Treatment of OAB in postmenopause

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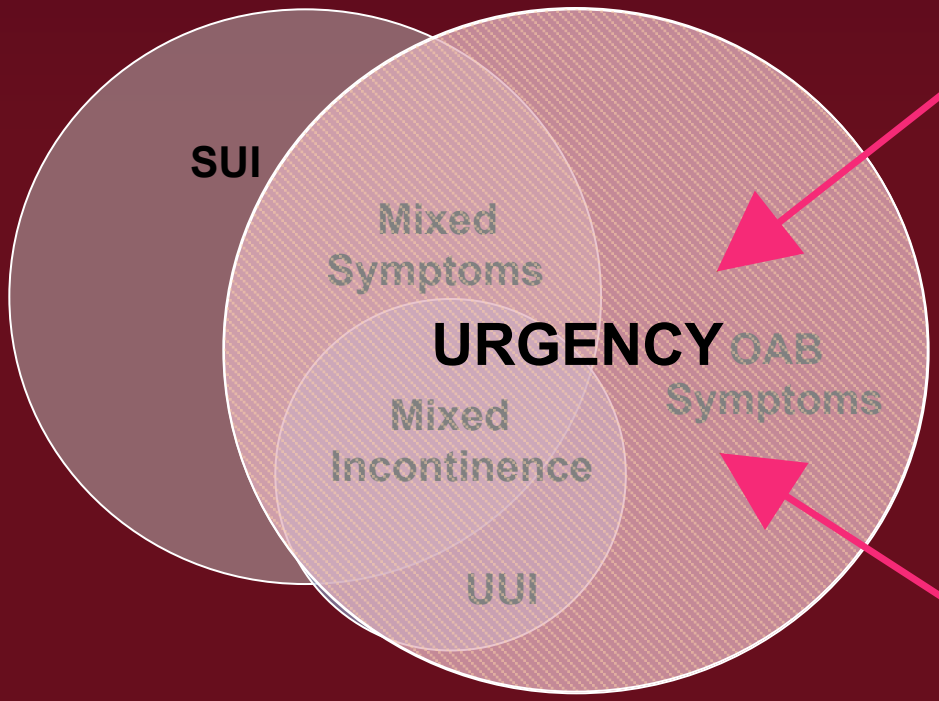
Spectrum of overactive bladder

'Urinary urgency usually accompanied by frequency and nocturia with or without urgency urinary incontinence in the absence of UTI or other obvious pathology'



Urgency: "a sudden compelling desire to pass urine, which is difficult to defer"[2]

Urgency: "the only symptom a patient *must* have to be described as having OAB"[1]

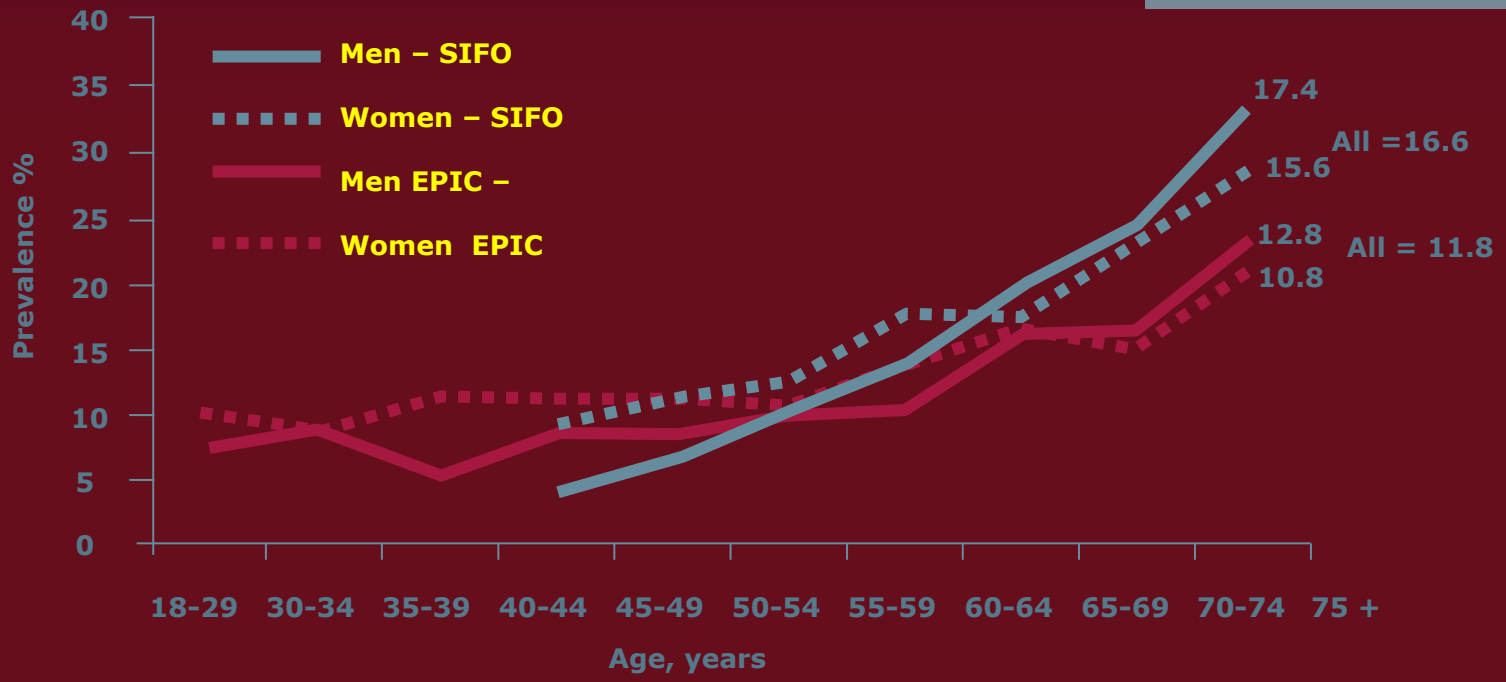
Haylen BT et al. *Neurourol Urodyn*. 2010; 29:4-20

SUI = stress urinary incontinence
UUI = urge urinary incontinence

1. Adapted from Wein AJ. Rackley RR. *J Urol* 2006; 175:s5-10
2. Abrams P et al *Neurourol Urodyn* 2002;21:167-178

Age and prevalence of OAB[1,2]

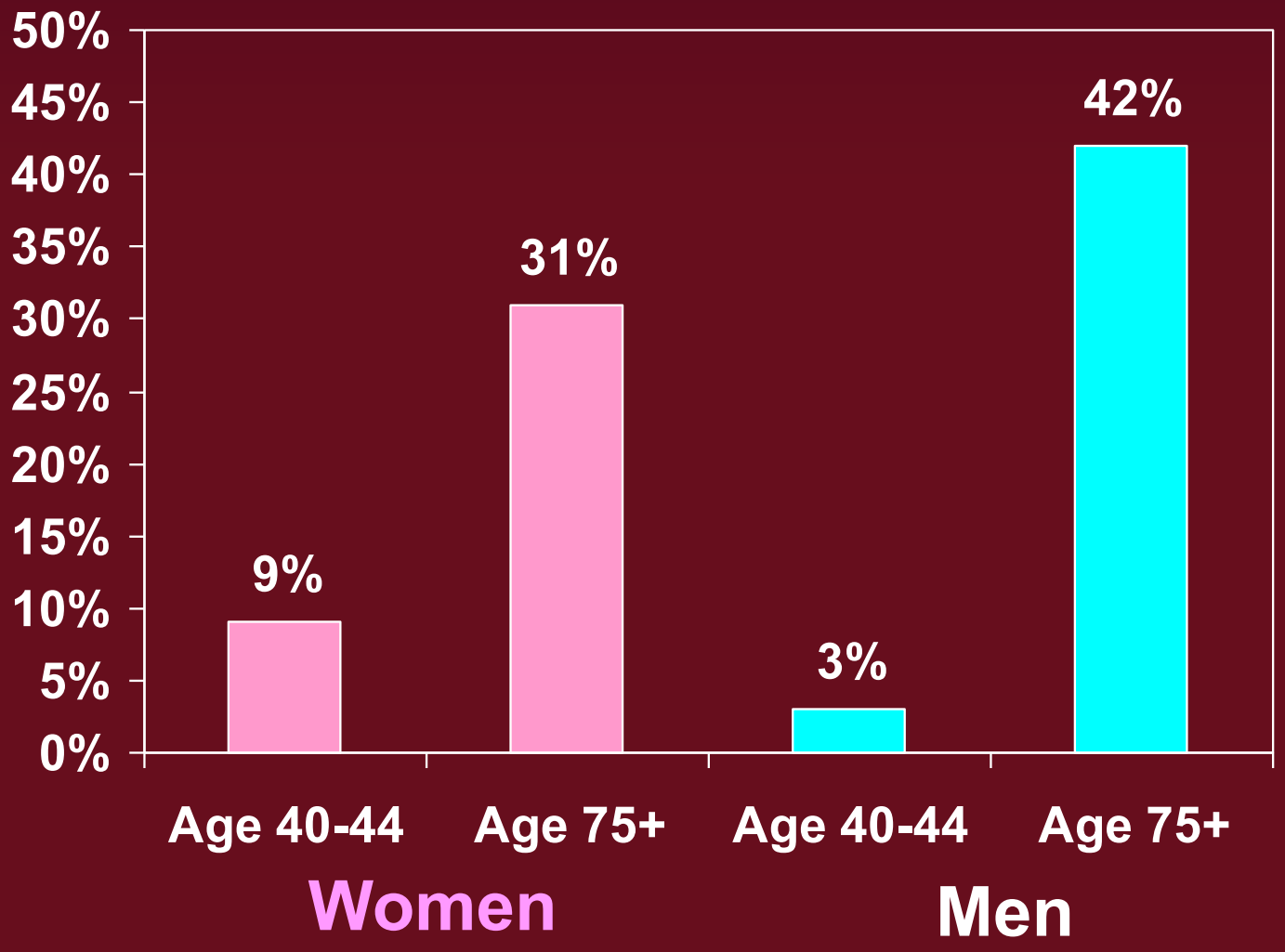
Prevalence of OAB
- Men: 16.0%
- Women: 16.9%



SIFO conducted in 6 European countries (n=16,776)
EPIC conducted in 4 European countries and Canada (n=19,165)

