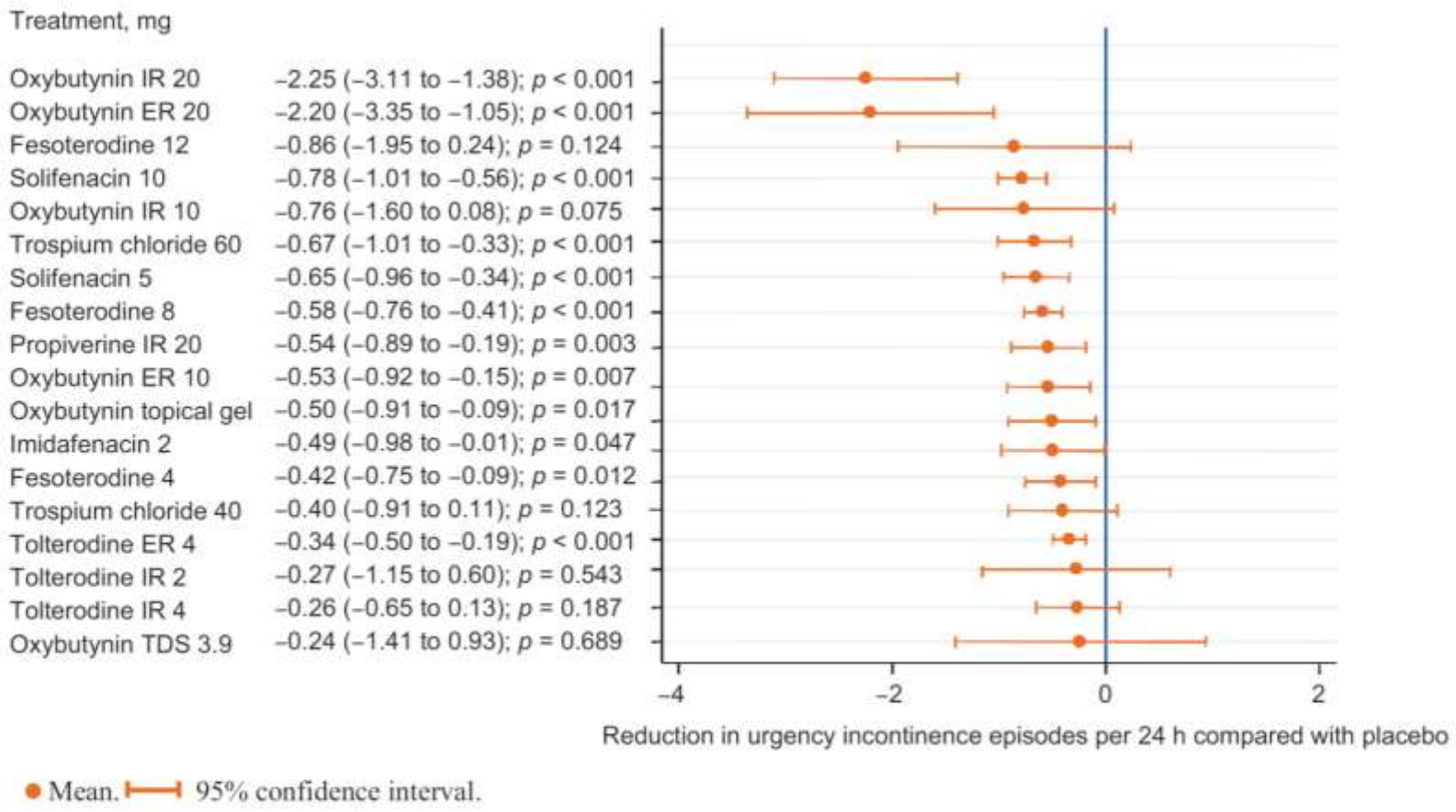


Fig. 5 – Reductions of urgency incontinence episodes per 24 h compared with placebo (red line), assessed in 17 251 patients. IR = immediate release; ER = extended release; TDS = transdermal system.

Buser N, Ivic S, Kessler TM, Kessels AG, Bachmann LM.
Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses.
Eur Urol. 2012 Dec;62(6):1040-60

Table 1. Categorization and grading of adverse events.

Type of adverse events	Grading using VAS
Gastrointestinal adverse events	
Dry mouth	4
Dry throat	4
Dysgeusia	4
Constipation	4
Diarrhoe	4
Abdominal pain	5
Gastritis	5
Dyspepsia	4
Nausea	5
Vomitus	6
Unspecified gastrointestinal adverse events	5
Ocular/visual adverse events	
Dry eye	4
Blurred vision	6
Urinary tract related adverse events	
Urinary retention	7
Voiding difficulty	5
Dysuria	5
Urinary tract infection	6
Unspecified urinary tract related adverse events	6
Neurological adverse events	
Fatigue	5
Somnolence	8
Sedation	7
Insomnia	6
Confusion	7
Cognitive impairment	7
Depression/lethargy	7
Dizziness/vertigo	5
Headache	5
Cardiac adverse events	
Palpitation/tachycardia	5
Hypertension	6
Orthostatic disturbance	6
Fall	8
Respiratory tract related adverse events	
Dry nose	3
Cough	4
Nasopharyngitis	4
Sinusitis	4
Upper respiratory tract infection	6
Influenza	6
Dermatological adverse events	
Dry skin	2
Erythema/exanthema	4
Pruritus	5

VAS: visual analogue scale (0 = minimum severity, 10 = maximum severity).
doi:10.1371/journal.pone.0016718.t001

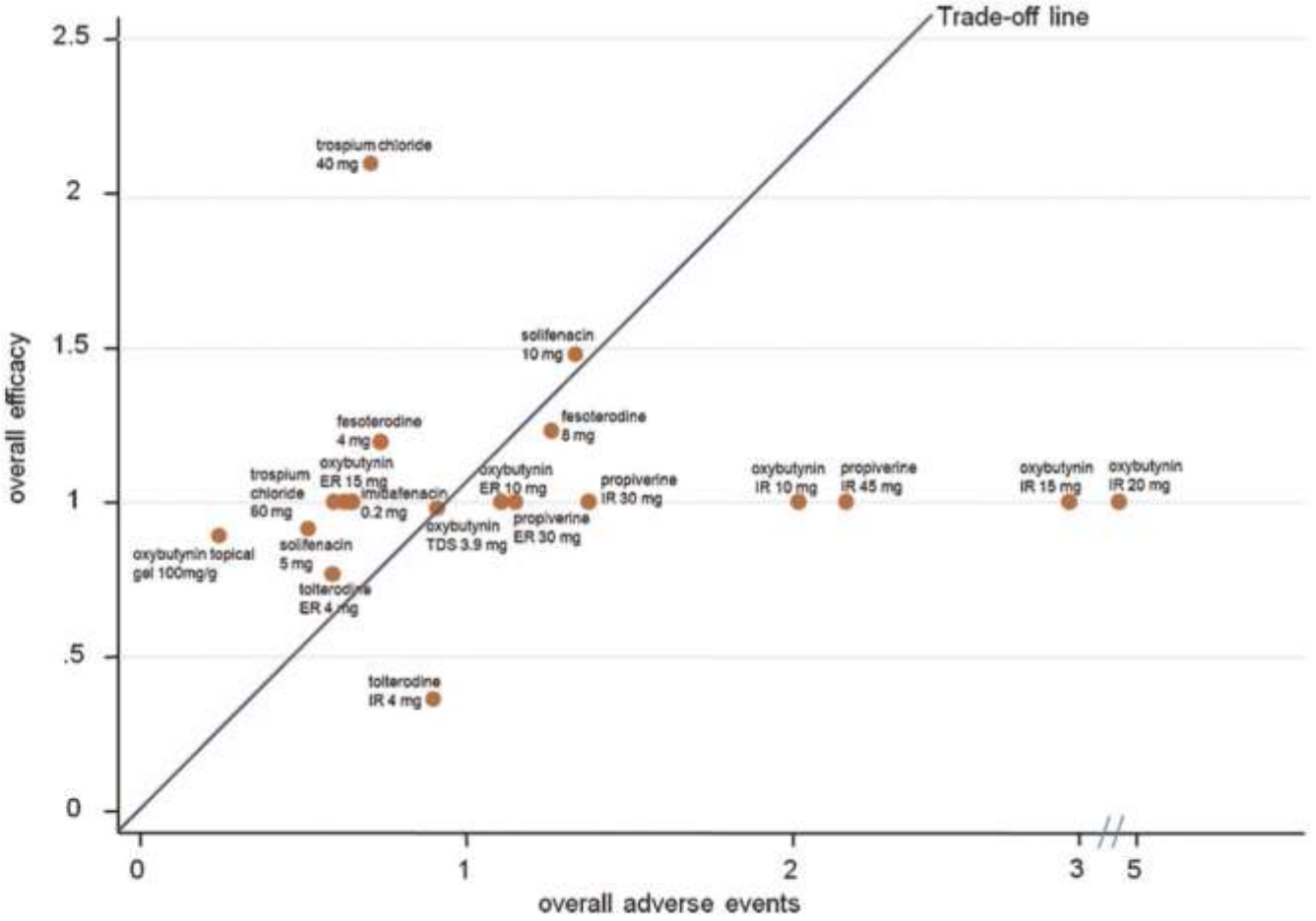
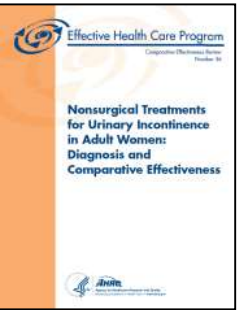


Fig. 10 – Trade-off between efficacy and adverse events of clinically relevant dosages of antimuscarinics. IR = immediate release; ER = extended release; TDS = transdermal system.

Buser N, Ivic S, Kessler TM, Kessels AG, Bachmann LM.
Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses.
Eur Urol. 2012 Dec;62(6):1040-60

- For urgency incontinence, antimuscarinic medications improved the clinical severity of incontinence relative to placebo
- Magnitude of treatment effects low: <200 cases of continence attributable to treatment per 1000 patients treated
- NNT to achieve complete continence in 1 individual did not vary markedly across drugs
  - 9 for oxybutynin, 12 for tolterodine, 8 for fesoterodine, 9 for solifenacin, and 9 for trospium
- Discontinuation of treatment because of adverse effects common
  - 1 woman for every 16 treated with oxybutynin, every 33 treated with fesoterodine, every 56 treated with trospium, and every 78 treated with solifenacin



Shamliyan T,Wyman J, Kane RL.
Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness.
Agency for Healthcare Research and Quality; April 2012.

Long-Term Adherence to Antimuscarinic Therapy in Everyday Practice: A Systematic Review

Paul W. Veenboer*,† and J. L. H. Ruud Bosch‡

From the Department of Urology, University Medical Centre Utrecht, Utrecht, The Netherlands

J Urol. 2014 Apr;191(4):1003-8

- Regardless of which specific antimuscarinic drug is studied, persistence rates are usually poor
- Considering all drugs together, median persistence rates were
  - 12.0 - 39.4% at 12 months
  - 8.0 - 15.0% at 18 months
  - 6.0 - 12.0% at 24 months
  - 0.0 (darifenacin) - 16.0% (trospium) at 36 months
- Mean reported medication possession rates were also low, with a mean of 0.37 at 12 months
- Risk factors for discontinuation: younger age group, use of oxybutynin and use of immediate release formulations

Int Urogynecol J (2013) 24:595–604
DOI 10.1007/s00192-012-1915-8

ORIGINAL ARTICLE

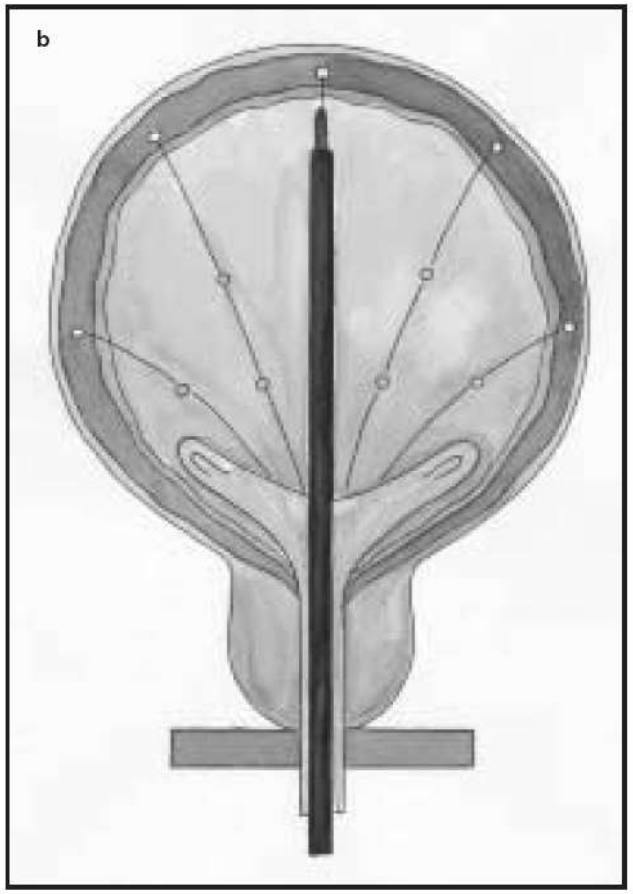
Oxybutynin: past, present, and future

Kelly Jirschele · Peter K. Sand

Table 1 Different oxybutynin formulations and common side effects

Medication	Half-life (h)	Adverse effects	
		Dry mouth	Constipation
Oxybutynin chloride IR (Ditropan®) [73]	2–3	71.4 %	15.1 %
Oxybutynin ER (Ditropan® XL) [40]	12–14	29.3 %	6.6 %
Oxybutynin transdermal (Oxytrol®) [52]	2	7 %	2.1 %
Oxybutynin chloride gel 10 % (Gelnique™) [28]	62–84	6.9 %	1.6 %
Oxybutynin vaginal ring [65]		4.9–10.6 %	
Oxybutynin rectal suppository [47]		48 %	

