

# Treatment of OAB in postmenopause

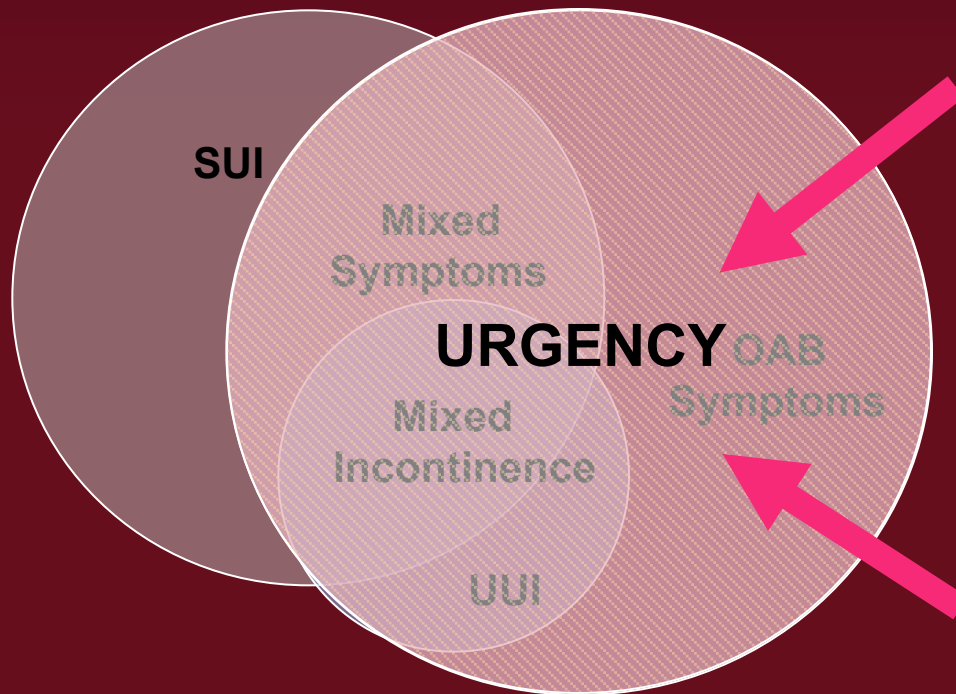
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# Spectrum of overactive bladder

*'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”<sup>2</sup>

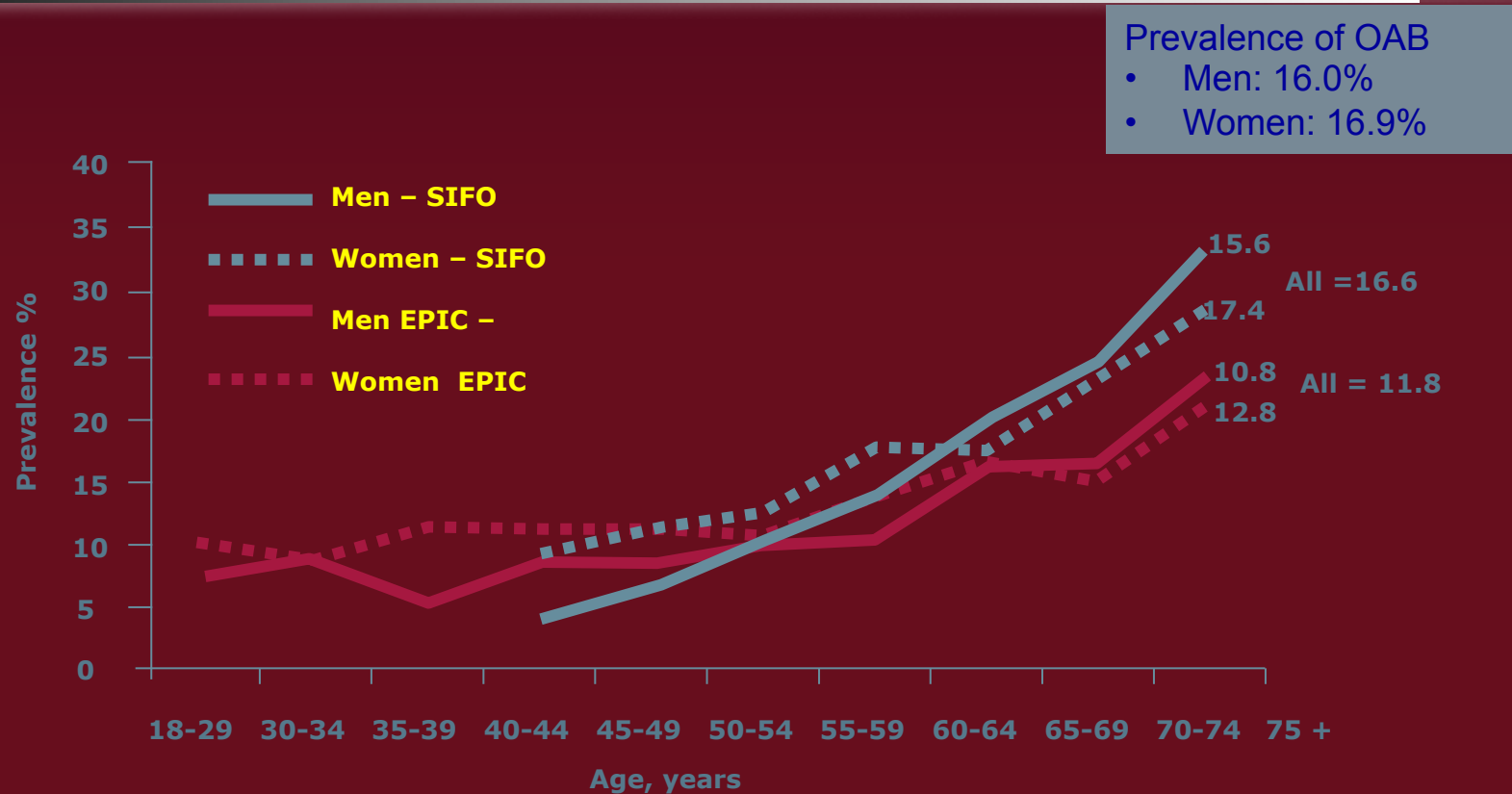
**Urgency:** “the only symptom a patient *must* have to be described as having OAB”<sup>1</sup>