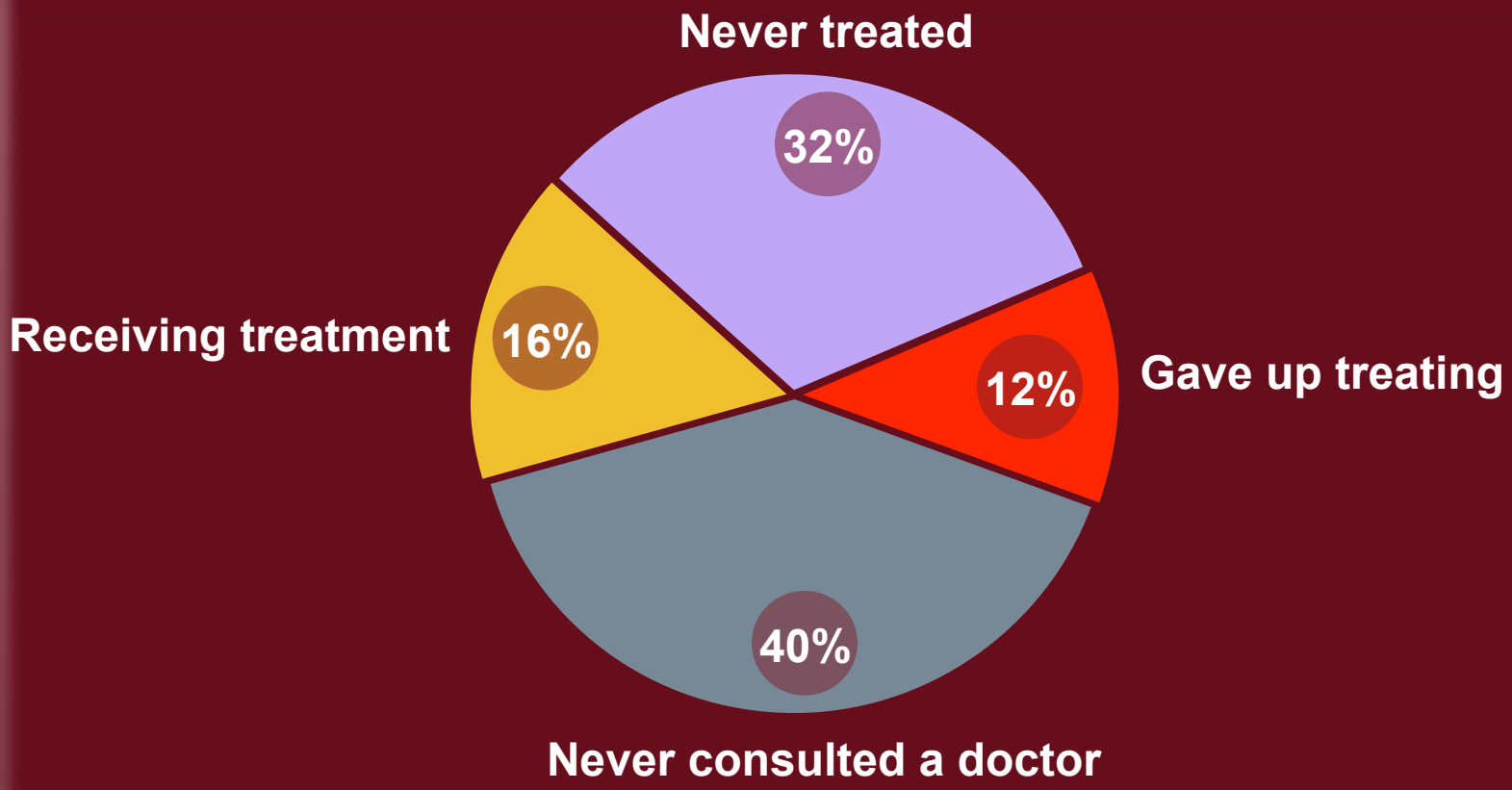
1. *Milsom I, et al. BJU Int 2001; 87: 760-766.*
2. *Milsom I, Irwin DE. Eur Urol Suppl 2007; 6: 4-9.*

Overactive Bladder
Prevalence



Overactive bladder

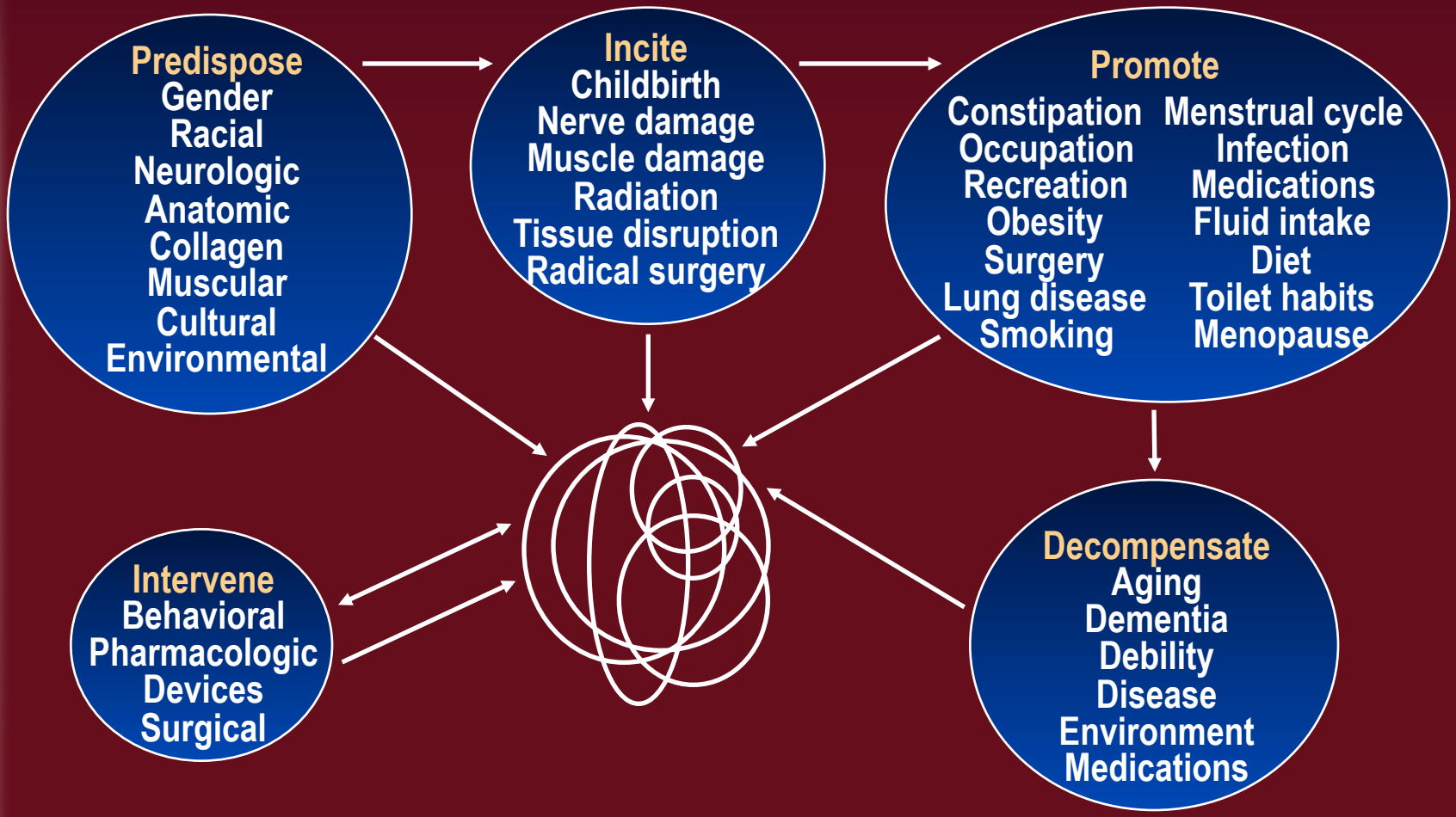
N=1916



Milsom I, Abrams P, Cardozo L, et al. BJU Int 2001;87:760–6

Geriatric Urinary Incontinence and OAB

Multi-factorial Pathophysiology



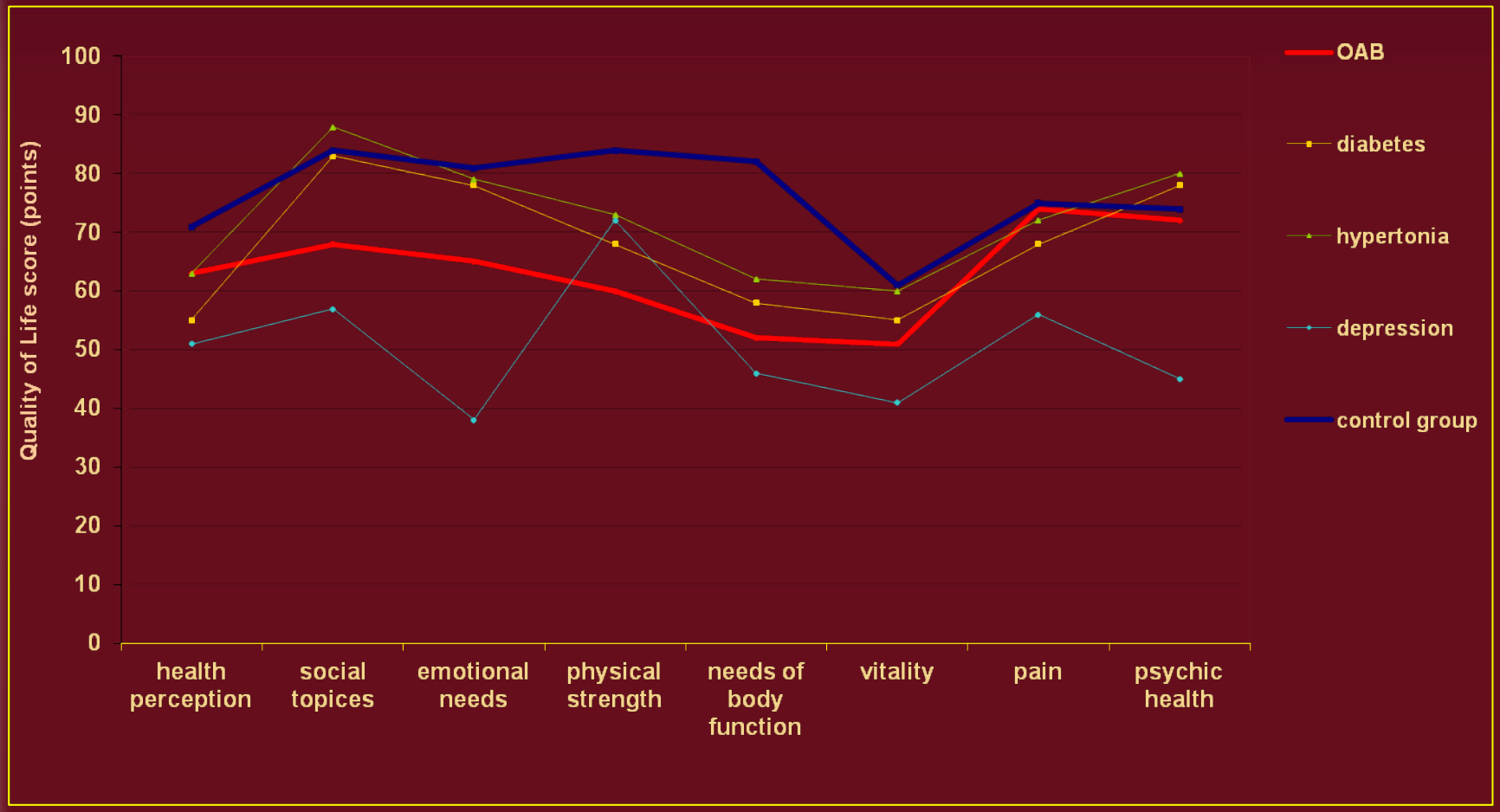
Abrams P, Wein A. Urology. 1997:50(suppl 6A):16.