Intradetrusor injections of botulinum toxin



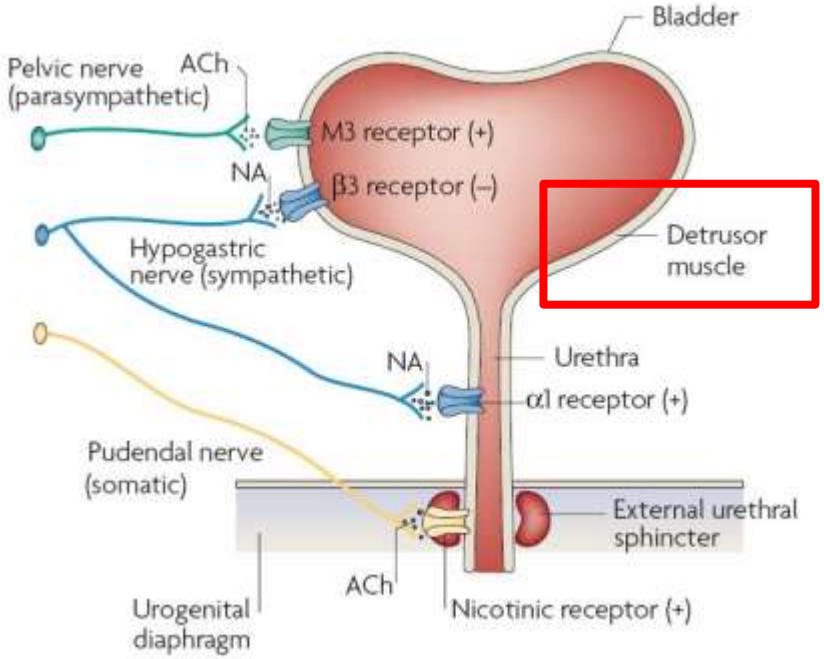


Fig. 1. (**a**) Flexible injection needle for detrusor muscle injection (Storz, Charr. 8, length: 50cm). (**b**) Mapping of the injection sites in the detrusor muscle.

Onabotulinumtoxin A in **Neurogenic Detrusor overactivity**

Table 1 Change from baseline in clinical and urodynamic data, at week 6

	Cruz *et al.*[1]			Ginsberg *et al.*[2]		
	Week 6, 275 patients			Week 6, 416 patients		
	Saline	200 U	300 U	Saline	200 U	300 U
Incontinence episodes (*n*)	−13.2	−21.8*	−19.4*	−8.8	−21*	−22.7*
Fully continent (% of patients)	7.60%	38.00%*	39.60%*	0.00%	36.00%*	41.00%*
MCC mean ± (SD)	6.5 ± 144.8	157.0 ± 164.8*	157.2 ± 185.2*	16.0 ± 127	151.0 ± 171*	168.0 ± 170*
PdetmaxIDC, cmH2O (mean ± SD)	6.4 ± 41.1	−28.5 ± 47.8*	−26.9 ± 33.2*	−2.4 ± (43.4)	−35.1 ± 35.7*	−33.3 ± 37.8*
Patients with no detrusor contraction (%)	17.40%	64.40%*	59.50%*	19.00%	64.00%*	69.0%*
I-QOL score	11.7	24.4*	24.3*	10.8	26.9*	32.9*

*$P < 0.05$. Reproduced from Cruz *et al.*[1] and Ginsberg *et al.*[2] with permission.

Santos-Silva A, da Silva CM, Cruz F.
Botulinum toxin treatment for bladder dysfunction.
Int J Urol. 2013 Oct;20(10):956-62

Table 2 Clinical and urodynamic data of the subpopulations (multiple sclerosis and spinal cord injury) in the Cruz *et al*. and Ginsberg *et al*. studies

Ginsberg *et al*.[2]

	MS			SCI		
	Saline	200 U	300 U	Saline	200 U	300 U
No. patients	81	77	69	68	58	63
Incontinence episodes (no. episodes)	−11.5	−20.4*	−23.8*	−5.7	−21.9*	−21.5*
MCC, mL (mean ± SD)	−7.5 ± 118	142 ± 179*	162 ± 171*	45 ± 134	163 ± 160*	175 ± 169*
MDP at 1st IDC, cmH2O (mean ± SD)	12.1 ± 42.3	−28.4 ± 31.9*	−29.0 ± 33.2*	−19.6 ± 38.5	−41.0 ± 38.4*	−36.3 ± 41.4*

Cruz *et al*.[1]

	MS			SCI		
	Saline	200 U	300 U	Saline	200 U	300 U
No. patients	50	53	51	42	39	40
Incontinence episodes (number of episodes)	−18.1	−25.9*	−24.4*	−7.5	−16.1*	−12.9*
MCC, mL (mean ± SD)	28.4 ± 121.6	159.2 ± 156.9*	168.7 ± 179*	−21.9 ± 167.8	153.8 ± 177.7*	140.6 ± 195.3*
MDP at 1st IDC, cmH2O (mean ± SD)	8.8 ± 43.0	−14.6 ± 36.0*	−20.2 ± 22.9*	3.2 ± 40.3	−45.6 ± 56.0*	−34.1 ± 41.1*

*$P < 0.05$. Reproduced from Cruz *et al*.[1] and Ginsberg *et al*.[2] with permission.

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Botulinum toxin treatment for bladder dysfunction.
Int J Urol. 2013 Oct;20(10):956-62

Table 5 – Adverse events overall and with incidence ≥5% during the first 12 wk of treatment cycle 1 and across the full treatment cycle 1 (safety population)

	Placebo (n = 90)	OnabotA 200 U (n = 91)	OnabotA 300 U (n = 89)
During the first 12 wk, n (%)*			
All AEs	50 (55.6)	63 (69.2)	68 (76.4)
AEs with incidence ≥5%			
UTI	20 (22.2)	25 (27.5)	34 (38.2)
Urinary retention	3 (3.3)	18 (19.8)†	28 (31.5)†
Haematuria	3 (3.3)	5 (5.5)	7 (7.9)
Dysuria	2 (2.2)	2 (2.2)	5 (5.6)
Constipation	2 (2.2)	1 (1.1)	5 (5.6)
Treatment cycle 1 overall			
Median duration of treatment cycle, wk	25.4	49.9	51.4
All AEs, n (%)	67 (74.4)	79 (86.8)	79 (88.8)
AEs with incidence ≥5%, n (%)			
UTI	36 (40.0)	51 (56.0)†	57 (64.0)†
Urinary retention	3 (3.3)	18 (19.8)†	28 (31.5)†
Haematuria	4 (4.4)	5 (5.5)	9 (10.1)
Fatigue	1 (1.1)	8 (8.8)†	3 (3.4)
Dysuria	2 (2.2)	5 (5.5)	7 (7.9)
Nasopharyngitis	3 (3.3)	6 (6.6)	6 (6.7)
Constipation	2 (2.2)	5 (5.5)	6 (6.7)
Diarrhoea	6 (6.7)	3 (3.3)	6 (6.7)
Muscle spasms	1 (1.1)	4 (4.4)	6 (6.7)
Muscular weakness	1 (1.1)	6 (6.6)	4 (4.5)
Pyrexia	3 (3.3)	6 (6.6)	1 (1.1)
Arthralgia	5 (5.6)	3 (3.3)	1 (1.1)
Influenza	0 (0.0)	5 (5.5)†	1 (1.1)
Urinary incontinence	2 (2.2)	5 (5.5)	1 (1.1)
Pain in extremity	3 (3.3)	5 (5.5)	2 (2.2)

	MS Patients			SCI Patients		
	Placebo (n = 50)	OnabotA 200 U (n = 53)	OnabotA 300 U (n = 50)	Placebo (n = 40)	OnabotA 200 U (n = 38)	OnabotA 300 U (n = 39)
UTI and urinary retention AEs by aetiology, n (%)						
UTI	16 (32.0)	31 (58.5)†	35 (70.0)†	20 (50.0)	20 (52.6)	22 (56.4)
Urinary retention	2 (4.0)	16 (30.2)†	27 (54.0)†	1 (2.5)	2 (5.3)	1 (2.6)

AE = adverse event; MS = multiple sclerosis; OnabotA = onabotulinumtoxinA; SCI = spinal cord injury; UTI = urinary tract infection.

* Placebo-controlled phase.

† $p < 0.05$ compared with placebo; chi-square test, or Fisher exact test,.

Cruz F, Herschorn S, Aliotta P, et al.
Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial.
Eur Urol. 2011 Oct;60(4):742-50

Table 6 – Postvoid residual and initiation of clean intermittent catheterisation in patients not using CIC before treatment (safety population)

	Placebo (n = 41)	OnabotA 200 U (n = 44)	OnabotA 300 U (n = 45)
PVR, ml			
Baseline, mean (SD)	57.1 (50.8)	79.3 (50.0)	64.3 (50.7)
Change from baseline at week 2, mean (SD)	−2.2 (58.8)	88.1 (185.2)*	183.8 (204.2)*
PVR ≥200 ml at week 2, % of patients	2.7	28.6	53.7
Initiation of CIC, % of patients[a]	12.2	29.5	42.2

CIC = clean intermittent catheterisation; OnabotA = onabotulinumtoxinA; PVR = postvoid residual; SD = standard deviation.

[a] Across treatment cycle 1.

* $p < 0.001$ among group comparison.

Cruz F, Herschorn S, Aliotta P, et al.
Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial.
Eur Urol. 2011 Oct;60(4):742-50

Onabotulinumtoxin A in **Idiopathic Detrusor overactivity**

TABLE I. Study and Patient Characteristics

Study	Therapy in experimental group	Therapy in control group	Country	Sample size		Administration method	Duration of treatment	Dosage	Inclusion population
				Experimental	Control				
Chapple et al.[20]	OnabotulinumtoxinA	Placebo	Europe and US	277	271	Intravesical injections (sparing the trigone)	12 weeks	100 U	Idiopathic OAB with UI, ≥3 UUI episodes in a 3-day bladder diary, ≥8 micturitions/day, and PVR ≤100 ml, inadequately managed by anticholinergic therapy
Nitti et al.[21]	OnabotulinumtoxinA	Placebo	US and Canada	280	277	Intravesical injections (sparing the trigone)	12 weeks	100 U	Idiopathic OAB with ≥3 UUI episodes in a 3-day bladder diary, ≥8 micturitions/day, and PVR ≤100 ml, inadequately managed by anticholinergic therapy
Fowler et al.[22]	OnabotulinumtoxinA	Placebo	US, Canada, and Europe	53	44	Intravesical injections (sparing the trigone)	12 weeks	200 U	Idiopathic OAB with ≥6 UUI episodes in a 7-day bladder diary, ≥8 micturitions/day, and PVR ≤200 ml, inadequately managed by anticholinergic therapy
Denys et al.[23]	OnabotulinumtoxinA	Placebo	France	30	31	Intravesical injections (sparing the trigone)	12 weeks	150 U	Idiopathic OAB with UI, ≥3 UUI episodes in a 3-day bladder diary, ≥8 micturitions/day, and PVR ≤150 ml, inadequately managed by anticholinergic therapy
Dowson et al.[24]	OnabotulinumtoxinA	Placebo	UK	10	13	Intravesical injections (sparing the trigone)	12 weeks	100 U	Idiopathic OAB inadequately managed by anticholinergic therapy
Rovner et al.[25]	OnabotulinumtoxinA	Placebo	US, Canada, and Europe	53	44	Intravesical injections (sparing the trigone)	12 weeks	200 U	Idiopathic OAB with ≥6 UUI episodes in a 7-day bladder diary, ≥8 icturitions/day, and PVR ≤200 ml, inadequately managed by anticholinergic therapy
Dmochowski et al.[26]	OnabotulinumtoxinA	Placebo	US, Canada, and Europe	53	44	Intravesical injections (sparing the trigone)	12 weeks	200 U	Idiopathic OAB with ≥6 UUI episodes in a 7-day bladder diary, ≥8 micturitions/day, and PVR ≤200 ml, inadequately managed by anticholinergic therapy
Sahai (2006)	OnabotulinumtoxinA	Placebo	UK	16	18	Intravesical injections (sparing the trigone)	12 weeks	200 U	Idiopathic OAB inadequately managed by anticholinergic therapy

OAB, overactive bladder; UI, urinary incontinence; UUI, urinary urgency incontinence; PVR, post-void residual urine volume.