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<sup>1,2</sup>



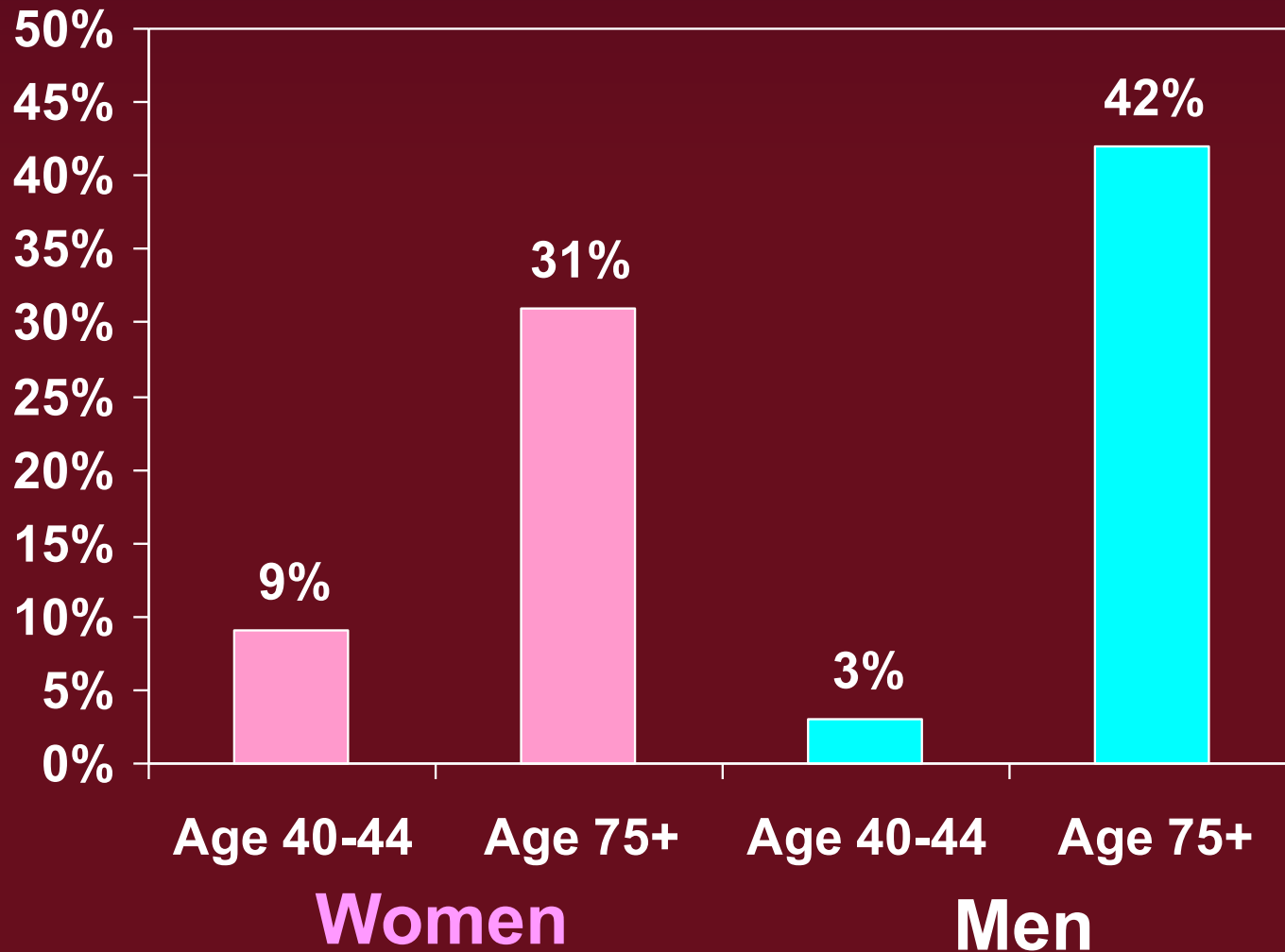
SIFO conducted in 6 European countries (n=16,776)