Impact of overactive bladder on quality of life

- In a survey of over 16,000 adult men and women in six European countries 65% of respondents indicated their daily lives were adversely affected[1]
- Symptoms can affect family, social and work life, as well as mental and physical wellbeing[2]
- **Emotional impact can include**
  - Reduced social and physical activities[2,3]
  - Embarrassment, shame, frustration and anxiety[2,3]
  - Seclusion, isolation and psychological stress[3]
  - Feeling ugly and undesirable[3]
  - Family caregivers may suffer as well
- **Physical impact can include**
  - Sleep disturbance, which may lead to daytime somnolence, lack of concentration and declining physical and mental health[2]
  - Falls and fractures[2]
  - Urinary tract and skin infections[2]
  - Several common chronic conditions, such as depression, constipation, neurological conditions, and erectile dysfunction, have also been associated with OAB.[4]

1. Milsom I. et al. *BJU Int* 2001; 87(9): 760-766
2. Brown J.S. et al. *Am J Manag Care* 2000; 6(11 Suppl): S574-579
3. ICM Market Research, Overactive Bladder Patient Report, April 2010
4. European Association of Urology (EAU). Guidelines on Urinary Incontinence. 2010

OAB – Impact on Quality of Life



[1)] Komaroff: Am J Med (1996) 101:281-290; Kobelt-Nguyen, ICS 1997

Elderly patients - specificities

Comorbidities – "DIPPERSA" contributing to symptoms

- Delirium
- Infection
- Pharmaceuticals
- Psychological
- Excess urine output
- Reduced mobility
- Stool impaction
- Avoid treatment of asymptomatic bacteriuria

Bladder's volume operating range

- Assess patient's bladder capacity
- Assess patient's post-void residual
- Difference between the volumes
- Primary problem:
  - Impaired urine storage
  - Inadequate bladder emptying

Measure total urine production per day!

UI / OAB treatment

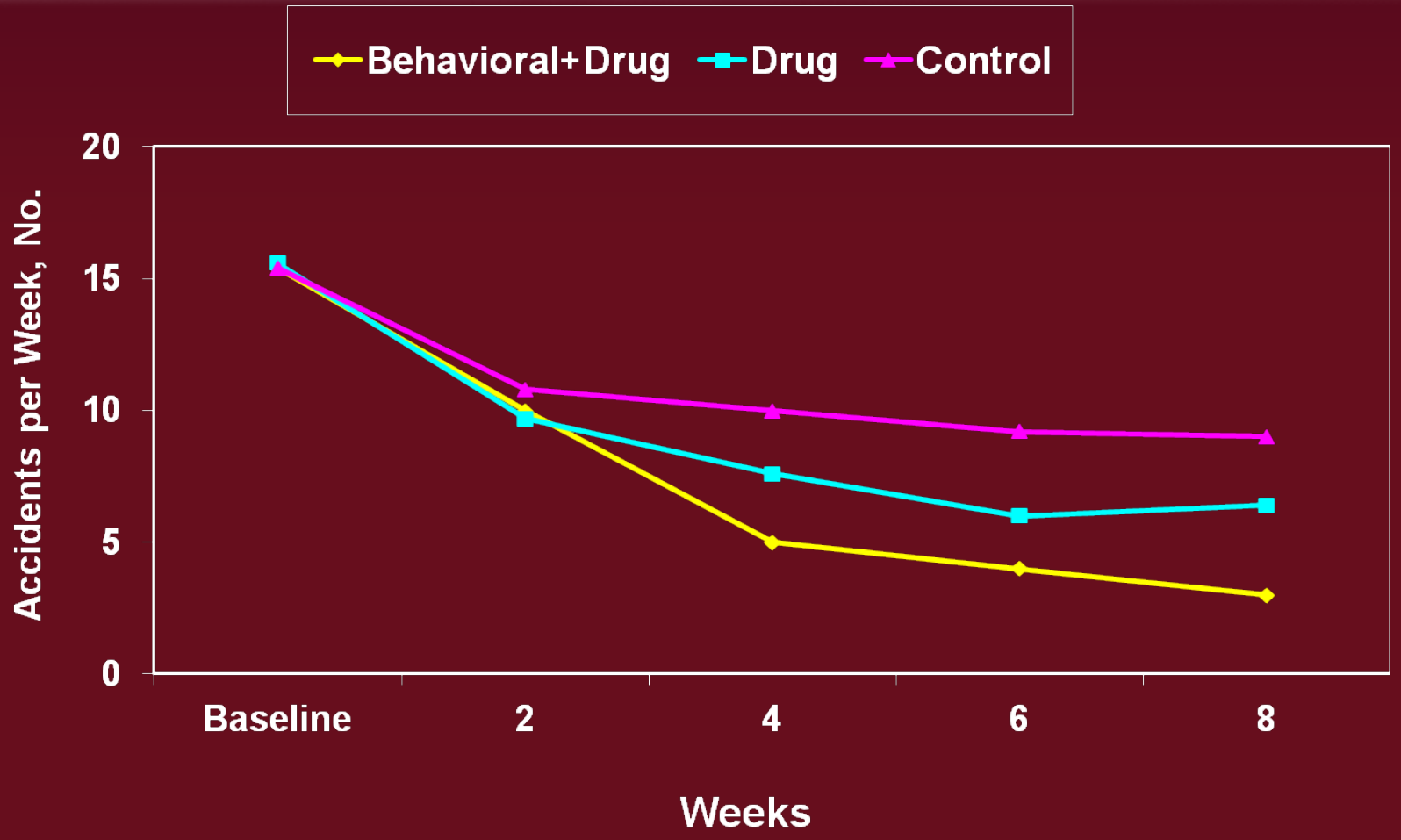
"Step by step" therapy

- Nonpharmachological
- → Pharmacotherapy
- → Electro - / ExMi stimulation
- → Sacral blockade
- → Surgical therapy

Nonpharmacologic treatment

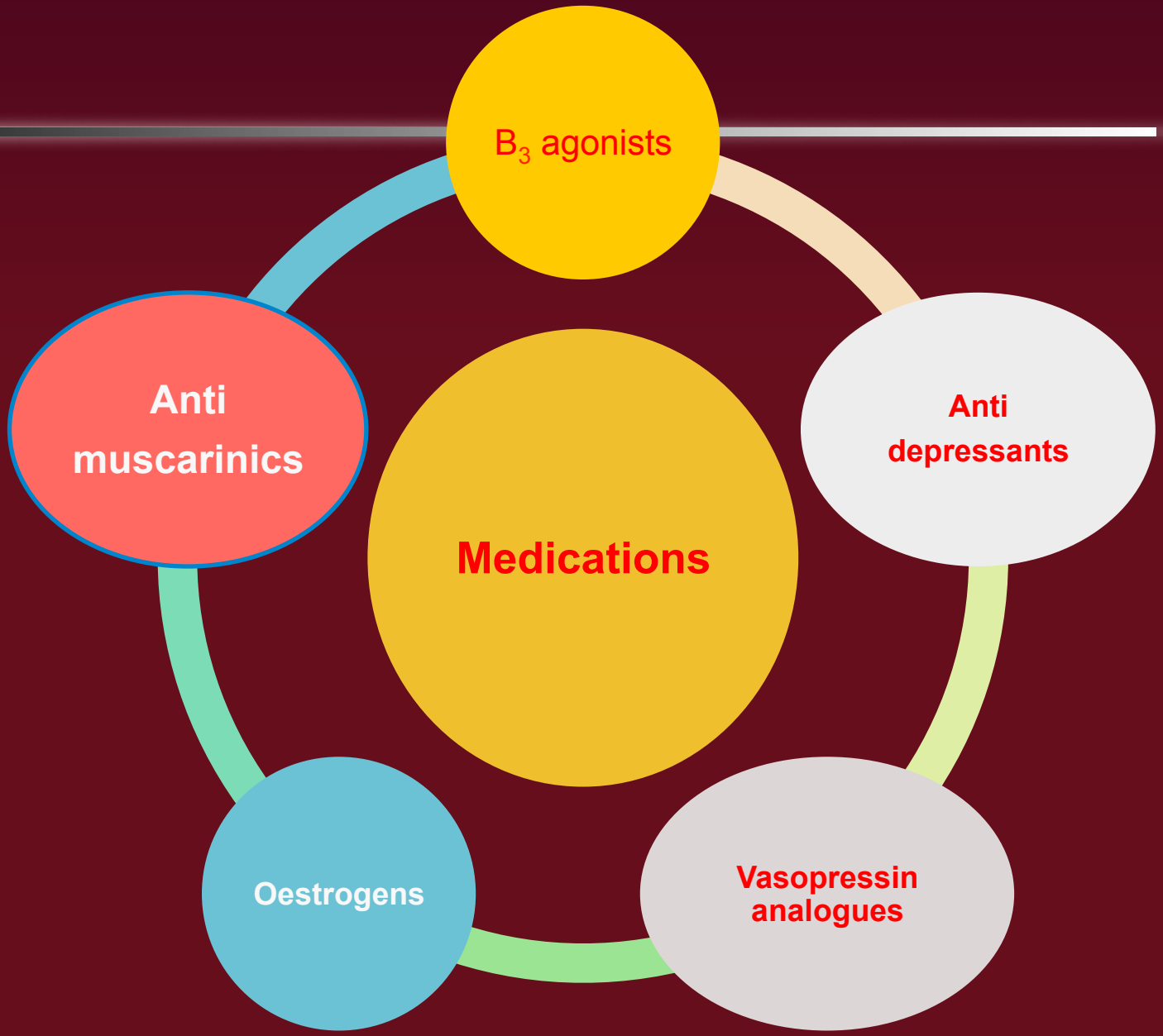
- Communication
- Diet modification
- behavior
  - bladder training
  - timed voiding
  - habit training
- training
  - PFMT
  - techniques for urge suppression
- supportive measures
  - physiotherapy, biofeedback or percutaneous tibial nerve stimulation