Cui Y, Zhou X, Zong H, Yan H, Zhang Y.
The efficacy and safety of onabotulinumtoxinA in treating idiopathic OAB: A systematic review and meta-analysis. Neurourol Urodyn. 2014 Mar 28. [Epub ahead of print]

Table 1 – Overview of demographics, outcome, and side effects of the two pivotal placebo-controlled trials for idiopathic overactive bladder

	Nitti et al. [3]		Chapple et al. [4]	
	Placebo	BoNT-ONA 100 U	Placebo	BoNT-ONA 100 U
Demographics				
Probands	277	280	271	277
Age, yr	61.0	61.7	59.2	59.5
Female gender, %	88.4	90	84.5	88.1
Duration of OAB, yr	6.6	6.8	5.7	5.2
Daily urge UI episodes	4.5	4.8	5.7	5.5
Daily urgency episodes	7.9	8.5	8.8	9.1
Daily micturition episodes	11.2	12.0	11.8	12.0
Nocturia episodes	2.0	2.2	2.1	2.2
Outcome*				
Reduction in daily micturition episodes	−0.91	−2.15	−0.83	−2.56
Reduction in daily UI episodes	−0.87	−2.65	−1.03	−2.95
Reduction in daily urgency episodes	−1.21	−2.93	−1.24	−3.67
Reduction in daily nocturia episodes	−0.24	−0.45	−0.25	0.054
Side effects*				
UTI, %	5.9	15.5	5.2	20.4
Urinary retention, %	0.4	5.4	0.4	5.8

BoNT-ONA = onabotulinumtoxinA; OAB = overactive bladder; UTI = urinary tract infection.
* As reported at week 12.

Madersbacher S.
Onabotulinumtoxin A for idiopathic overactive bladder symptoms: many answers but more questions.
Eur Urol. 2013 Aug;64(2):257-9

Novel drug:
Selective Beta-3 adrenoceptor agonist

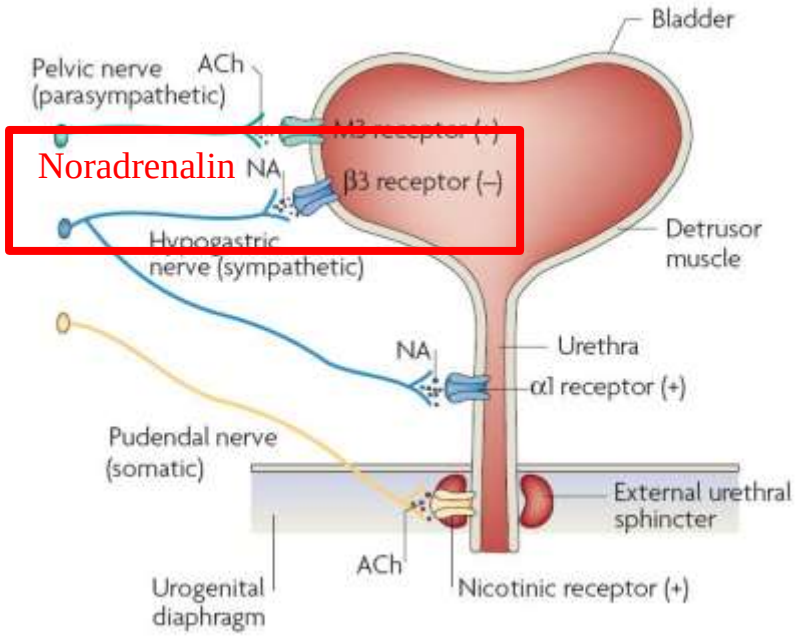
- Mirabegron

Table 2. Summary of Mirabegron Clinical Trials

Reference	Design	Intervention	Primary and Secondary End Points: Mean Incontinence Episodes/ 24 hours, mean	Mean Micturition Episodes/ 24 hours, mean	Mean Volume Voided, mL	Other Secondary End Points
Chapple (2013)[28]	N = 260 Phase 2a, proof of concept 4 weeks R, DB, PC, AC, MC, parallel group		Secondary	Primary	Secondary	Urge incontinence episodes/ 24 hours, mean
		Mirabegron 100 mg twice daily	−2.17*	−2.19*	+26.0	−2.06*
		Mirabegron 150 mg twice daily	−1.56	−2.21*	+32.7*	−1.44
		Tolterodine ER 4 mg/day	−1.65	−1.49	+23.8	−1.53
		Placebo	−1.01		+10.5	−1.09
Chapple (2010)[21]	N = 1108 Phase 2b dose range 4 weeks R, DB, PC, AC, MC, parallel group		Secondary	Primary	Secondary	Urge incontinence episodes/ 24 hours
		Mirabegron 25 mg/day	−1.4*	−1.9	+15.3	1.3*
		Mirabegron 50 mg/day	−1.2*	−2.1*	+27.3*	1.1*
		Mirabegron 100 mg/day	−1.1	−2.1*	+25.8*	1.2*
		Mirabegron 200 mg/day	−1.1	−2.2*	+33.3*	1.2*
		Placebo	−0.4	−1.4	+7.3	0.5
Khullar (European-Australian) (2013)[22-24]	N = 1978 Phase 3 12 weeks R, DB, PC, AC, MC, parallel group		Primary	Primary	Secondary	Mean incontinence episodes and micturitions/24 hours at week 4
		Mirabegron 50 mg/day	−1.57*	−1.93*	+24.1*	−1.04* / −1.16*
		Mirabegron 100 mg/day	−1.46*	−1.77*	+25.5*	−1.03* / −1.29*
		Tolterodine SR 4 mg/day	−1.27	−1.58	+25.0*	−1.00* / −1.10*
		Placebo	−1.17	−1.34	+12.4	−0.65 / −0.77
Nitti (North-American) (2013)[25-27]	N = 1329 randomized Phase 3 12 weeks R, DB, PC, MC, parallel group		Primary	Primary	Secondary	Mean incontinence episodes and micturitions/24 hours at week 4
		Mirabegron 50 mg daily	−1.47*	−1.66*	+18.22*	−1.20* /−1.19*
		Mirabegron 100 mg daily	−1.63*	−1.75*	+18.0*	−1.18* /−1.37*
		Placebo	−1.13	−1.05	+7.0	−0.72 /−0.77

AC = active control; DB = double-blind; ER = extended-release; MC = multicenter; PC = placebo-controlled; R = randomized; SR = slow-release.
*Significant at $p < 0.05$ vs placebo.

Bridgeman MB, Friia NJ, Taft C, Shah M.
Mirabegron: β3-adrenergic receptor agonist for the treatment of overactive bladder.
Ann Pharmacother. 2013 Jul-Aug;47(7-8):1029-38



ORIGINAL PAPER

Mirabegron for the treatment of overactive bladder: a prespecified pooled efficacy analysis and pooled safety analysis of three randomised, double-blind, placebo-controlled, phase III studies

V. W. Nitti,[1] V. Khullar,[2] P. van Kerrebroeck,[3] S. Herschorn,[4] J. Cambronero,[5] J. C. Angulo,[6] M. B. Blauwet,[7] C. Dorrepaal,[8] E. Siddiqui,[9,10] N. E. Martin[11]

Int J Clin Pract, July 2013, 67, 7, 619–632.

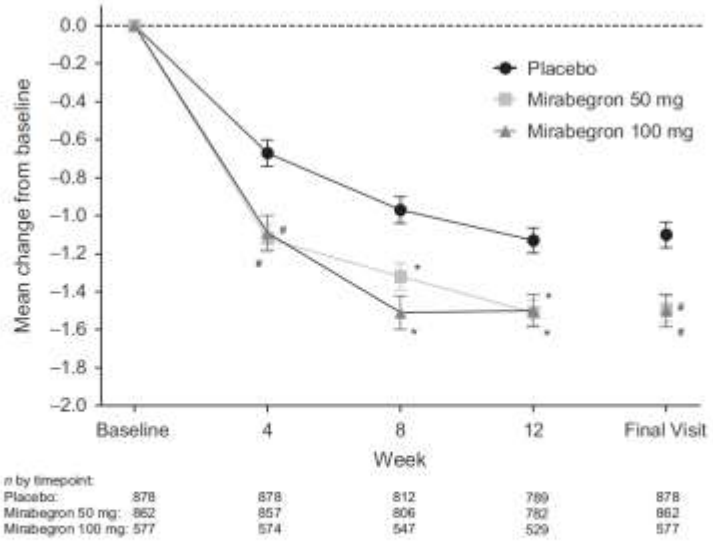


Figure 3 Adjusted mean change from baseline (±SE) by time point in the mean number of incontinence episodes/24 h for the pooled placebo, mirabegron 50 and 100 mg groups (FAS-I). #Statistically significant treatment benefit relative to placebo ($p < 0.05$) with multiplicity adjustment. *Statistically significant treatment benefit relative to placebo ($p < 0.05$) without multiplicity adjustment. SE, standard error; FAS-I, full analysis set-incontinence.

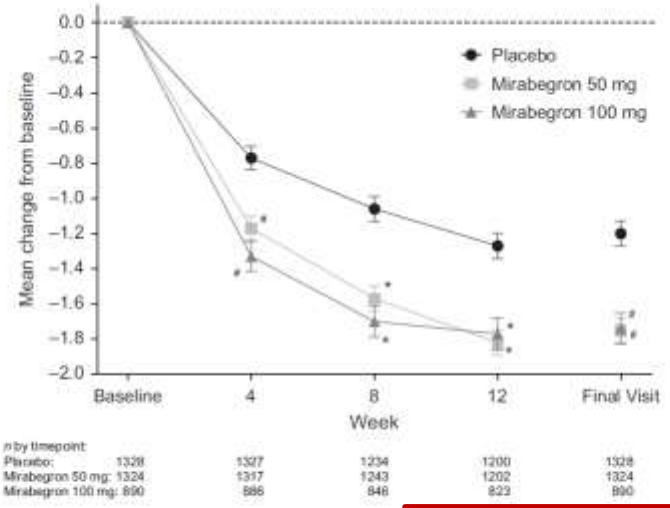


Figure 4 Adjusted mean change from baseline (±SE) by time point in mean number of micturitions/24 h for the pooled placebo, mirabegron 50 and 100 mg groups (FAS). #Statistically significant treatment benefit relative to placebo ($p < 0.05$) with multiplicity adjustment. *Statistically significant treatment benefit relative to placebo ($p < 0.05$) without multiplicity adjustment. SE, standard error; FAS, full analysis set.

Table 3 Overview of treatment-emergent adverse events in the pooled safety analysis (SAF)

Number of patients (%)	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Mirabegron Total (n = 2736)	Tolterodine ER 4 mg (n = 495)
Any TEAE	658 (47.7)	210 (48.6)	647 (47.1)	402 (43.3)	1259 (46.0)	231 (46.7)
Drug-related TEAE	232 (16.8)	87 (20.1)	256 (18.6)	172 (18.5)	515 (18.8)	131 (26.5)
TEAE leading to discontinuation	46 (3.3)	17 (3.9)	53 (3.9)	34 (3.7)	104 (3.8)	22 (4.4)
Drug-related TEAE leading to discontinuation	27 (2.0)	11 (2.5)	35 (2.5)	25 (2.7)	71 (2.6)	20 (4.0)
SAE	29 (2.1)	7 (1.6)	29 (2.1)	26 (2.8)	62 (2.3)	11 (2.2)
Drug-related SAE	6 (0.4)	3 (0.7)	7 (0.5)	3 (0.3)	13 (0.5)	6 (1.2)
Common TEAEs by preferred term (reported by $\geq$ 3% in total mirabegron group)						
Hypertension	105 (7.6)	49 (11.3)	103 (7.5)	48 (5.2)	200 (7.3)	40 (8.1)
Nasopharyngitis	35 (2.5)	15 (3.5)	54 (3.9)	25 (2.7)	94 (3.4)	14 (2.8)
Urinary tract infection	25 (1.8)	18 (4.2)	40 (2.9)	25 (2.7)	83 (3.0)	10 (2.0)
Antimuscarinic AEs of interest by preferred term (reported by $\geq$ 2% in any group)						
Headache	43 (3.1)	10 (2.3)	47 (3.4)	23 (2.5)	80 (2.9)	18 (3.6)
Dry mouth	29 (2.1)	8 (1.9)	23 (1.7)	23 (2.5)	54 (2.0)	50 (10.1)
Constipation	20 (1.4)	7 (1.6)	22 (1.6)	15 (1.6)	44 (1.6)	10 (2.0)
Drug-related* TEAEs by preferred term (reported by $\geq$ 2% in any group)						
Hypertension	63 (4.6)	30 (6.9)	65 (4.7)	32 (3.4)	127 (4.6)	30 (6.1)
Headache	18 (1.3)	4 (0.9)	28 (2.0)	12 (1.3)	44 (1.6)	11 (2.2)
Dry mouth	22 (1.6)	7 (1.6)	13 (0.9)	20 (2.2)	40 (1.5)	47 (9.5)

SAF, safety analysis set; ER, extended release; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

*Possible or probable, as assessed by the investigator, or records where relationship was missing.