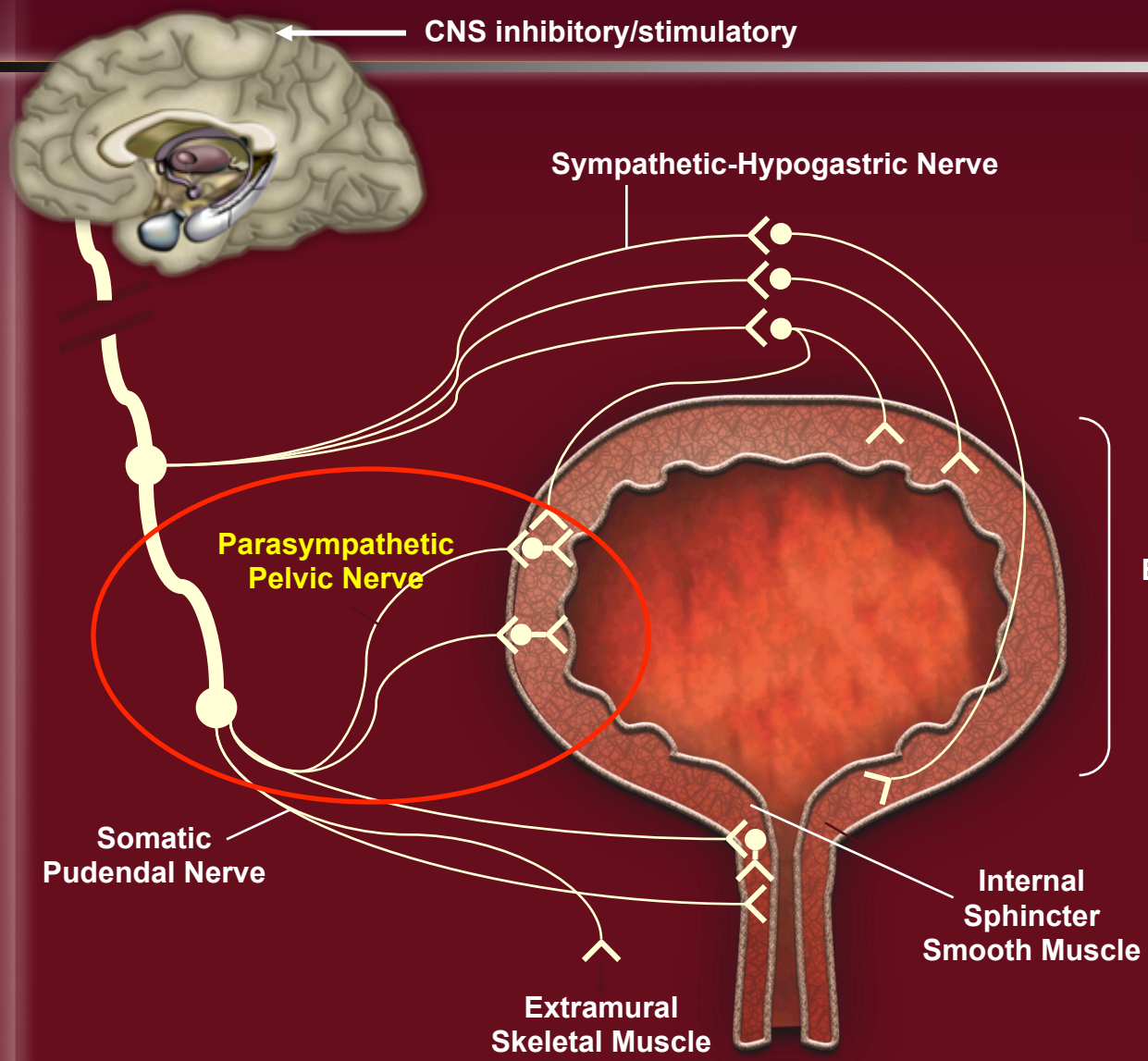
Combined pharmacologic and behavioral therapy provides improved outcomes



Burgio et al: JAMA 280: 1995, 1998

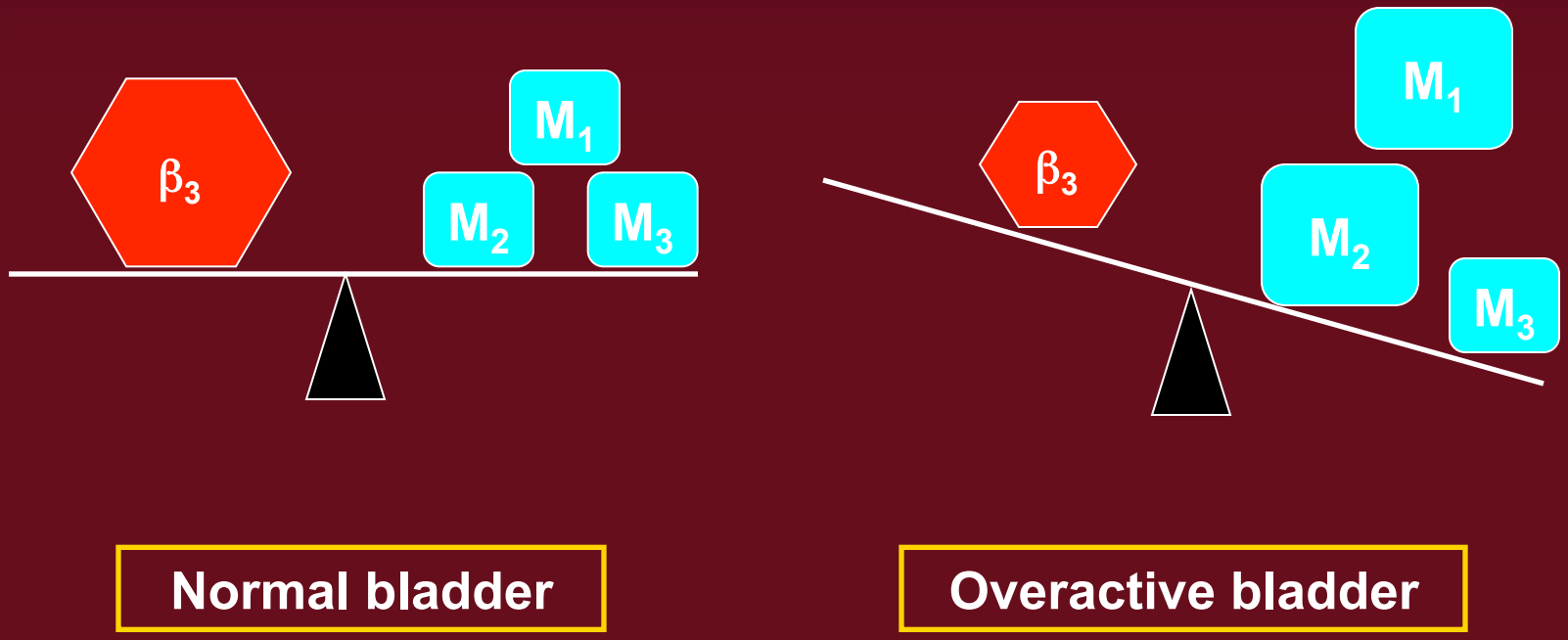
Medications for overactive bladder





Wein, Exp. Opin. Invest. Drugs 10(1): 65-83, 2001

Pharmacotherapy of OAB



Normal bladder

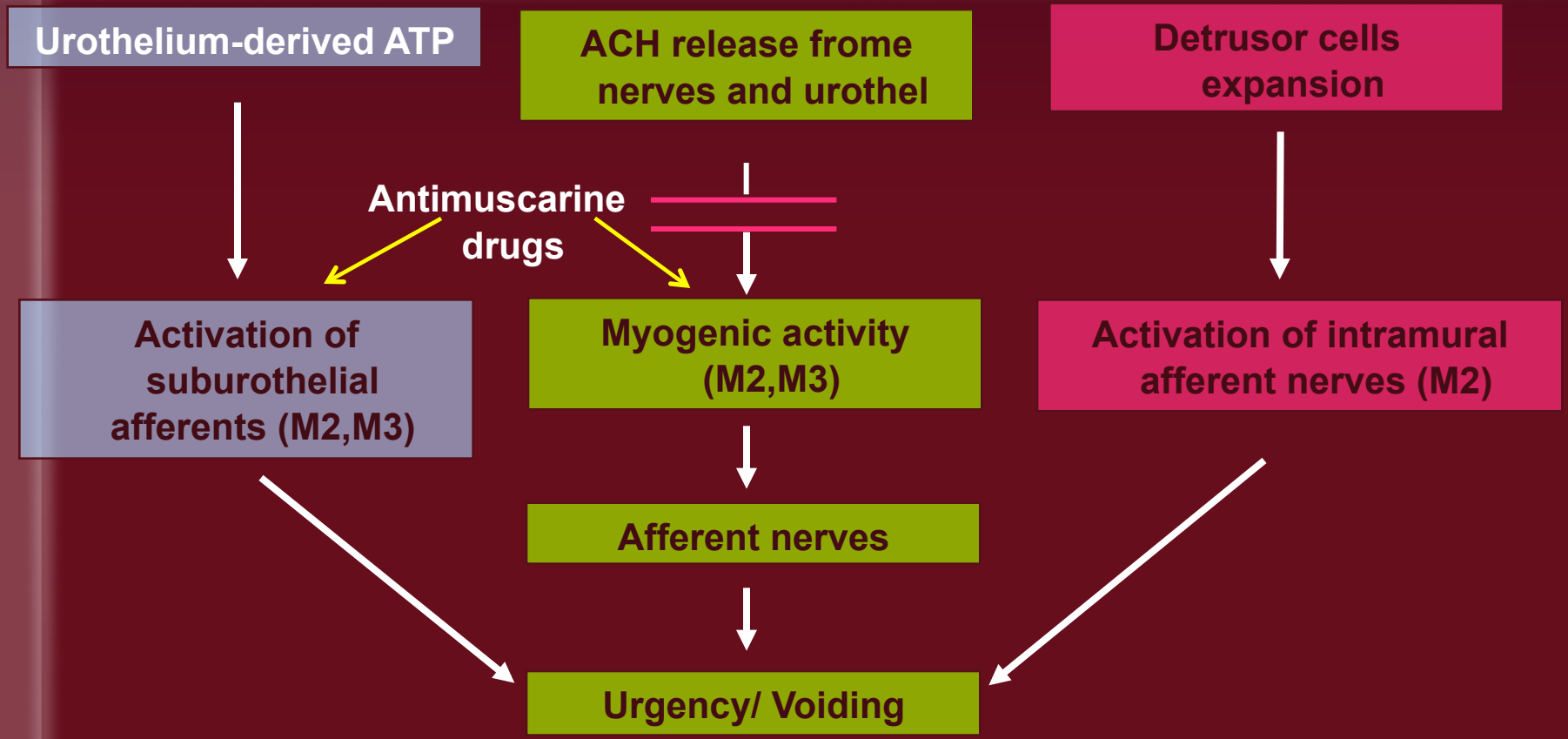
Overactive bladder

Igawa, BJU 2000

Pharmacologic Therapy for the Treatment of OAB

- Antimuscarinic agents are the mainstay for treating OAB
- OAB symptoms relieved by
  - inhibition of involuntary bladder contractions
  - increased bladder capacity