EUROPEAN UROLOGY 62 (2012) 834–840

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journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Voiding Dysfunction

Editorial by Christopher R. Chapple on pp. 841–842 of this issue

A Multicenter, Double-blind, Randomized, Placebo-controlled Trial of the β3-Adrenoceptor Agonist Solabegron for Overactive Bladder

Eliot H. Ohlstein [a,*], *Alexander von Keitz* [b], *Martin C. Michel* [c]

[a] *AltheRx Pharmaceuticals, Malvern, PA, USA;* [b] *Urology Practice, Marburg Germany;* [c] *Department of Pharmacology, Johannes Gutenberg University, Mainz, Germany*

Phase II trial

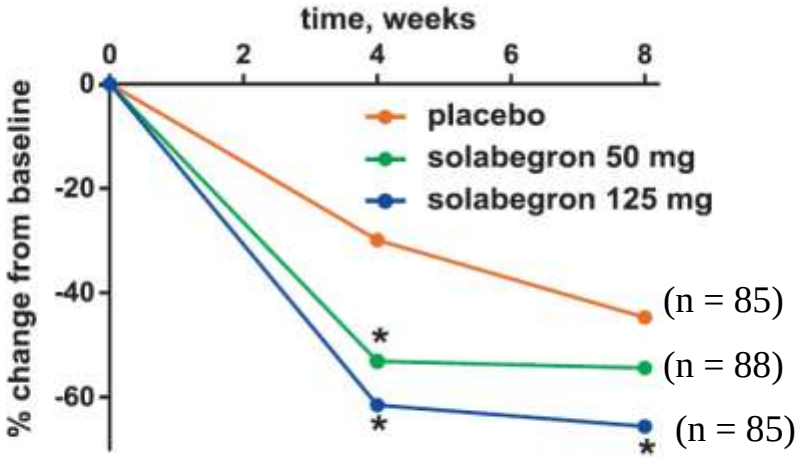
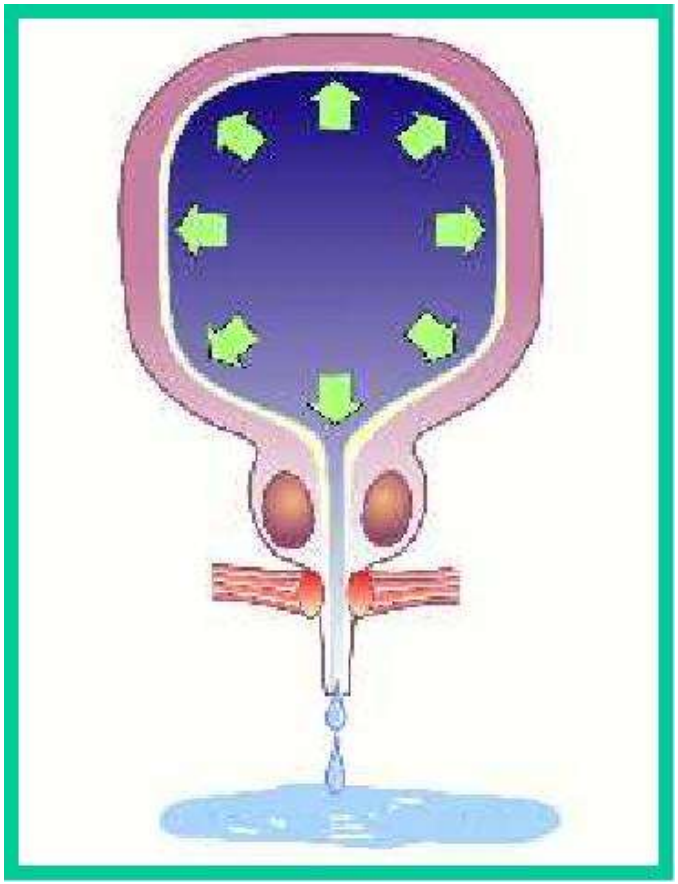
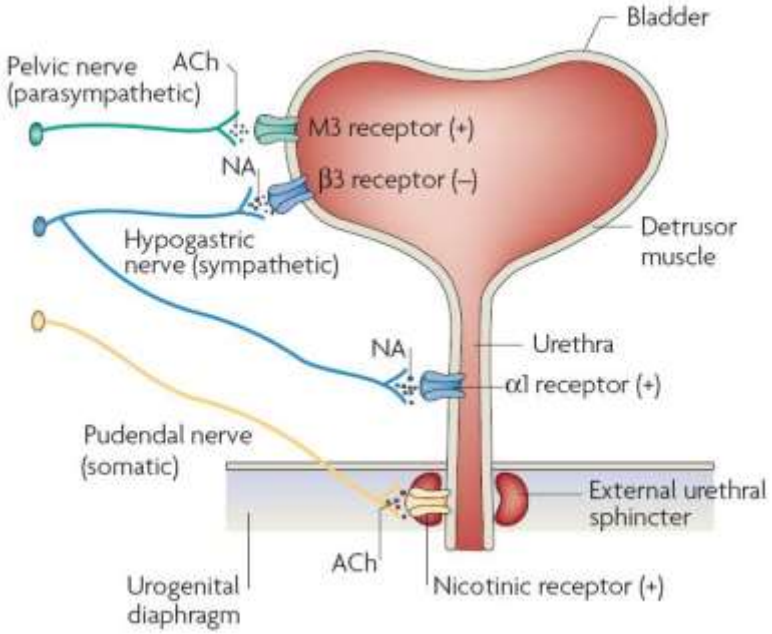


Fig. 3 – Adjusted mean percentage change from baseline at 4 wk and 8 wk of treatment (secondary and primary end points, respectively) in incontinence episodes per 24 h in the intention-to-treat population. Actual baseline values are shown in Table 2.
* $p < 0.05$ vs placebo.

Drugs for outflow obstruction

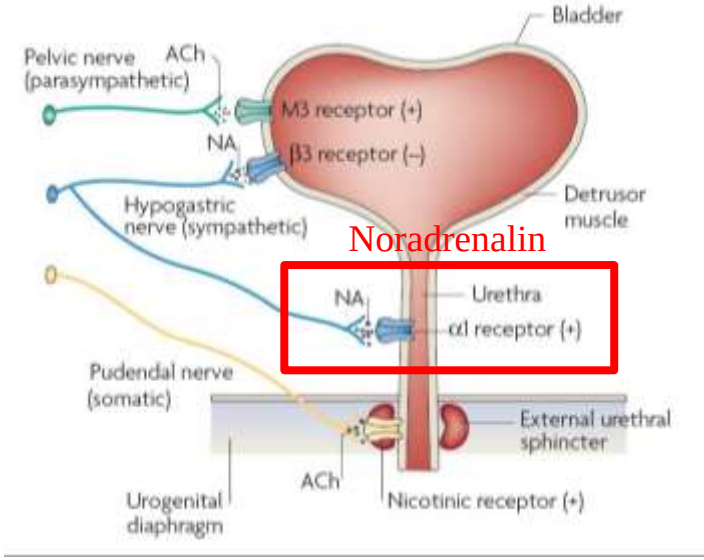




Drugs for outflow obstruction

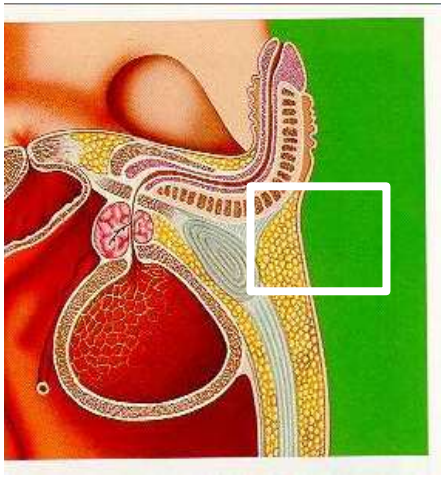
Alpha adrenergic blocker

- Prazocin (Minipress)
- Terazocin (Hytrin)
- Doxazocin (Cardura)
- Alfuzosin (Xatral RS/XL)
- Tamsulosin (Harnal)



5-alpha reductase inhibitor

- Finasteride (Proscar)
- Dutasteride (Avodart)



Drugs for BPH

- Alpha blocker has a more immediate action
- Alfuzosin and Tamsulosin are better tolerated, Tamsulosin has least effect on BP Eur Urol 1999;36:1-13
- Prostate volume predicts outcome of treatment with Finasteride- 40 ml Urology 1996;48: 398-405 Dutasteride is effective for prostate size >30 ml J Urol 2006; 176:1045-50
- Combination therapy NEJM 2003, 349;2387-98
  - reduced the risk of overall clinical progression
  - Combination therapy and finasteride monotherapy reduced the long-term risk of acute urinary retention and the need for invasive therapy
  - greater improvement in the AUA symptom score and the maximal urinary flow rate than did either drug alone.

Table 3. The incidence of postural hypotension during long-term therapy of hypertension

Drug	Incidence of postural hypotension, %	Reference
α_1-Blockers	0–22.4	Svetky et al., 1988; Langdon & Packard, 1994; Maslowski, 1991; Nomura et al., 1996; Itskovitz, 1994 [28–30, 32, 34]
β-Blockers	7.8–9.0	Svetky et al., 1988; Räihä et al., 1995 [8, 32]
Diuretics	4.6–60	Heseltine & Bramble, 1988; Myers et al., 1978; Räihä et al., 1995 [6, 8, 26]
Other hypertensives (drugs not specified)	7.9	Räihä et al., 1995 [8]
ACE inhibitor (lisinopril)	0.25[a]	Fallowfield et al., 1993 [33]

[a] Data show number of patients withdrawn from therapy with postural hypotension.

Meredith PA
Cardiology 2001; 96(Suppl 1):19-24

J. C. Nickel, S. Sander, T. D. Moon
Int J Clin Pract, October 2008, 62, 10, 1547–1559

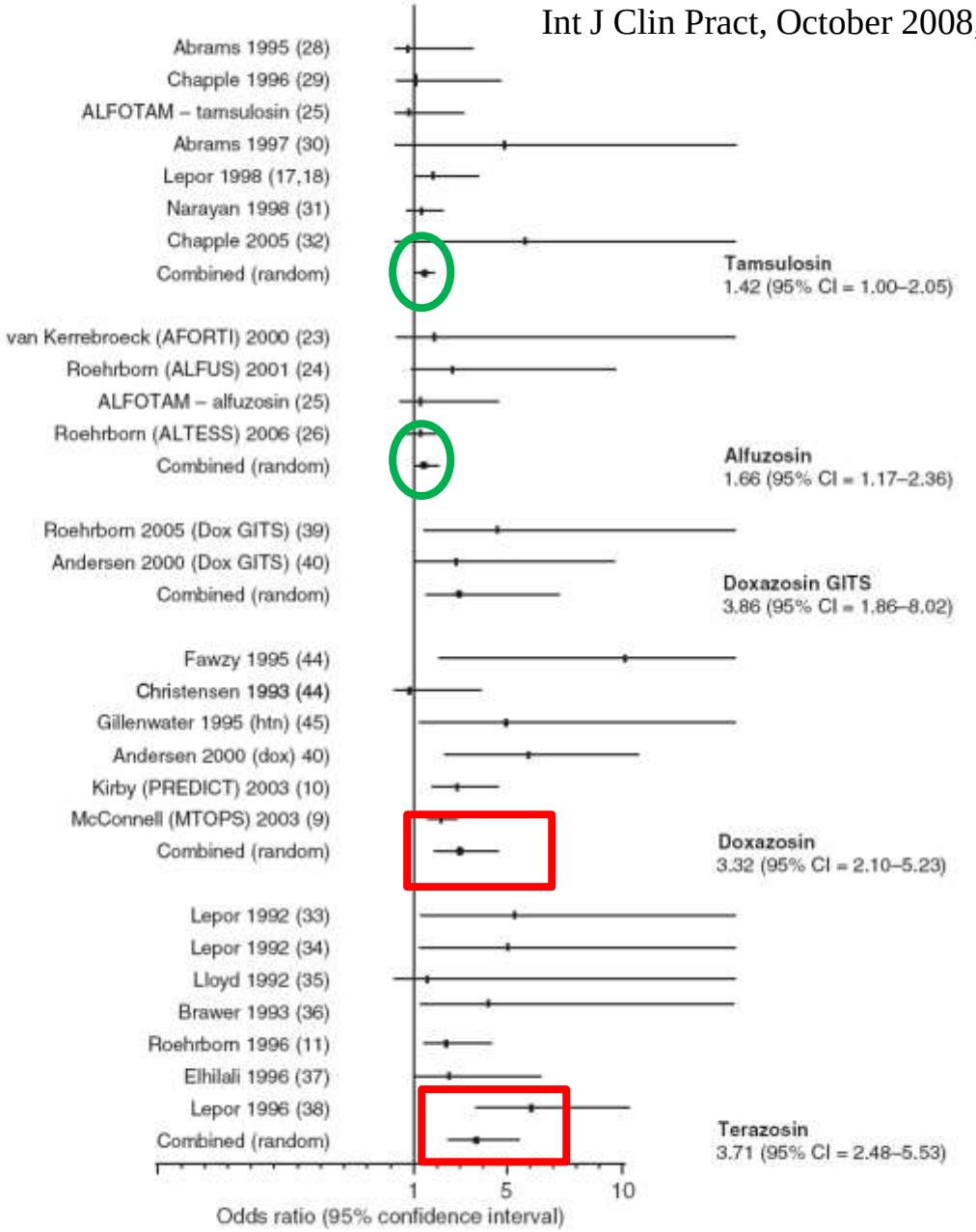


Figure 4 Odds of developing a vascular-related adverse event while on specific α1-adrenergic receptor blockers. Sizes of the data markers are indicative of the relative weight of each study. The bar is representative of the 95% confidence interval

dizziness, hypotension or syncope

Intraoperative Floppy Iris syndrome

- Pooled OR after Tamsulosin use ~40 fold greater than that after Alfuzosin use. Alfuzosin>Terazosin>Doxazosin Opthalmology 2011; 118:730-735
- Iris fluttering, iris prolapse towards incision and progressive pupillary constriction leading to high rate of complication during cataract surgery Acta Opthal 2009; 87:704-8

Combination treatment with Alpha-blocker plus Anti-cholinergic

EUROPEAN UROLOGY 60 (2011) 94–105

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European Association of Urology

Collaborative Review – Bladder Outlet Obstruction

The Role of Antimuscarinics in the Management of Men With Symptoms of Overactive Bladder Associated With Concomitant Bladder Outlet Obstruction: An Update

Anastasios Athanasopoulos[a,], Christopher Chapple[b], Clare Fowler[c], Christian Gratzke[d], Steven Kaplan[e], Christian Stief[d], Andrea Tubaro[f]*

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[b] Department of Urology, Royal Hallamshire Hospital, Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, UK
[c] Institute of Neurology, University College London, National Hospital for Neurology and Neurosurgery, University College London Hospital, London, UK
[d] Department of Urology, Ludwig-Maximilians-University Munich, Munich, Germany
[e] Department of Urology, Weill Cornell Medical College, Cornell University, New York, NY, USA
[f] Department of Urology, Sant'Andrea Hospital 2nd School of Medicine, "La Sapienza" University of Rome, Rome, Italy

- The sequential use of a-blockers and antimuscarinics seems to be the most appropriate approach
- use of antimuscarinics and a-blockers appears generally to be safe and efficacious
- Efficacy of antimuscarinics has been proven in different trials regarding different storage symptom end points, but not all end points regarding OAB reached significance.
- All the reported trials are of short duration (4–12 wk) and include only men with low postvoid residual urine volumes (<200 ml) at baseline .