Inhibitory effect of antimuscarinics

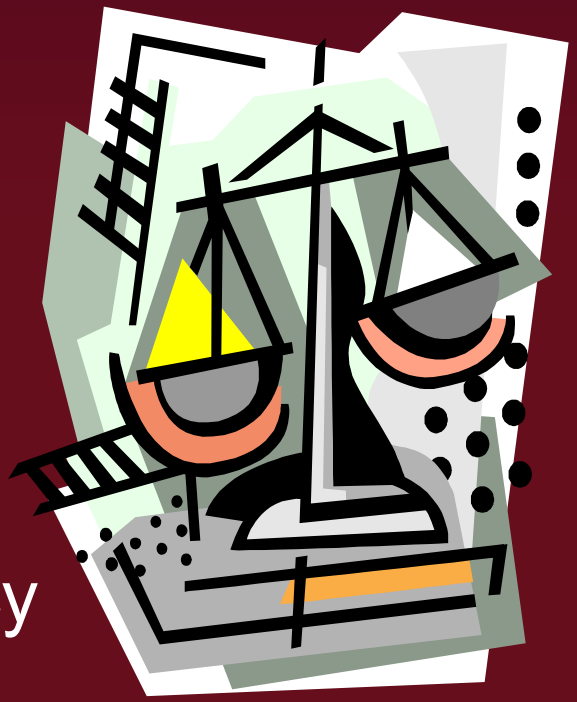


Andersson K. Lancet Neurol 2004; 3: 46-53

Ideal Muscarinic Receptor Antagonist

- Efficacious
  - **inhibits involuntary bladder contractions**
  - **does not adversely affect volitional detrusor activity**
- Organ selective
  - **preferentially affects the bladder over other organs**
  - **results in minimal side effects and improved tolerability**
- Durable effects
  - **improves compliance and/or persistency**
- Provides clinical effectiveness
  - **the optimal balance of efficacy, tolerability, and compliance/persistency**

Anticholinergics
A Delicate Balance

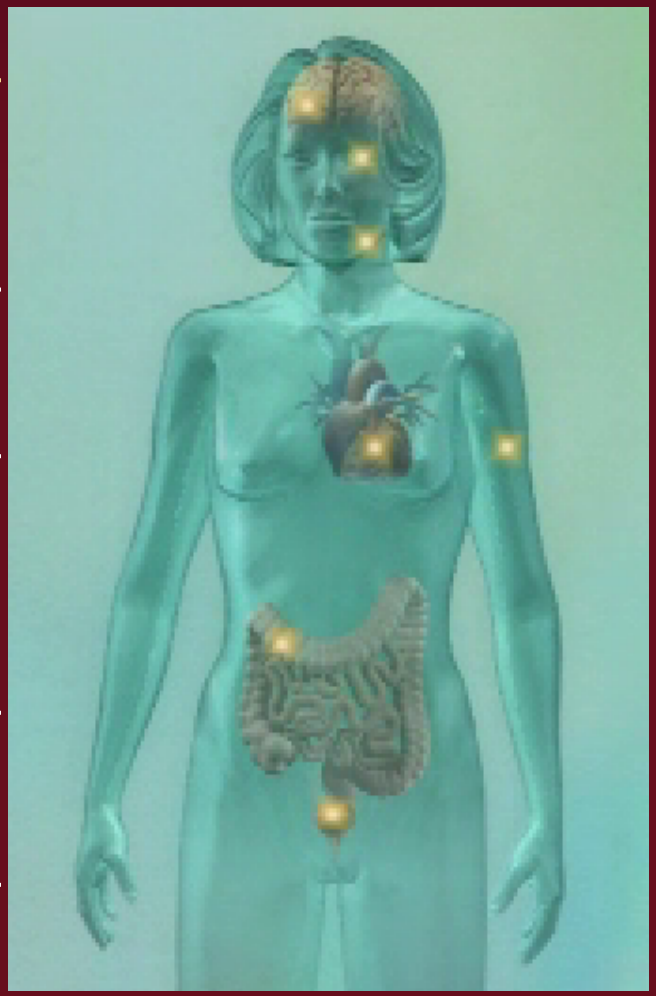


Efficacy
- Less frequency
- Less UUI
- Increased voided volume

Adverse effects
- Dry mouth
- Constipation
- CNS

Distribution and function of muscarinic receptors

	Distribution	Function
M1	Cortex, hypocampus, secretory organs, sympatic ganglia	Cognitive functions, memory, secretion of saliva etc.
M2	Heart	Heart frequency, pyloric tone
M3	Smooth muscles of secretory organs, eyes, bronchi	Detrusor contractions, bowel motility, lacrimal secretion, visual accomodation, bronchoconstriction
M4	Basal cortex, striatum, secretory organs	Unknown
M5	Substantia nigra, ciliar muscles	Unknown



Potential Side Effects of Antimuscarinic Drugs

CNS

Somnolence

Impaired Cognition

Iris/Ciliary Body = Blurred Vision

Lacrimal Gland = Dry Eyes

Salivary Glands = Dry Mouth

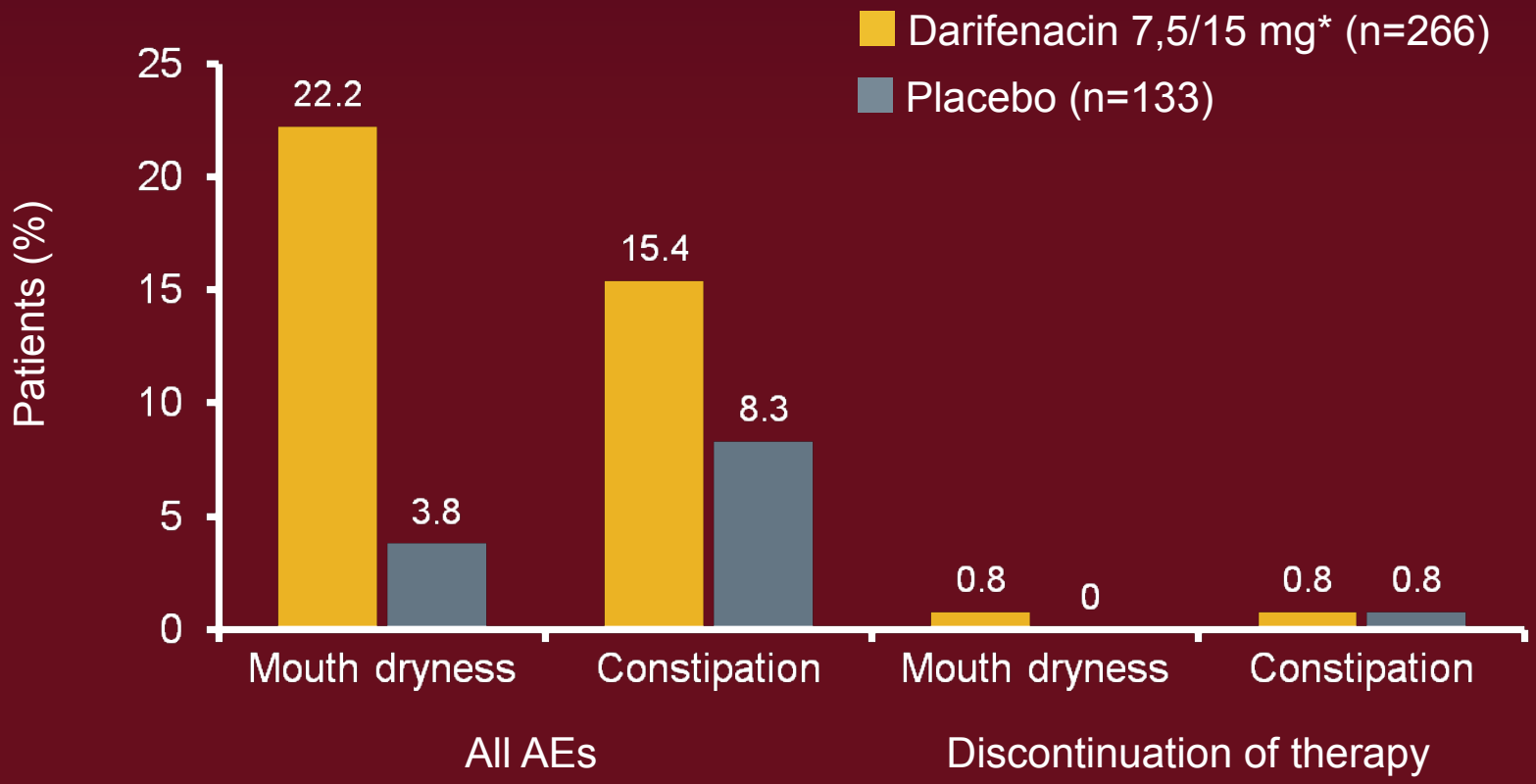
Heart = Tachycardia

Stomach = GERD

on = Constipation

Bladder = Retention

Patients older ≥65 yrs – adverse events (12 weeks)



Chapple C. et al. Curr Med Res Opin 2007;23:2347–58

Almost 47% patients with OAB have concomitant CVD

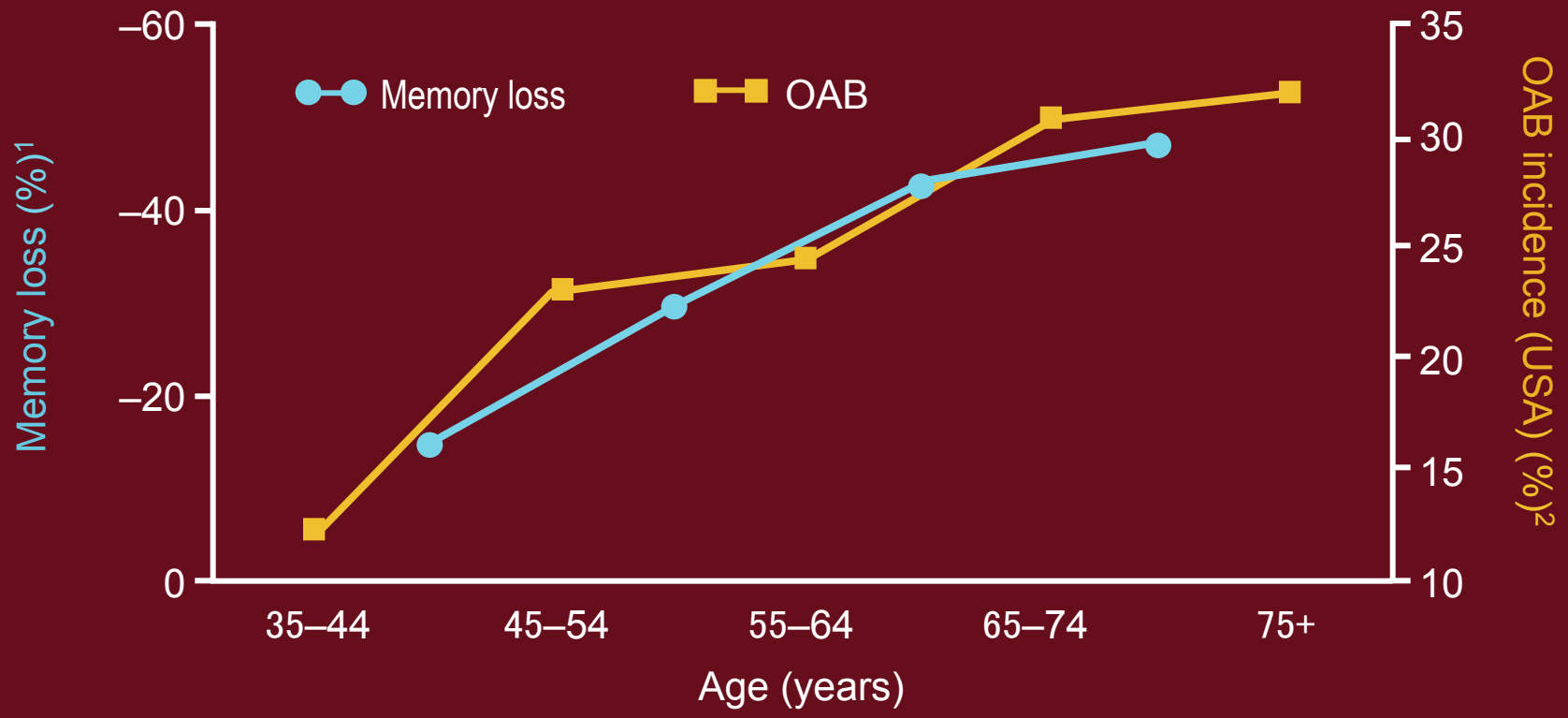
- Incidence of OAB and CVD increased with age[1,2]
- Numerous patients with OAB have CVD
  - Retrospective analysis on 78.291 patients who started treatment with antimuscarinics, shown that 47% of OAB patients have concomitant CVD[3]
  - Study on 16833 patients included in database GE Healthcare -38,8% patients with OAB have accelerated pulse (≥80 heart beats/min)[4]
- In those patients the risk of CV accidents can be increased[5]
- Introduction of antimuscarinics – take care of CV risks[5]

  - **Due to M_2 receptors blockage some antimuscarinics could accelerate puls or prolong QT interval[5]**

1. Stewart WF. et al. World J Urol 2003;20:327–36
2. National Center for Health Statistics 2005
3. Andersson K-E. et al. Prikazano na ICS-u 2007. (Abstract 40)
4. Andersson K-E. et al.Prikazano na ICS-u 2007. (Abstract 41)
5. Andersson K-E. Olshansky B. BJU Int 2007;100:1007–14

Women with OAB could have related CNS diseases

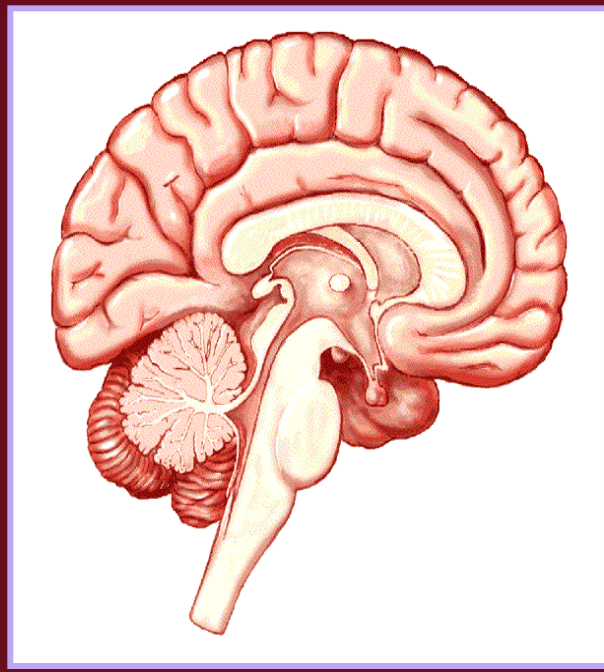
(OAB incidence and cognitive dysfunction increased with age [1,2])



1. Crook TH. et al. Dev Neuropsychol 1993;9:103–13
2. Stewart WF. et al. World J Urol 2003;20:327–36

The degree of cognitive risk with antimuscarinics

- the differences in receptor binding profiles
- the extent to which they cross the blood-brain barrier (BBB)
- the lipid solubility of the molecule
- the degree of ionization
- the permeability of the BBB (ageing?)
- age-related changes in neurotransmission brought about by changes in the number of receptor sites



Anticholinergic load of other drugs

- ACE inhibitors
- tricyclic antidepressants
- bronchodilatators
- ranitidine
- antipsychotics

Mean binding affinities (pKi) of antimuscarinic drugs for M1 and M3 receptors

Antimuscarinic	pKi for M_1 receptors	pKi for M_3 receptors
Oxybutynin (42)	9.9	12.3
Desethyloxybutynin* (42)	6.0	5.5
Darifenacin (43)	8.2	9.1
Solifenacin (44)	7.6	8.0
Tolterodine (45)	8.5	7.9
Fesoterodine (45)	6.2	< 6
5-HMT† (45)	8.7	8.2
Trospium (43)	9.1	9.3
Propiverine (43)	6.6	6.4

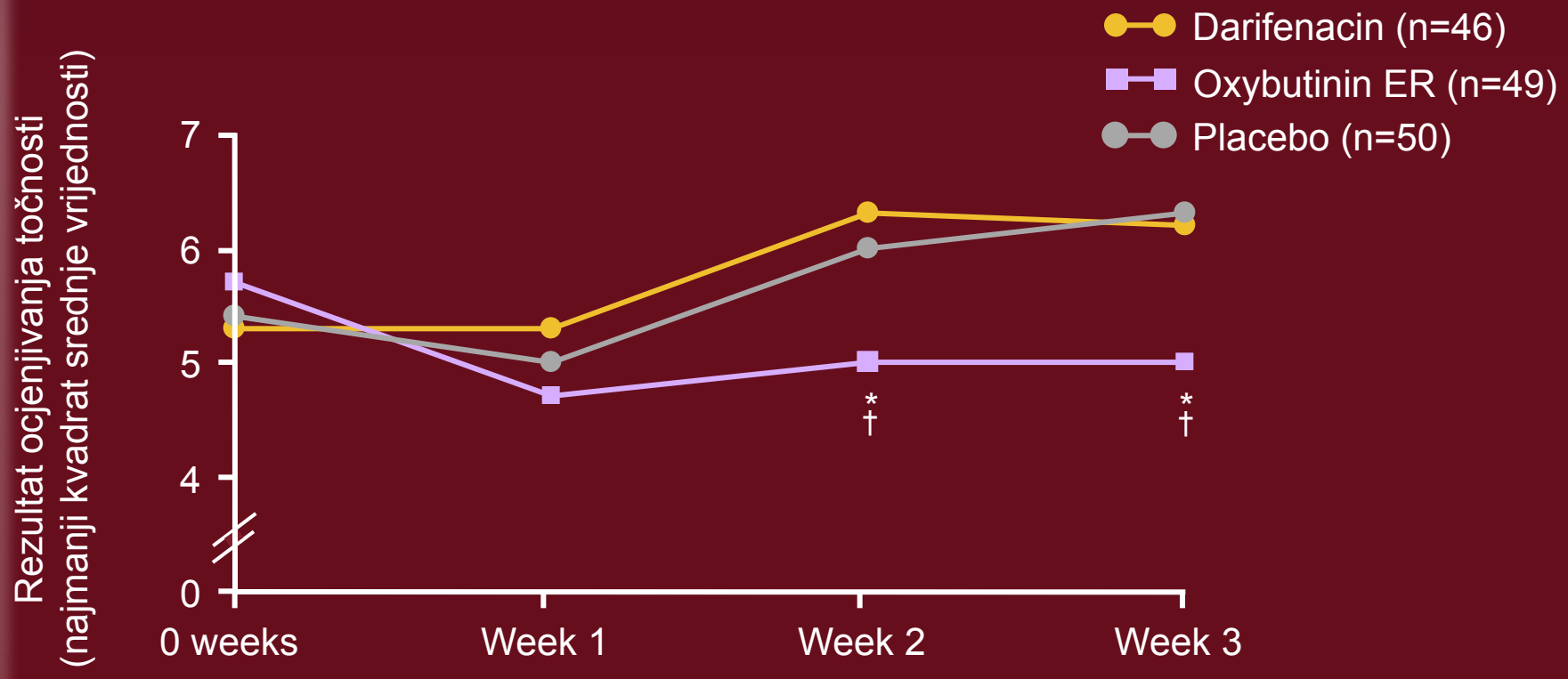
Molecular weight of antimuscarinics

Table 1 Pharmacokinetic characteristics of commonly used antimuscarinics for treatment of OAB. Data from ref. (38–41)

Antimuscarinic	Chemical structure (type of amine)	Molecular weight of the base compound (kDa) (the MW of the conjugated salt is given in parenthesis)	Lipophilicity
Oxybutynin	Tertiary	357.5 (chloride: 393.9)	High
Darifenacin	Tertiary	426.6 (hydrobromide: 507.5)	Moderate
Solifenacin	Tertiary	362.5 (succinate: 480.6)	Low-moderate
Tolterodine*	Tertiary	325.5 (tartrate: 475.6)	Low-moderate
Fesoterodine*	Tertiary	411.6 (fumarate: 527.7)	Low-moderate
5-Hydroxymethyl tolterodine*	Tertiary	341.49 (not applicable)	Low-moderate
Trospium	Quaternary	392.1 (chloride: 428.0)	Very low (hydrophilic)

*Fesoterodine and tolterodine are both rapidly hydrolysed to an active metabolite, 5-hydroxymethyl tolterodine (5-HMT).
OAB, overactive bladder.