Silodosin: a new subtype selective alpha-1 antagonist for the treatment of lower urinary tract symptoms in patients with benign prostatic hyperplasia

Nadir I Osman, Christopher R Chapple†, Francisco Cruz, François Desgrandchamps, Carlos Llorente & Francesco Montorsi
†*Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Department of Urology, Sheffield, UK*

Expert Opin. Pharmacother. (2012) 13(14):2085-2096

Table 1. Comparison in experimental selectivity parameters.

	Silodosin	Tamsulosin
Receptor selectivity [16] (for the α_{1A} receptor over α_{1B})	162-fold	9.55-fold
Tissue selectivity [16,24] (for the α_{1A} receptor over α_{1B})	280-fold	20-fold
In vivo selectivity [25] (Uroselectivity index)	> 3.79	1.09

Table 2. Change in total IPSS and subscores Phase III studies.

Study	No of patients	Mean decrease total IPSS (SD)	Mean decrease Voiding IPSS (SD)	Mean decrease Storage IPSS (SD)
Kawabe et al. [29]				
Silodosin 4 mg bd	175	-8.3 (6.4)*	-5.8 (4.6)*	-2.5 (2.9)*
Tamsulosin 0.2 mg od	192	-6.8 (5.7)	-4.8	-2.1 (2.6)
Placebo	89	-5.3 (6.7)	-3.8	-1.5 (2.6)
Marks et al. [30]				
Silodosin 8 mg od	466	-6.4(6.63)*	-4.0 (4.31)*	-2.3 (2.93)*
Placebo	457	-3.5(5.84)	-2.1 (3.76)	-1.4 (2.99)
Chapple et al. [28] *(intention to treat)*				
Silodosin 8 mg od	381	-7.0*	-4.5*	-2.5*
Tamsulosin 0.4 mg od	384	-6.7*	-4.2*	-2.4*
Placebo	190	-4.7	-2.9	-1.8

*Significant over placebo.

Table 3. Change in Qmax ml/s Phase III studies.

Study	No of patients	Baseline Qmax (SD)	Mean change (SD)
Kawabe et al. [29]			
Silodosin 4 mg bd	175	9.88 (2.75)	1.70 (3.31)
Tamsulosin 0.2 mg od	192	9.41 (2.81)	2.60 (3.98)
Placebo	89	10.18 (2.72)	0.26 (2.21)
Marks et al. [30]			
Silodosin 8 mg od	466	8.7(2.60)	2.6 (4.43)*
Placebo	457	-3.5(2.80)	1.5 (4.36)
Chapple et al. [28] *(intention to treat)*			
Silodosin 8 mg od	381	10.78	3.77
Tamsulosin 0.4 mg od	384	10.27	3.53
Placebo	190	10.32	2.93

*Significant over placebo.

Table 4. Comparison in key adverse events of silodosin compared to placebo and tamsulosin (as a percentage of total patients).

Study	Silodosin		Tamsulosin	Placebo
Kawabe *et al.* [29]				
Ejaculatory dysfunction (EjD)	22.3%		1.6%	0
Dizziness	5.1%		7.3%	4.5%
Orthostatic hypotension*	-		-	-
Discontinuation rate	10.2% (2.9% due to EjD)		5.7%	4.5%
Marks *et al.* [30]				
Ejaculatory dysfunction (EjD)	28%		-	0.9%
Dizziness	3.2%		-	1.1%
Orthostatic hypotension	2.6%		-	1.5%
Discontinuation rate‡	8.3% (2.8% due to EjD)		-	11.4%
Chapple *et al.* [28]				
Ejaculatory dysfunction (EjD)	14.2%		2.1%	1.1%
Dizziness	-		-	-
Orthostatic hypotension	0		0	0
Discontinuation rate	2.1% (1.3% due to EjD)		1.0%	1.6%
Marks *et al.* [37] (open-label study)	*De novo* group	Continuation group	-	-
Ejaculatory dysfunction (EjD)	31.1%	9.6%	-	-
Dizziness	3.5%	2.2%	-	-
Orthostatic hypotension	2.9%	2.2%	-	-
Discontinuation rate	16.1% (7.5% due to EjD)	9.6% (1.9% due to EjD)		
Tammela and Chapple [39] (open-label study)	All patients including continuation of silodosin, previous tamsulosin and *de novo* groups			
Ejaculatory dysfunction (EjD)	9.0%			
Dizziness	0.8%			
Orthostatic hypotension	0.0%			
Discontinuation rate	11%			

*Not assessed but no significant difference in heart rate and blood pressure between groups.

‡Including those lost to follow up.

Expert Opin. Pharmacother. (2012) 13(14):2085-2096

Table 4. Comparison in key adverse events of silodosin compared to placebo and tamsulosin (as a percentage of total patients).

Study	Silodosin		Tamsulosin	Placebo
Kawabe *et al.* [29]				
Ejaculatory dysfunction (EjD)	22.3%		1.6%	0
Dizziness	5.1%		7.3%	4.5%
Orthostatic hypotension*	-		-	-
Discontinuation rate	10.2% (2.9% due to EjD)		5.7%	4.5%
Marks *et al.* [30]				
Ejaculatory dysfunction (EjD)	28%		-	0.9%
Dizziness	3.2%		-	1.1%
Orthostatic hypotension	2.6%		-	1.5%
Discontinuation rate‡	8.3% (2.8% due to EjD)		-	11.4%
Chapple *et al.* [28]				
Ejaculatory dysfunction (EjD)	14.2%		2.1%	1.1%
Dizziness	-		-	-
Orthostatic hypotension	0		0	0
Discontinuation rate	2.1% (1.3% due to EjD)		1.0%	1.6%
Marks *et al.* [37] (open-label study)	*De novo* group	Continuation group	-	-
Ejaculatory dysfunction (EjD)	31.1%	9.6%	-	-
Dizziness	3.5%	2.2%	-	-
Orthostatic hypotension	2.9%	2.2%	-	-
Discontinuation rate	16.1% (7.5% due to EjD)	9.6% (1.9% due to EjD)		
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EUROPEAN UROLOGY 61 (2012) 994–1003

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journal homepage: www.europeanurology.com

European Association of Urology

A Systematic Review and Meta-analysis on the Use of Phosphodiesterase 5 Inhibitors Alone or in Combination with α-Blockers for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia

Mauro Gacci[a,], Giovanni Corona[b,c], Matteo Salvi[a], Linda Vignozzi[c], Kevin T. McVary[d], Steven A. Kaplan[e], Claus G. Roehrborn[f], Sergio Serni[a], Vincenzo Mirone[g], Marco Carini[a], Mario Maggi[c]*

[a] Department of Urology, University of Florence, Florence, Italy; [b] Endocrinology Unit, Maggiore-Bellaria Hospital, Bologna, Italy; [c] Sexual Medicine and Andrology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy; [d] Northwestern University, Feinberg School of Medicine, Department of Urology, Chicago, IL, USA; [e] Institute of Bladder and Prostate Health, Weill Cornell Medical College, Cornell University, New York, NY, USA; [f] Department of Urology, UT Southwestern Medical Center, Dallas, TX, USA; [g] Department of Urology, University Federico II of Naples, Naples, Italy

Table 1 – Characteristics of the studies included in the meta-analysis

Study	Baseline characteristics			Treatment				Population characteristic			
	Age, yr	Body mass index	IPSS	Drug	Dosage, mg	Pills per week	Run-in, wk	No. of patients active, completed	No. of patients control, completed	Study duration, wk	Jadad score
					PDE5-Is alone						
McVary et al. [21]	60	–	–	Sildenafil	50 (2 wk); 100	7	4	168	155	12	4
McVary et al. [16]	61.5	–	17.9	Tadalafil	20 (2 wk); 100	7	4	125	126	12	3
Stief et al. [22]	55.9	27.3	16.8	Vardenafil	10	14	4	105	110	8	3
Roehrborn et al. [23]	62.0	28.5	17.2	Tadalafil	2.5; 5; 10; 20	7	4	701	185	12	3
Porst et al. [24]	61.9	28.3	16.1	Tadalafil	2.5; 5; 10; 20	7	4	386	105	12	3
Tamimi et al. [25]	60.9	26.9	19.0	UK-369003	10;25; 50; 100	7	2	246	37	12	3
Porst et al. [26]	64.8	27.8	16.8	Tadalafil	5	7	4	148	152	12	4
					PDE5-Is plus α-blockers						
Kaplan et al. [27]	63.4	25.4	17.3	Sildenafil plus alfuzosin	25	7	–	19*	18†	12	3
Bechara et al. [28]	63.7	–	19.4	Tadalafil plus tamsulosin	20	7	2	13*	14†	12	3
Liguori et al. [29]	61.3	–	15	Tadalafil plus alfuzosin	20	7	–	21*	18†	12	3
Tuncel et al. [30]	58.8	–	15.4	Sildenafil plus tamsulosin	25	4	–	20*	20†	8	2
Gacci et al. [31]	68.0	25.7	19.6	Vardenafil plus tamsulosin	10	7	2	30*	29†	12	3

PDE5-Is = phosphodiesterase type 5 inhibitors.
* With α-blockers.
† α-Blockers alone.

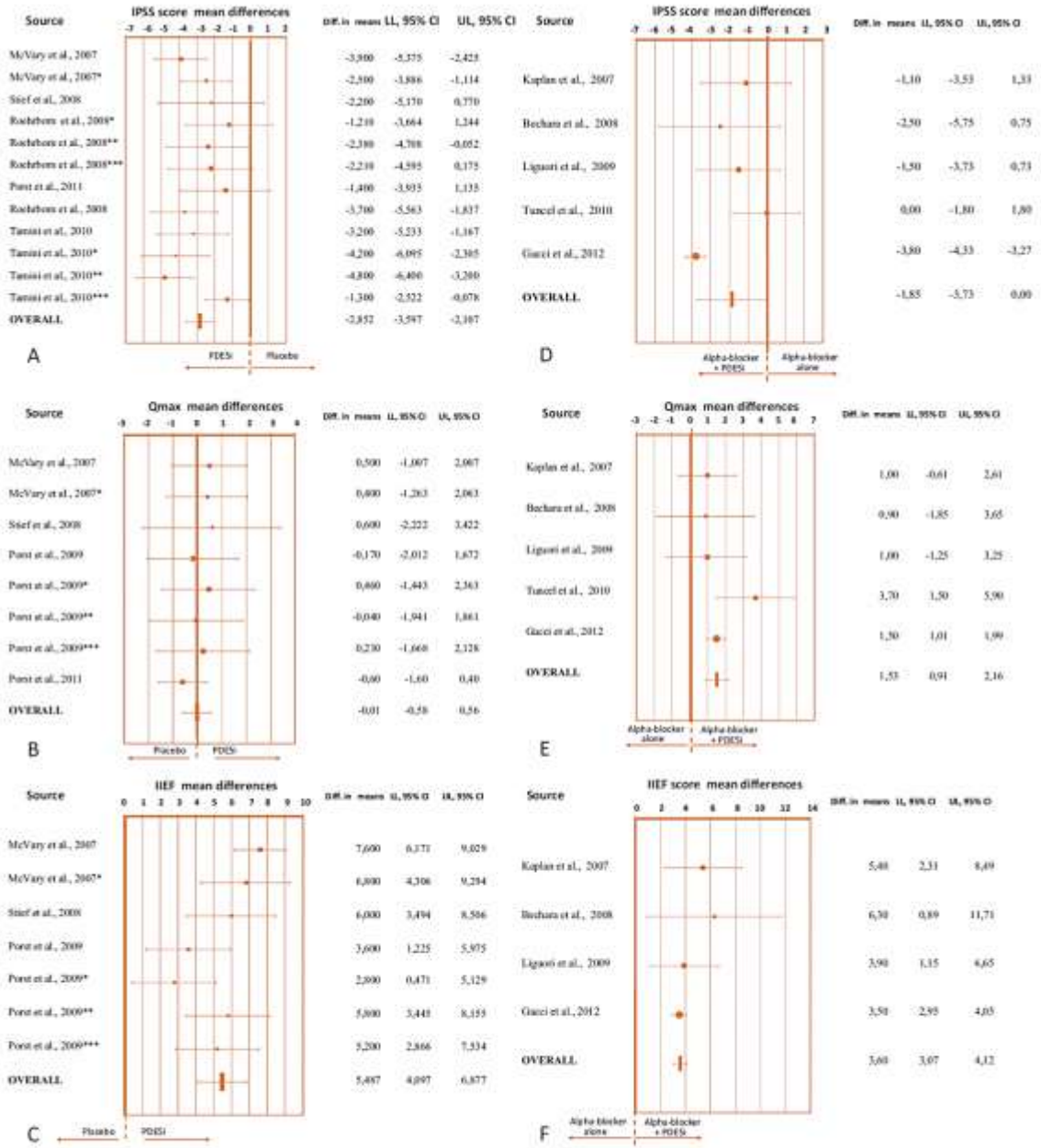


Fig. 2 – Weighted differences (with 95% confidence interval [CI]) of International Prostate Symptom Score (IPSS), maximum flow rate (Q_{max}), and International Index of Erectile Function (IIEF) score for the studies on phosphodiesterase type 5 inhibitors (PDE5-Is) versus placebo (A, B, and C, respectively) and PDE5-Is plus α-blocker versus α-blocker alone (D, E, and F, respectively).
LL = lower limit; UL = upper limit.

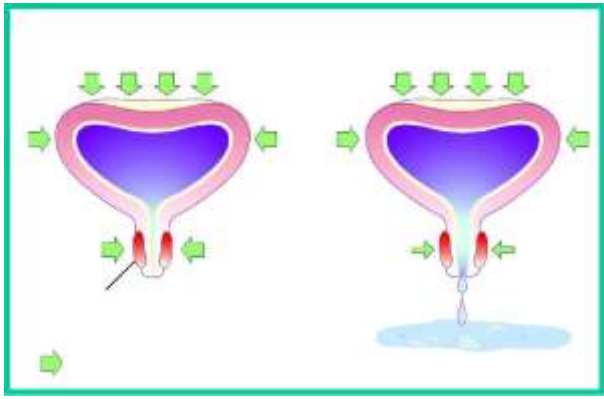
Drugs for stress incontinence

Alpha adrenergic agonists

Phenylpropanolamine

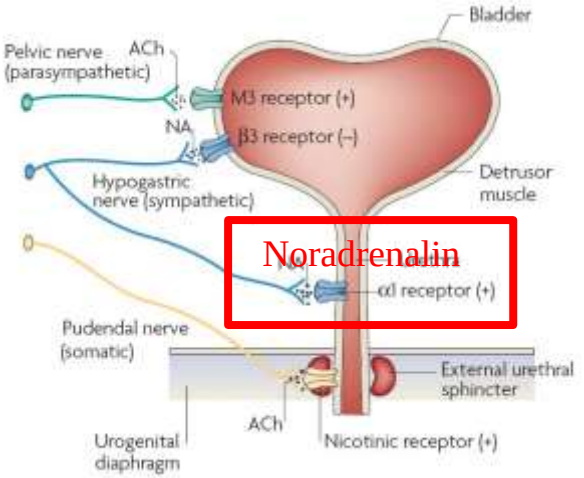
Ephedrine

Pseudoephedrin



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

Phenylpropanolamine hydrochloride (PPA)
FDA is taking steps to remove phenylpropanolamine hydrochloride from all drug products due to the risk of hemorrhagic stroke. FDA has significant concerns because of the seriousness of stroke and the inability to predict who is at risk.
[November 6, 2000 - Public Health Advisory - FDA



Good News

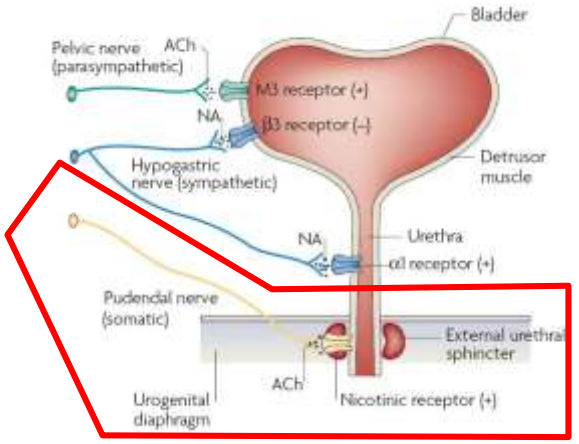
新藥治失禁

英國剛批准一種含 duloxetine 藥物治療失禁，此藥作用爲刺激陰部神經，强化位於膀胱口的尿道括約肌，以免婦女於運動、咳嗽、打噴嚏等的時候失禁。研究指服藥的婦女患者認爲症狀減輕 50%、對照組只有近三分之一。

失禁患者多爲生育後、癡肥及便秘婦女，現時的治療建議爲做盆骨運動控制病徵，或接受手術。此症令患者生活大受困擾，如不能到一些沒洗手間的地方，而研究中，服藥者認爲有助改善生活質素。

Duloxetine Drugs 2004; 64(22):2567-73

- Serotonin and Norepinephrine reuptake inhibitor (SNRI)
- Block the reuptake of S and N at Onuf's nucleus in sacral spinal cord, activating pudendal motor neuron causing an increase in urethral striated muscle tone and the force of contraction
- ? A central effect resulting in increase in bladder capacity



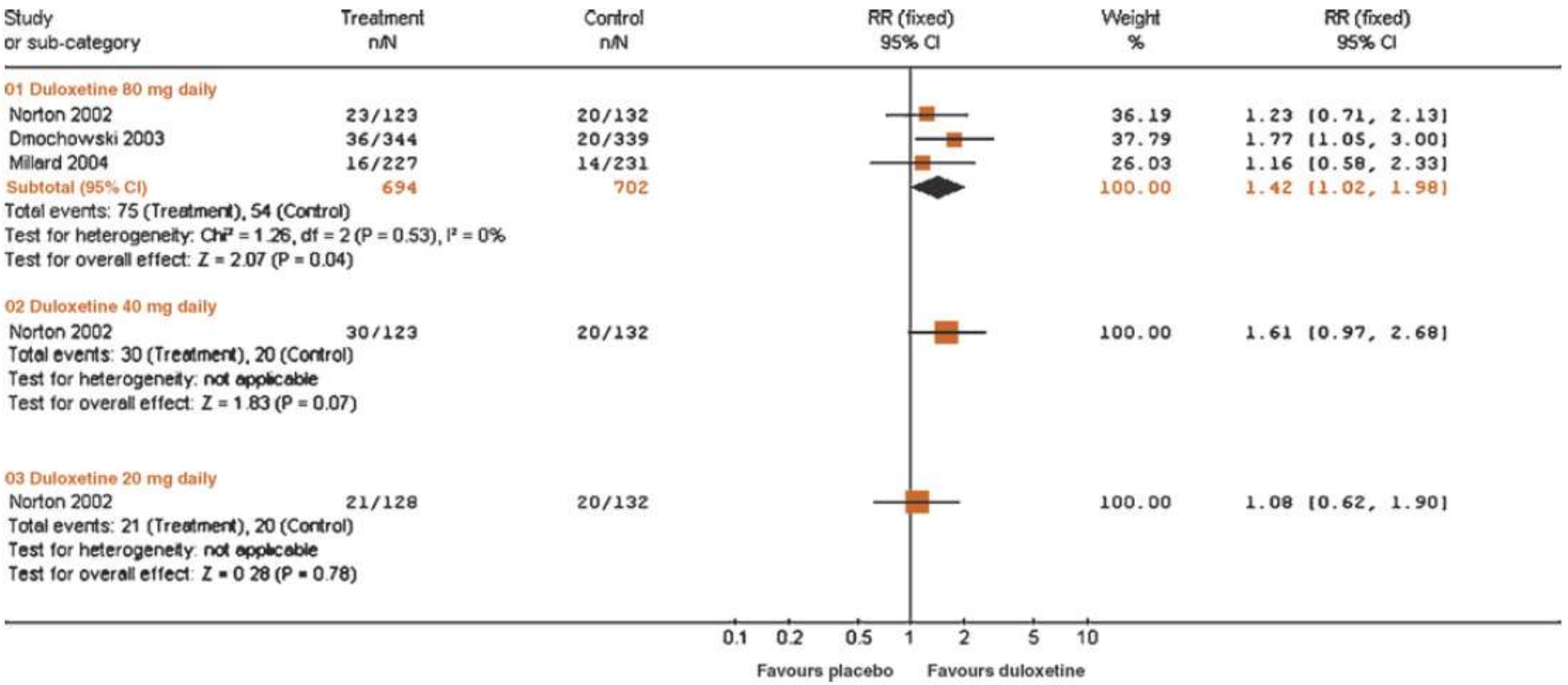


Fig. 1 – Numbers cured during treatment: Duloxetine vs placebo.

Duloxetine, a Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) for the Treatment of Stress Urinary Incontinence: A Systematic Review. European Urology 51 (2 0 0 7) 67–74

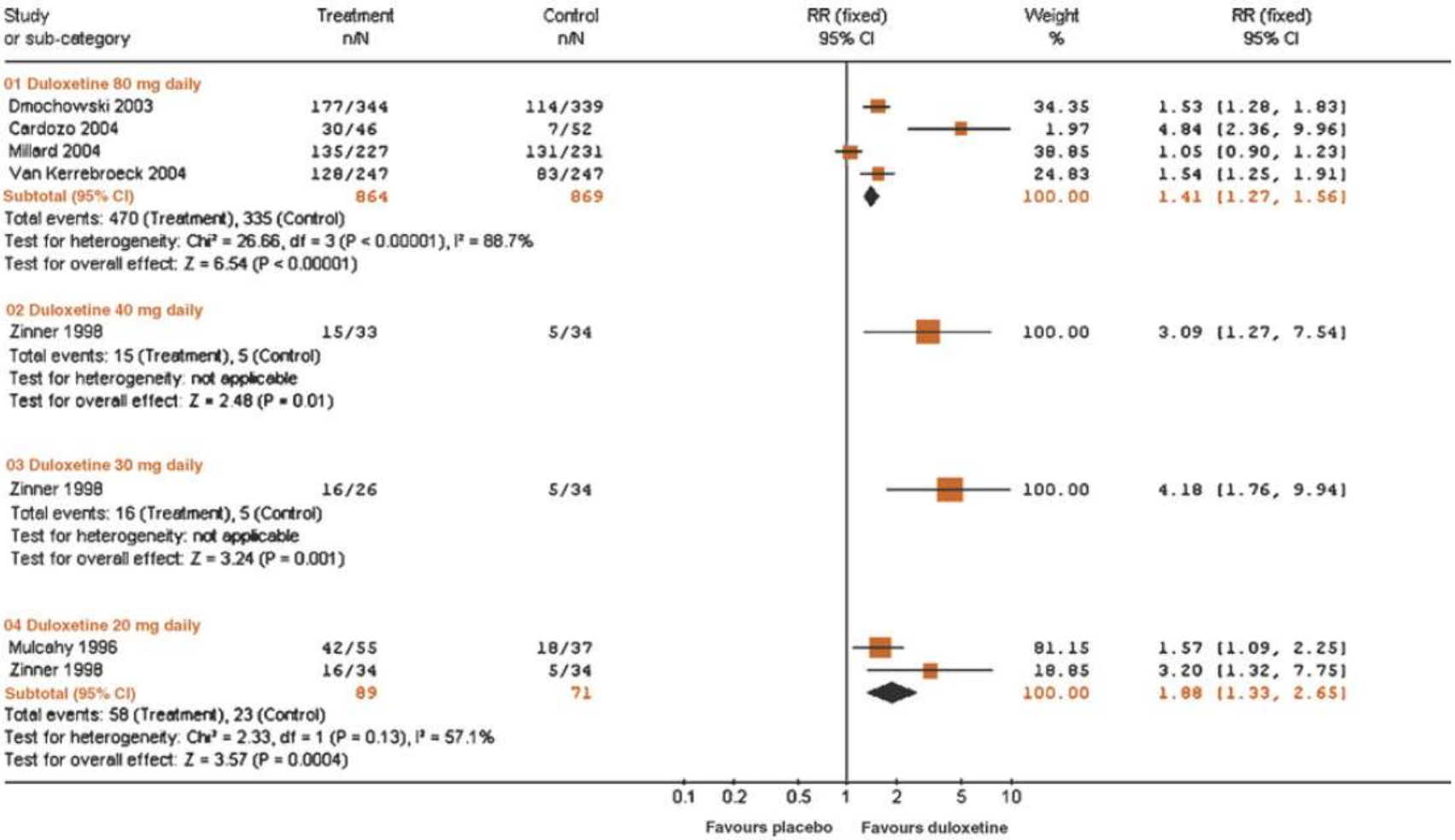


Fig. 2 – Numbers improved during treatment: Duloxetine vs placebo.