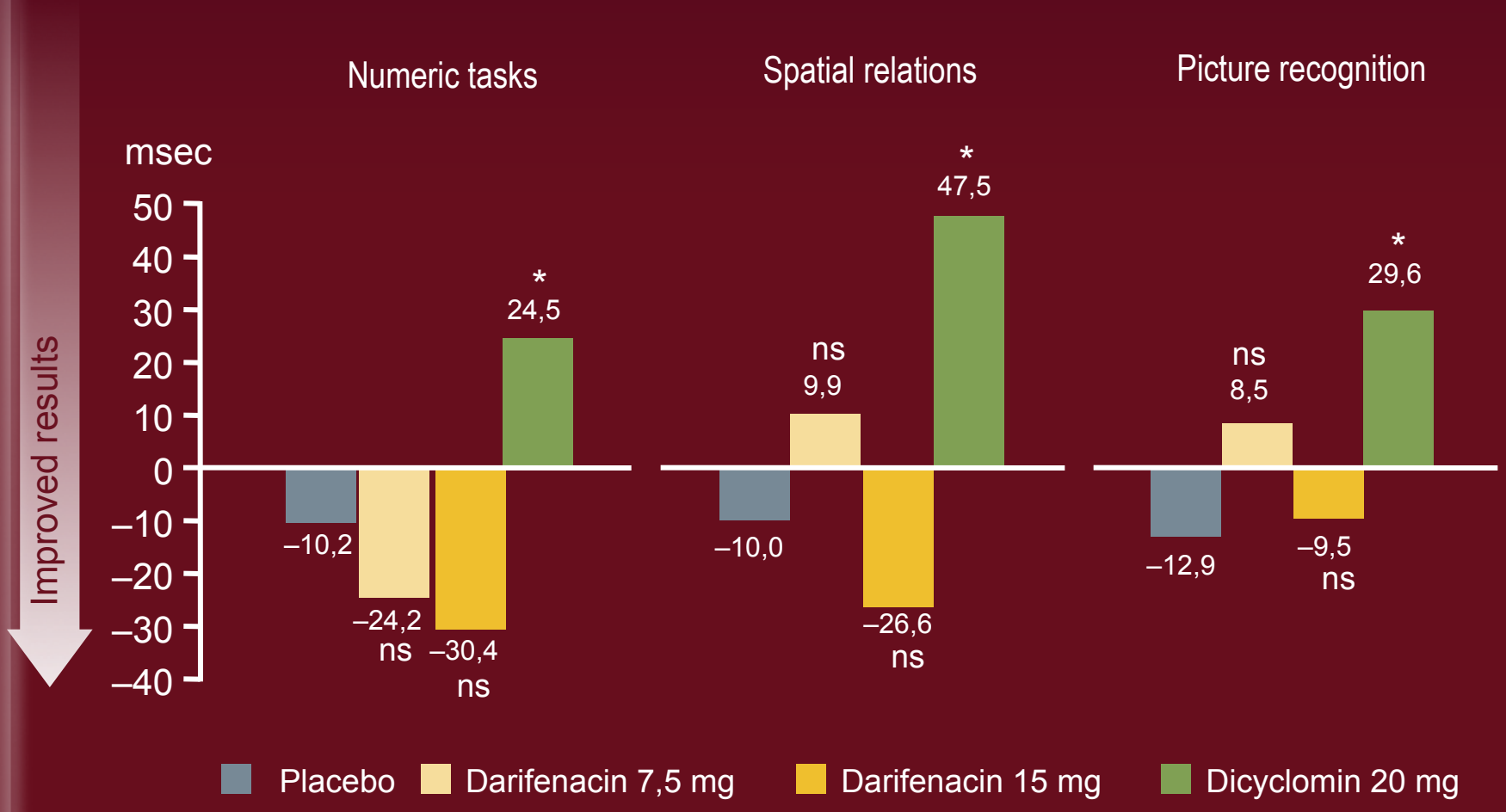
In comparison to oxybuthinin, darifenacin has no influence on memory processes



*p<0,05 Vs placebo; †p<0,05 Vs darifenacin

Kay G. et al. Eur Urol 2006;50:317–26

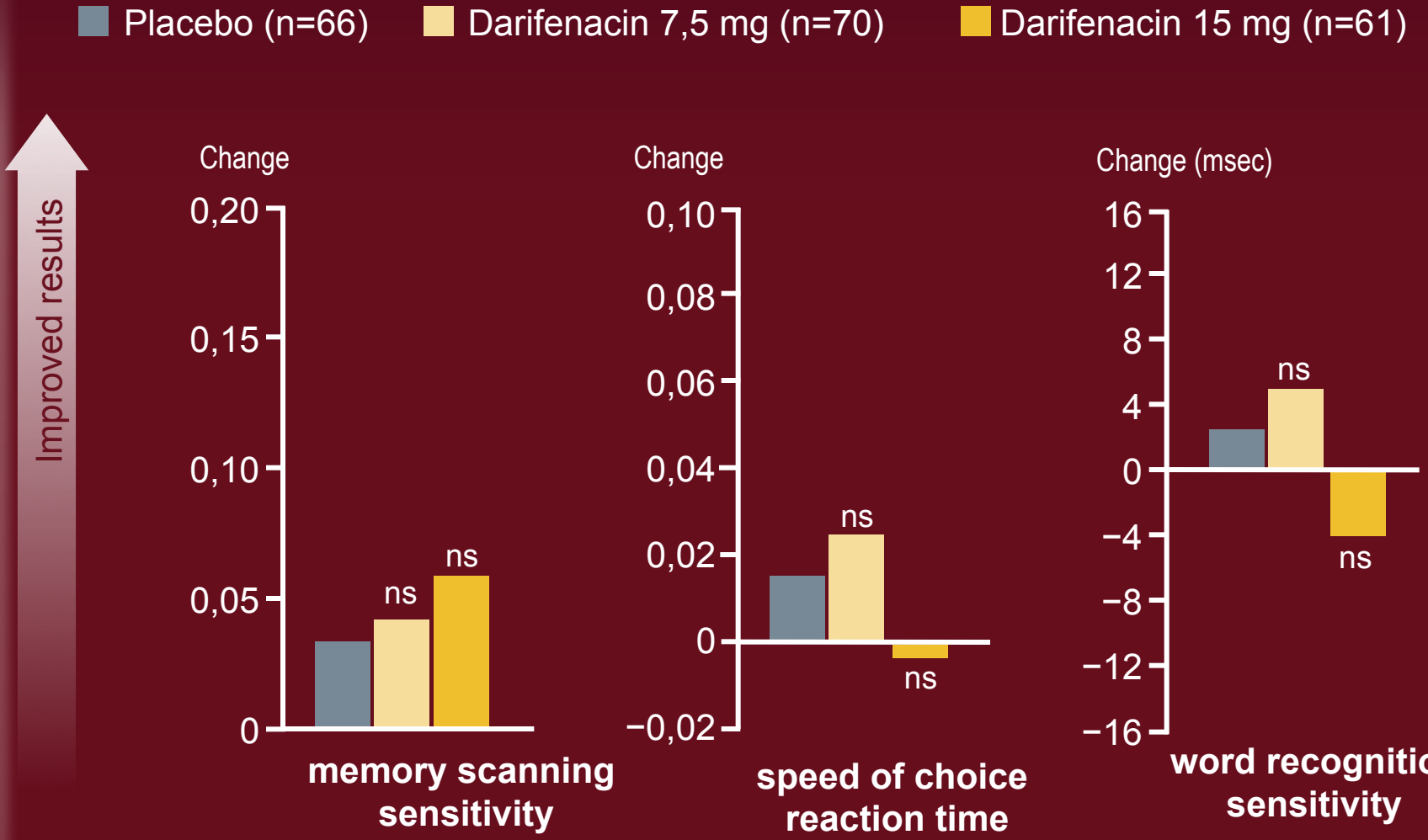
Selective M3 antimuscarinics - no influence on memory process (Age 28 yrs)



ns = *not statistically significant*, *p<0,05 Vs placebo

Kay G. et al. BJU Int 2005;96:1055–62

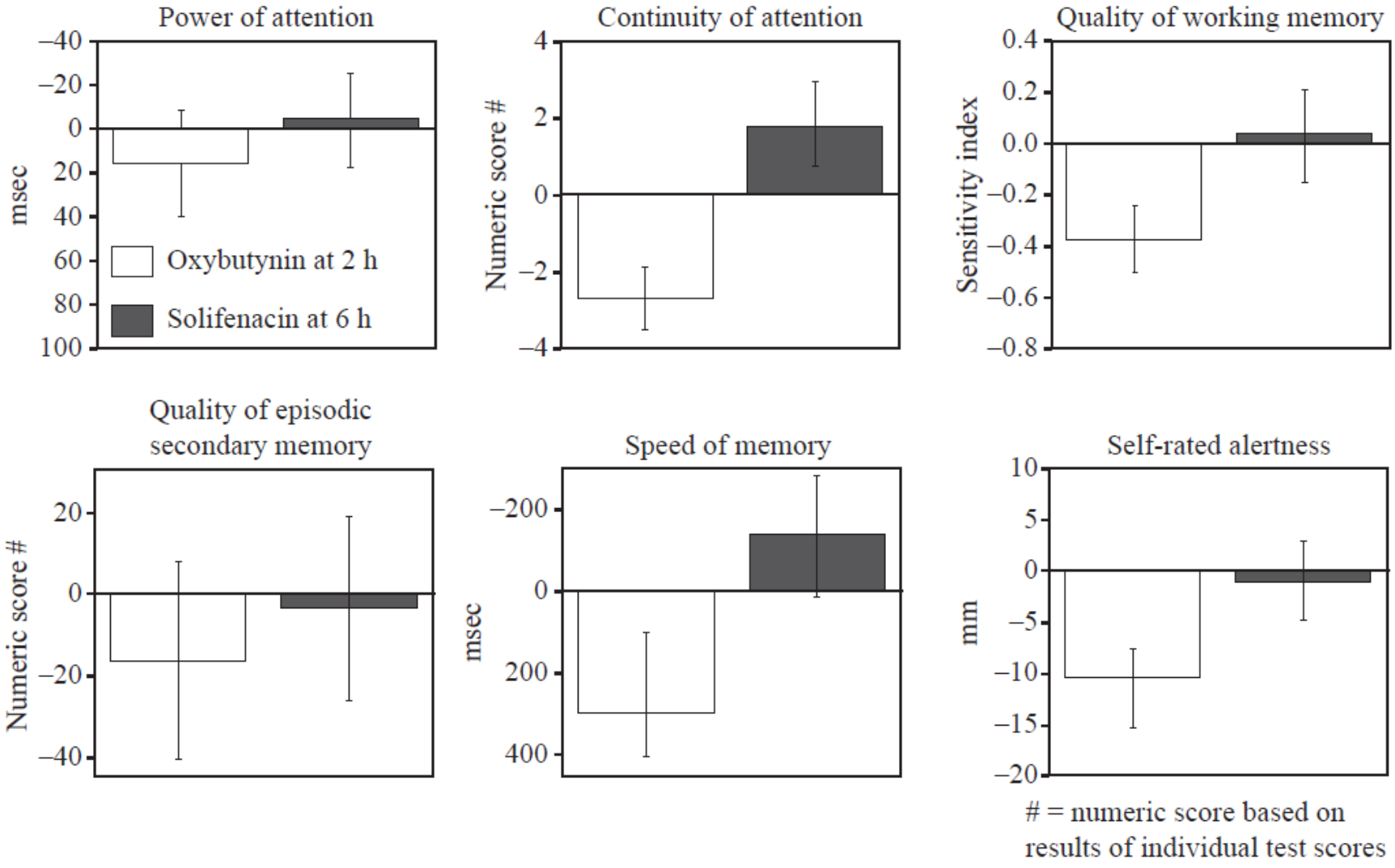
Selective M3 antimuscarinics – no influence on cognitive function (Age >65 yrs)



ns = non significant; SI = standard SI units

Lipton RB. et al. J Urol 2005;173:493–8

Solifenacin Vs Oxybutynin



Effect of Fesoterodine in Vulnerable Elderly Subjects with Urgency Incontinence: A Double-Blind, Placebo Controlled Trial