Duloxetine, a Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) for the Treatment of Stress Urinary Incontinence: A Systematic Review. European Urology 51 (2 0 0 7) 67–74

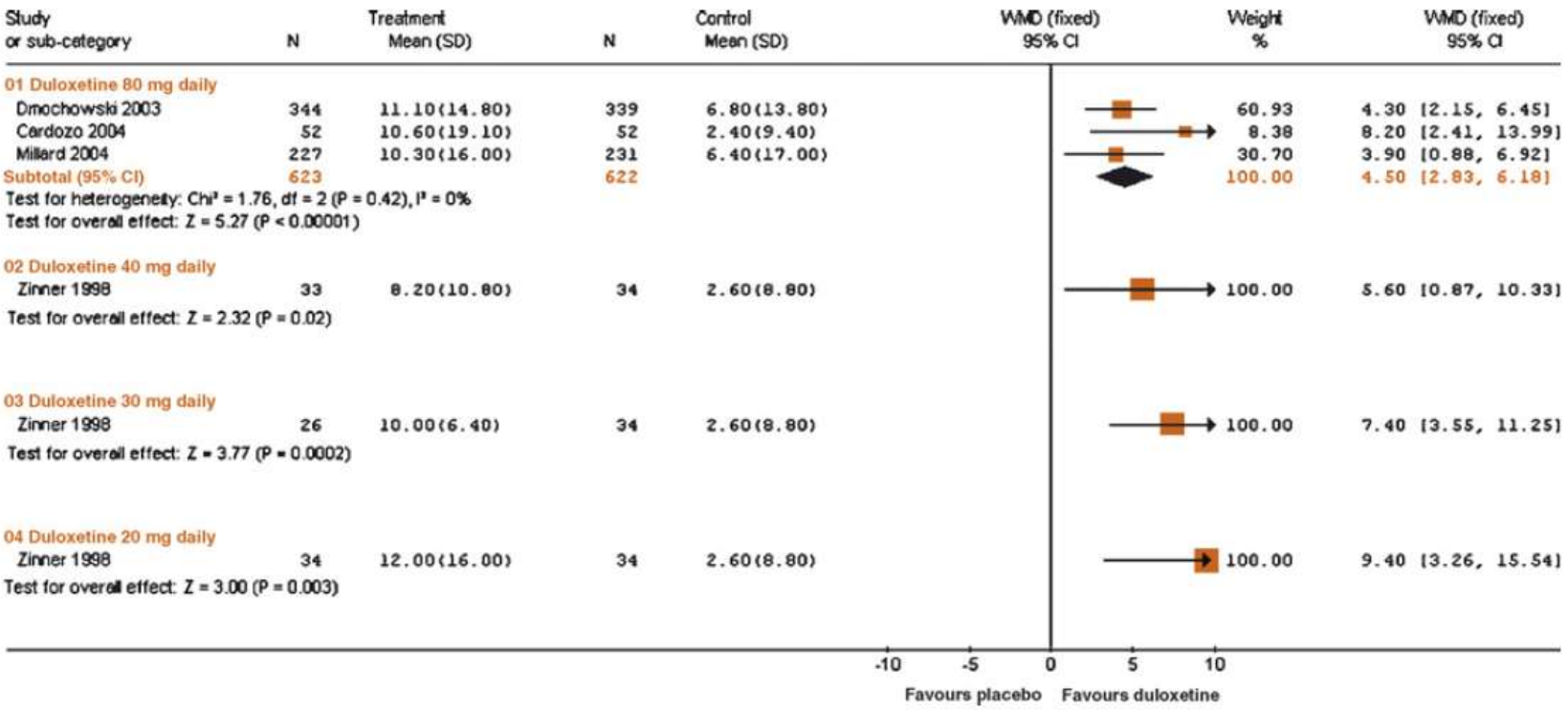


Fig. 3 – Assessment of I-QoL change: Duloxetine vs placebo.

Duloxetine, a Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) for the Treatment of Stress Urinary Incontinence: A Systematic Review. European Urology 51 (2 0 0 7) 67–74

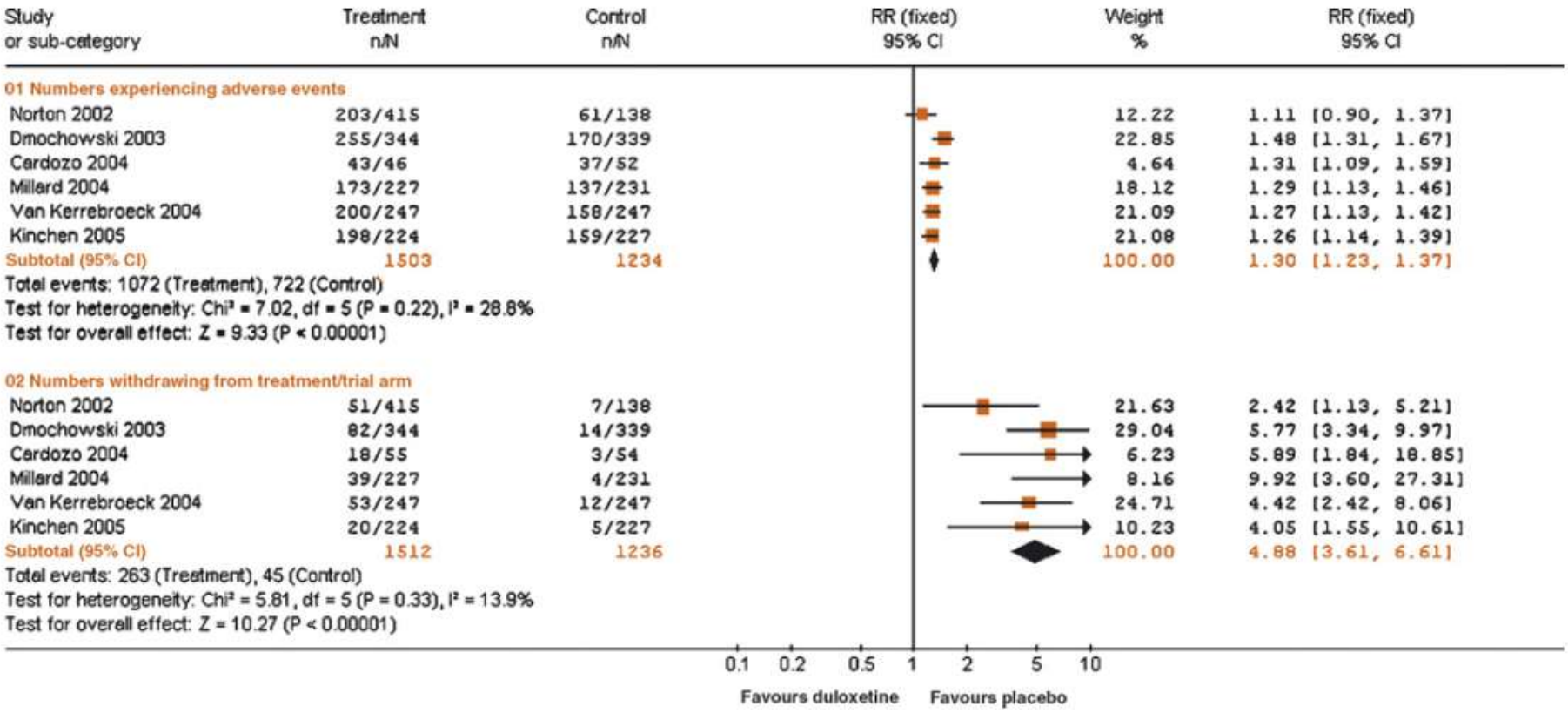


Fig. 4 – Adverse events and discontinuation rates: Duloxetine vs placebo.

Nausea is the most common side-effect. Other side-effects reported were vomiting, constipation, headache, dry mouth, fatigue, dizziness, and insomnia

Duloxetine, a Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) for the Treatment of Stress Urinary Incontinence: A Systematic Review. European Urology 51 (2 0 0 7) 67–74

Tolerability and efficacy of duloxetine in a nontrial situation

JRA Duckett, M Vella, G Kavalakuntla, M Basu

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Correspondence: JRA Duckett, Consultant Gynaecologist, Medway Maritime Hospital, Windmill Road, Gillingham, Kent ME7 5NY, UK.
Email jraduckett@hotmail.com

BJOG 2007;114:543–547.

- Overall rate of improvement was 37%.
- 66% women discontinued therapy due to adverse effects or lack of efficacy
- Conclusion: In a non-trial situation duloxetine is poorly tolerated

Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness

Shamliyan T,Wyman J, Kane RL.
Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness.
Agency for Healthcare Research and Quality; April 2012.

- duloxetine hydrochloride reduced the clinical severity of incontinence but was not more likely to resolve incontinence (ie, result in continence) relative to placebo.
- Based on 24 published studies, the benefit-to-risk ratio of duloxetine was low:
  - improved incontinence severity in 75 to 140 women per 1000 treated, and
  - 129 women per 1000 treated stopped using the medication due to adverse effects

Estrogen and UI

- Oral estrogen supplement: Subjective improvement without objective reduction of urine leaked Obstet Gynecol 83:12-8, 1994

Oestrogen therapy for urinary incontinence in post-menopausal women (Review)

Cody JD, Jacobs ML, Richardson K, Moehrer B, Hextall A

Analysis 1.3. Comparison 1 Oestrogen versus placebo or no treatment, Outcome 3 Incontinence not improved (generic inverse variance) (women's observations).

Review: Oestrogen therapy for urinary incontinence in post-menopausal women

Comparison: 1 Oestrogen versus placebo or no treatment

Outcome: 3 Incontinence not improved (generic inverse variance) (women's observations)

Study or subgroup	Oestrogen N	Placebo / no treatment N	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Systemic administration (any incontinence)						
Cardozo 1993 S	36	33	-0.1393 (0.2098)		8.1 %	0.87 [0.58, 1.31]
Hendrix (hysterectomy) S	2950	2970	0.4637 (0.0688)		75.2 %	1.59 [1.39, 1.82]
Jackson 1999 S	29	32	-0.3011 (0.2305)		6.7 %	0.74 [0.47, 1.16]
Rufford 2003 S	25	21	-0.1744 (0.2469)		5.8 %	0.84 [0.52, 1.36]
Walter 1978 S	11	10	-0.9163 (0.4134)		2.1 %	0.40 [0.18, 0.90]
Wilson 1987 S	16	18	-0.5798 (0.4187)		2.0 %	0.56 [0.25, 1.27]
Subtotal (95% CI)					**100.0 %**	**1.32 [1.17, 1.48]**
Heterogeneity: Chi? = 33.45, df = 5 (P<0.00001); I? =85%						
Test for overall effect: Z = 4.63 (P < 0.00001)						
2 Local administration (any incontinence)						
Dessole 2004 L	44	44	-0.9676 (0.2295)		10.5 %	0.38 [0.24, 0.60]
Henalla 1989 L	24	25	-0.1278 (0.0868)		73.6 %	0.88 [0.74, 1.04]
Kurz 1993 L	21	21	-1.3863 (0.4654)		2.6 %	0.25 [0.10, 0.62]
Sacco 1990 L	17	17	-0.5108 (0.204)		13.3 %	0.60 [0.40, 0.89]
Subtotal (95% CI)					**100.0 %**	**0.74 [0.64, 0.86]**
Heterogeneity: Chi? = 18.91, df = 3 (P = 0.00028); I? =84%						
Test for overall effect: Z = 4.02 (P = 0.000058)						

- Combined result of six trials of systemic administration (of oral systemic oestrogens) resulted in worse incontinence than on placebo (RR 1.32, 95% CI 1.17 to 1.48)

- Some evidence that oestrogens used locally (for example vaginal creams or pessaries) may improve incontinence (RR 0.74, 95% CI 0.64 to 0.86).