Catherine E. DuBeau,*,† Stephen R. Kraus,‡ Tomas L. Griebling,§
Diane K. Newman,‖ Jean F. Wyman,¶ Theodore M. Johnson, 2nd,**
Joseph G. Ouslander,†† Franklin Sun,‡‡ Jason Gong‡‡ and Tamara Bavendam‡‡

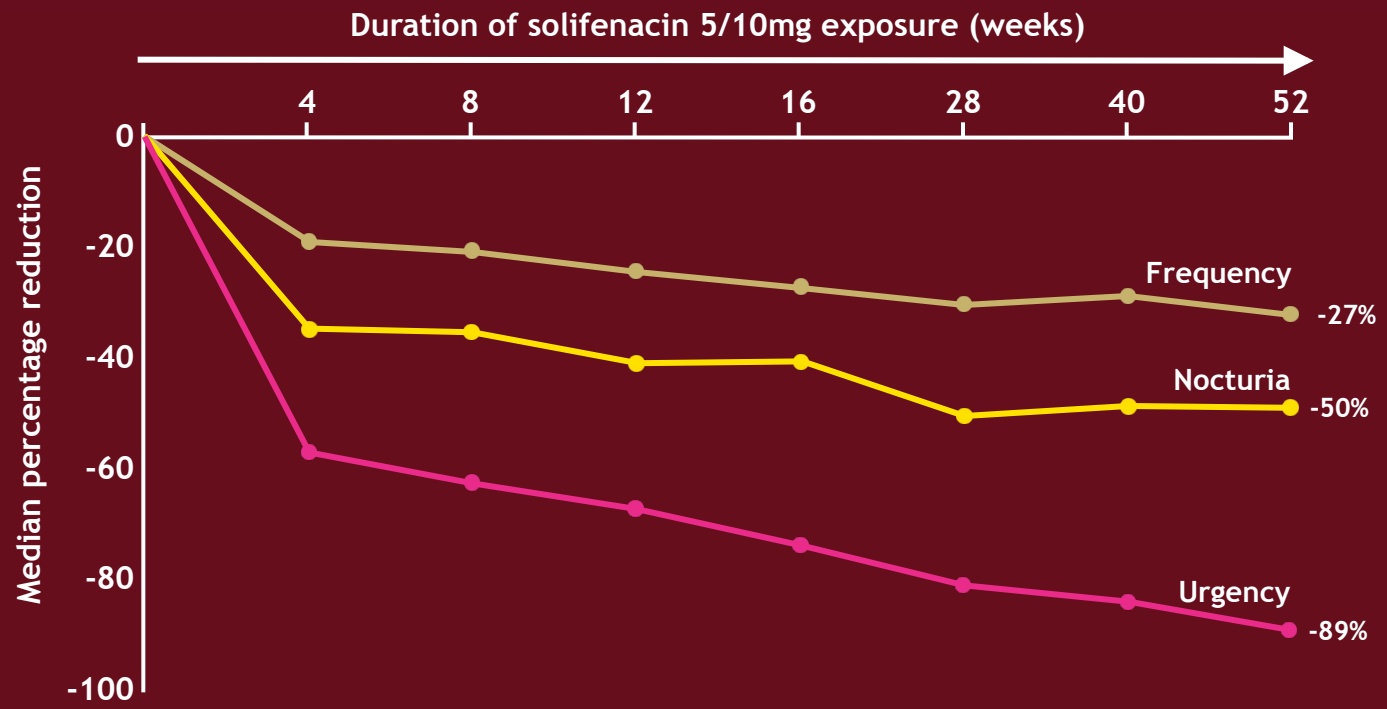
From the University of Massachusetts Medical School and UMass Memorial Medical Center, Worcester, Massachusetts (CED), University of Texas Health Science Center at San Antonio, San Antonio, Texas (SRK), University of Kansas, Kansas City, Kansas (TLG), University of Pennsylvania, Philadelphia, Pennsylvania (DKN), University of Minnesota, Minneapolis, Minnesota (JFW), Atlanta VA Medical Center and Emory University, Atlanta, Georgia (TMJ), Florida Atlantic University, Boca Raton, Florida (JGO), and Pfizer Inc, New York, New York (FS, JG, TB)

Table 4. *Exploratory analyses of risk difference of treatment emergent AEs*

	No. Placebo (%)	No. Fesoterodine (%)	RD (95% CI)	p Value
AEs of special interest:				
Palpitations	2 (0.7)	0	−0.007 (−0.053, 0.026)	0.776
Peripheral edema	6 (2.1)	6 (2.1)	0.000 (−0.057, 0.045)	1.000
Increased residual urine vol	0	1 (0.4)	0.004 (−0.029, 0.049)	0.924
Memory impairment	0	2 (0.7)	0.007 (−0.026, 0.053)	0.776
Somnolence	2 (0.7)	0	−0.007 (−0.053, 0.026)	0.776
Confusional state	0	1 (0.4)	0.004 (−0.029, 0.049)	0.924
Urinary retention	0	9 (3.2)	0.032 (−0.006, 0.081)	0.108
Dysuria	3 (1.1)	4 (1.4)	0.004 (−0.037, 0.056)	0.937
Pruritus	0	2 (0.7)	0.007 (−0.026, 0.053)	0.776
Urticaria	0	1 (0.4)	0.004 (−0.029, 0.049)	0.924

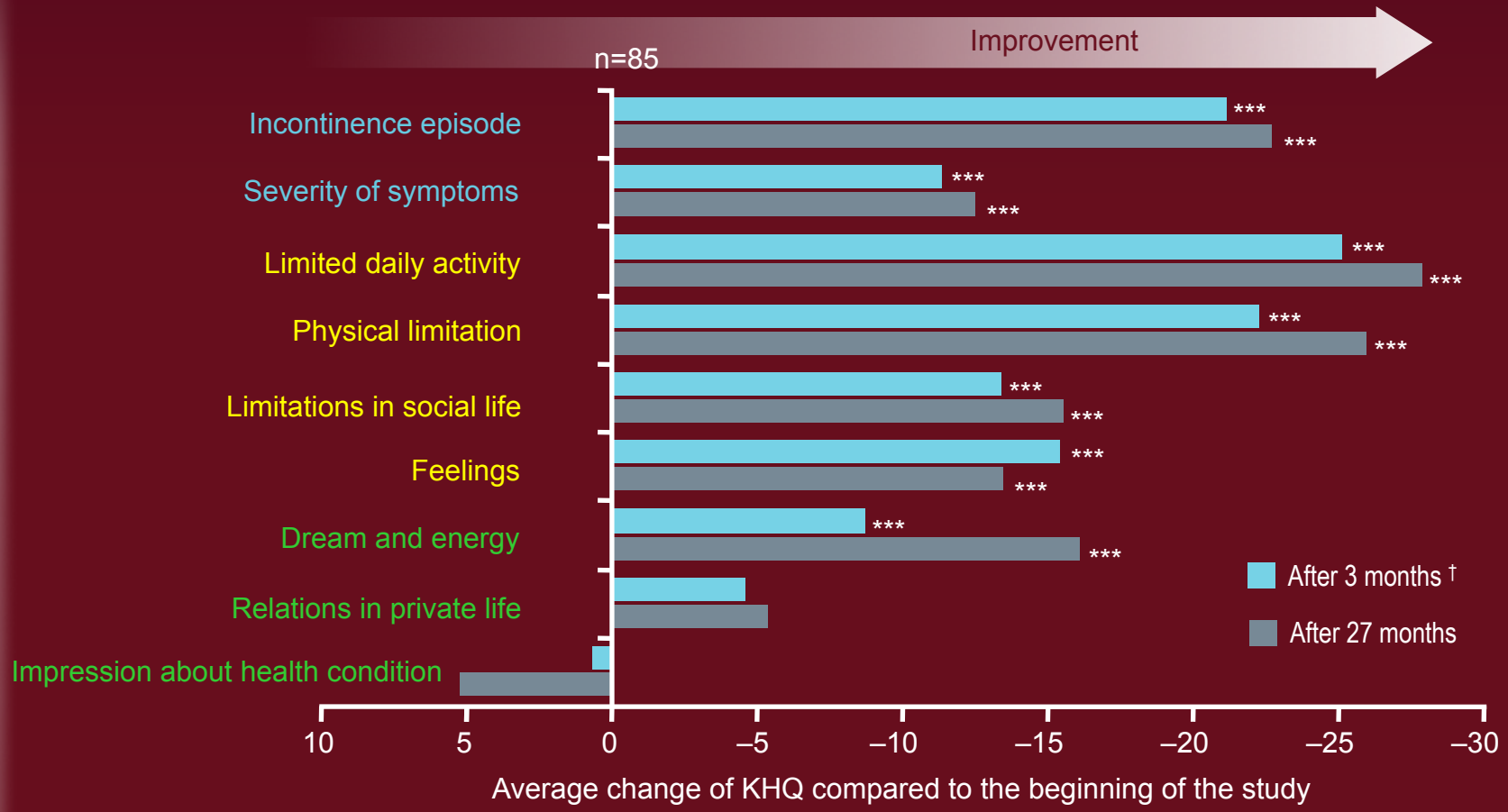
Antimuscarinic drug therapy improves OAB symptoms

- 40-week open-label extension trial with patients completing treatment in the two previous randomised, double-blind, 12-week studies



Adapted from: Haab F, *et al*. *Eur Urol*. 2005;47:376-384

High HRQoL* in patients older ≥65 years with long-term treatment with M3 antagonists



*KHQ = King's Health Questionnaire
***p<0,001

Dwyer P. et al.
Neurourol Urodyn 2008;27:540–7

Take Home Messages

- Voiding dysfunction (OAB) can significantly affect quality of life in the elderly but is not an inevitable part of ageing
- Careful consideration of comorbidities, effects of medications, drug interaction, altered pharmacokynetics of drugs
- Conservative measures should be considered before pharmacotherapy and invasive tests
- Advantage of M3 antagonists in older patients due to no influence on cognitive function or adverse events on CNS or CVD
- New class with innovative mode of action (Mirabegron?)

Hvala na pažnji !