Effects of Estrogen With and Without Progestin on Urinary Incontinence

Susan L. Hendrix, DO
Barbara B. Cochrane, RN, PhD
Ingrid E. Nygaard, MD
Victoria L. Handa, MD
Vanessa M. Barnabei, MD, PhD
Cheryl Iglesia, MD
Aaron Aragaki, MS
Michelle J. Naughton, PhD
Robert B. Wallace, MD
S. Gene McNeeley, MD

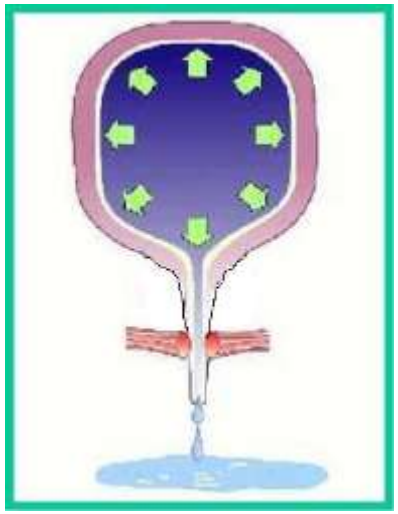
JAMA, February 23, 2005—Vol 293, No. 8

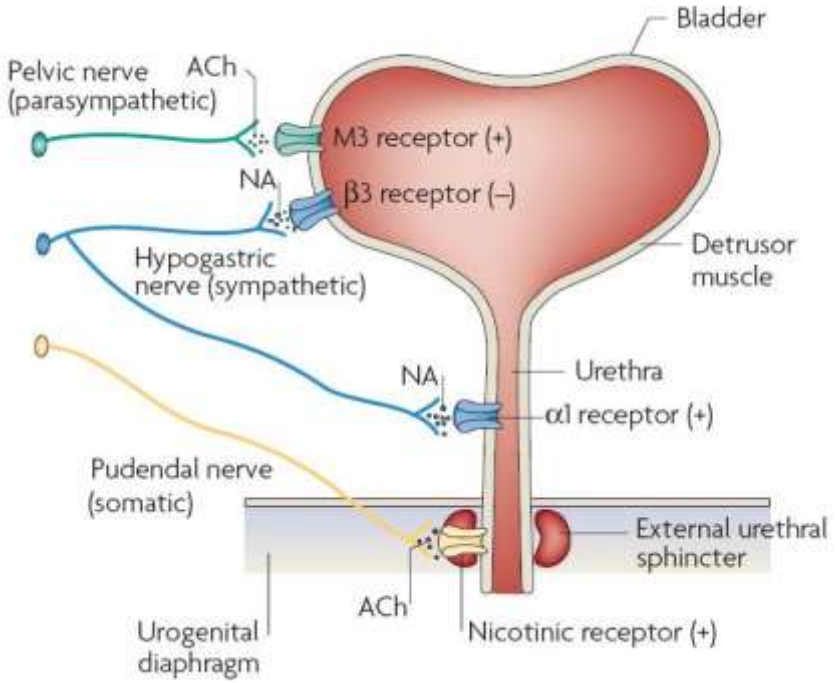
Table 5. Sensitivity Analysis of Definitions of Incident Urinary Incontinence at 1 Year in Asymptomatic Women

Frequency of Urinary Incontinence at Baseline and 1 Year	Relative Risk (95% Confidence Interval)	
	CEE + MPA vs Placebo	CEE Alone vs Placebo
Stress		
Within last year	1.87 (1.61-2.18)	2.15 (1.77-2.62)
>1/mo but <1/wk	1.93 (1.67-2.23)	2.21 (1.85-2.65)
≥1/wk but <1/d	2.28 (1.91-2.73)	2.59 (2.10-3.18)
Daily	2.48 (1.84-3.33)	2.39 (1.75-3.27)
Urge		
Within last year	1.15 (0.99-1.34)	1.32 (1.10-1.58)
>1/mo but <1/wk	1.12 (0.97-1.30)	1.36 (1.15-1.61)
≥1/wk but <1/d	1.02 (0.87-1.20)	1.31 (1.08-1.59)
Daily	1.12 (0.84-1.49)	1.36 (1.01-1.83)
Mixed		
Within last year	1.49 (1.10-2.01)	1.79 (1.26-2.53)
>1/mo but <1/wk	1.69 (1.35-2.11)	1.83 (1.42-2.36)
≥1/wk but <1/d	1.72 (1.40-2.12)	1.99 (1.58-2.50)
Daily	1.73 (1.33-2.24)	2.17 (1.66-2.85)

Abbreviations: CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate.

Drugs for underactive detrusor



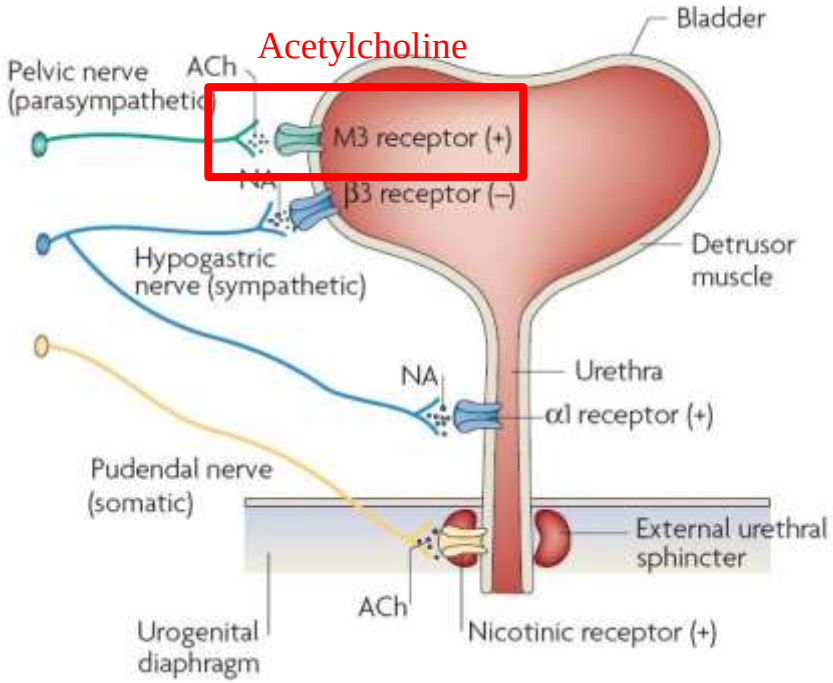


Drugs for underactive detrusor

Cholinergic agents

Distigmine (Ubetid)

Bethanechol (Urecholine)



Is the use of parasympathomimetics for treating an underactive urinary bladder evidence-based?

Maurits M. Barendrecht*†, Matthias Oelke*, Maria P. Laguna* and Martin C. Michel†
*Departments of *Urology, and †Pharmacology and Pharmacotherapy, Academic Medical Center, Amsterdam, the Netherlands*

The currently available data show little if any benefit of using parasympathomimetics agents in preventing or treating underactive urinary bladder

2007 BJU INTERNATIONAL | 99, 749–752 |

Requirements in achieving continence

- Lower urinary tract function
- Mental function
- Mobility and dexterity
- Environment
- Motivation- both patients and cares

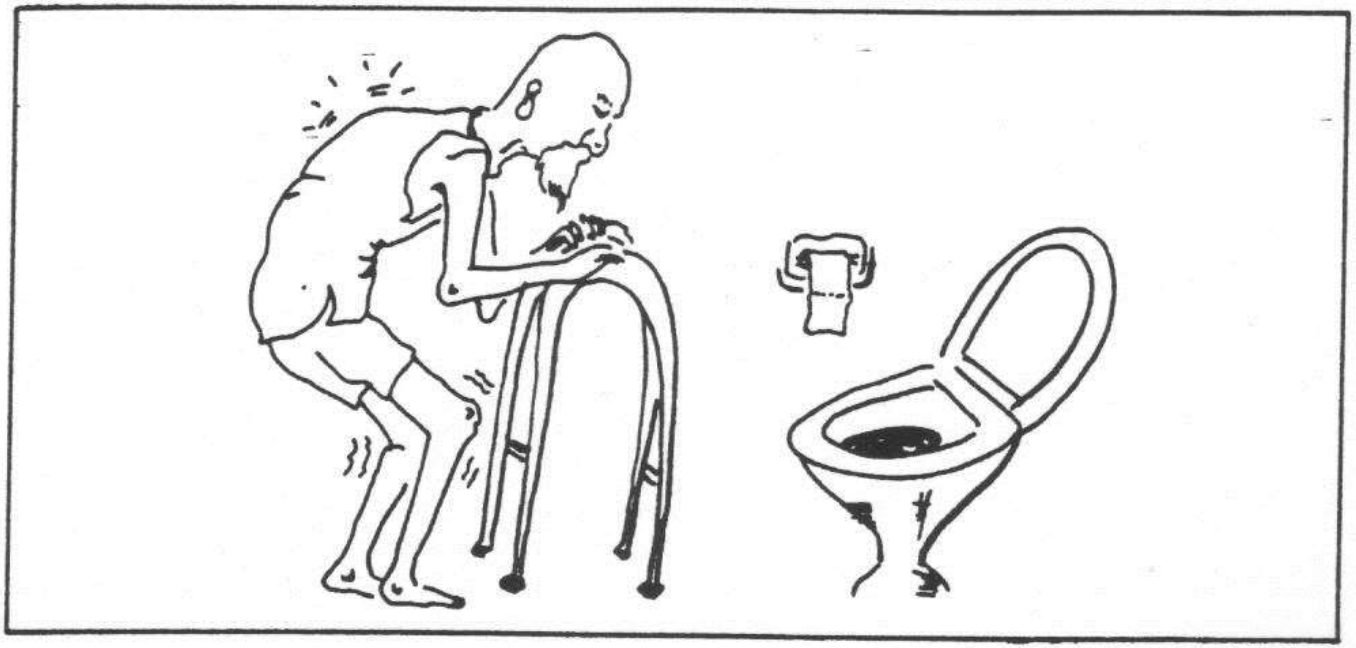
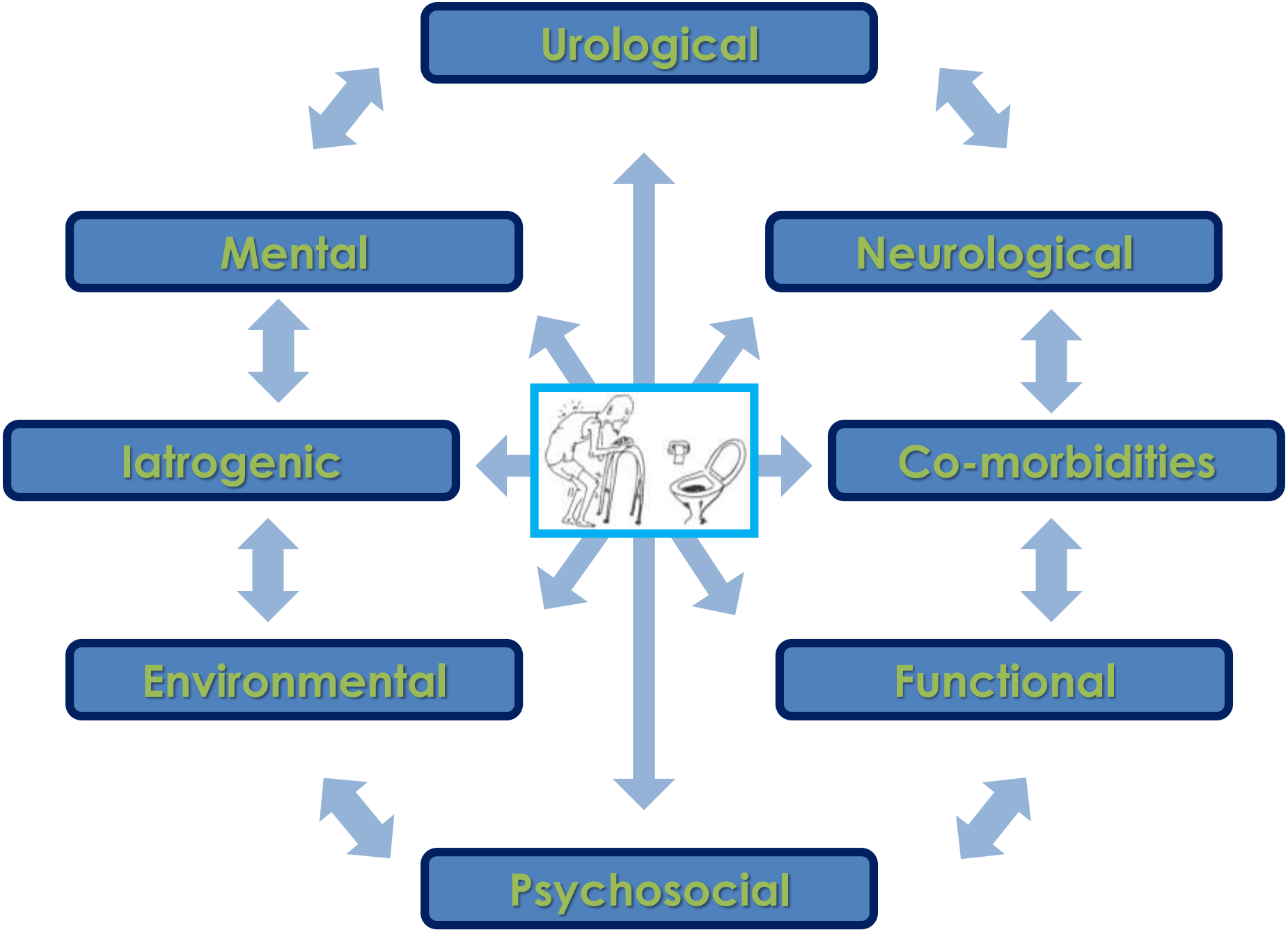


Fig. 5.3 Distant toilet + slow painful mobility + urgency = incontinence.


Urological
Mental
Neurological
Iatrogenic
Co-morbidities
Environmental
Functional
Psychosocial

Thank you

送客新松

黃山十大名松之一的「送客松」由於樹齡老化，雖經多種措施搶救仍然枯死。據新華社昨日表示，黃山景區管委會已初步為送客松選定了「接班人」。小圖為枯死的送客松。「送客松」的接班人距離「迎客松」五十餘米，樹幹挺拔、分枝合理，呈旗形樹冠，與原「送客松」形神相似、體量略大，長勢旺盛；該樹依託的背景與原樹相同，均為蓮花峰，非常適合遊人觀賞和拍照留影。

資料顯示，關於迎客松、送客松的最早紀錄是一六三五年明代許楚寫的《黃山遊記》，稱作迓、送松，但因自然的因素，送松於一七九九年死亡，迎松於一八三二年死亡，現在黃山上的迎客松、送客松是一八五九年重新擇樹命名的。

新華社