EPIC conducted in 4 European countries and Canada (n=19,165)

1. Milsom I, et al. *BJU Int* 2001; 87: 760-766.

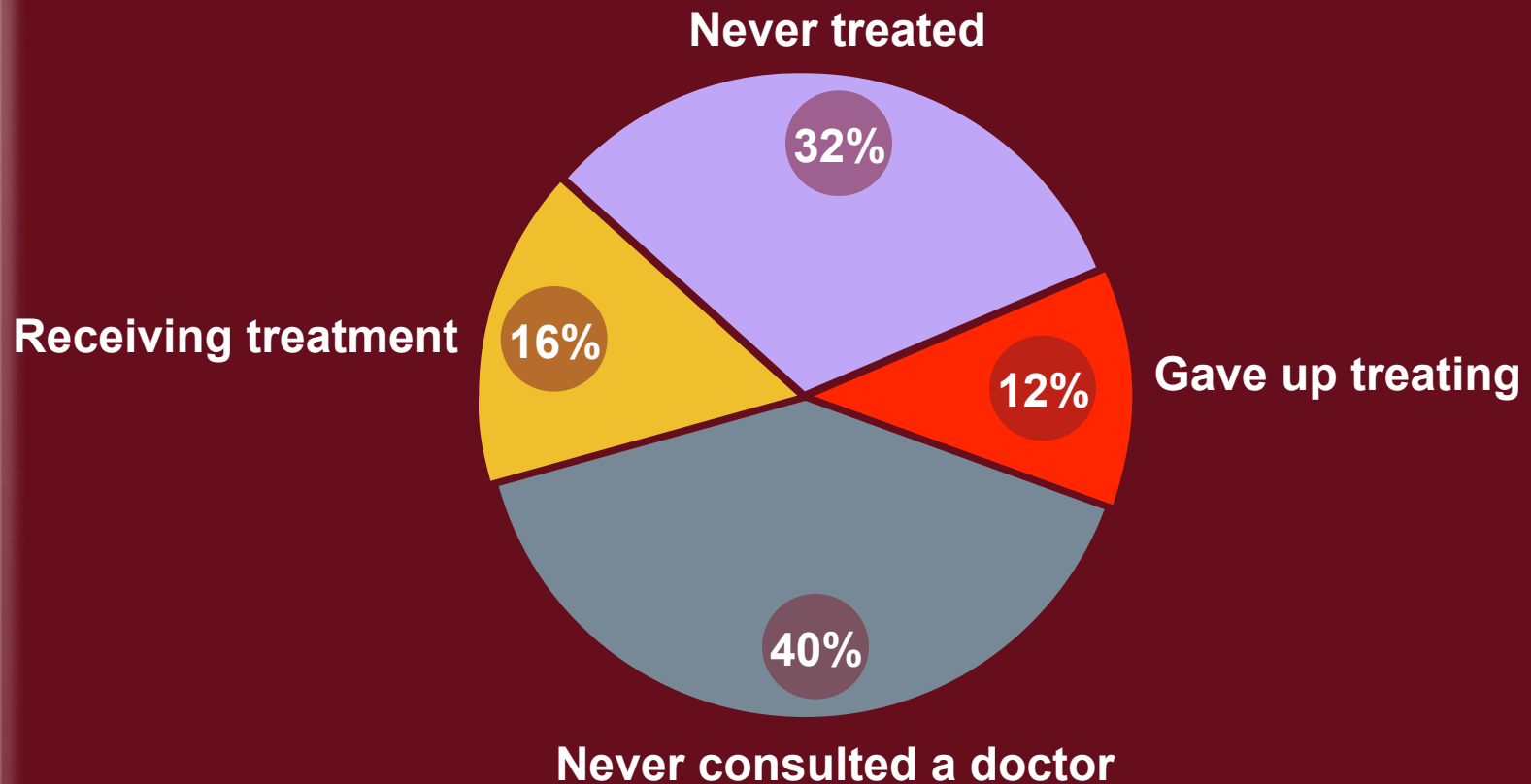
2. Milsom I, Irwin DE. *Eur Urol Suppl* 2007; 6: 4-9.

# Overactive Bladder Prevalence



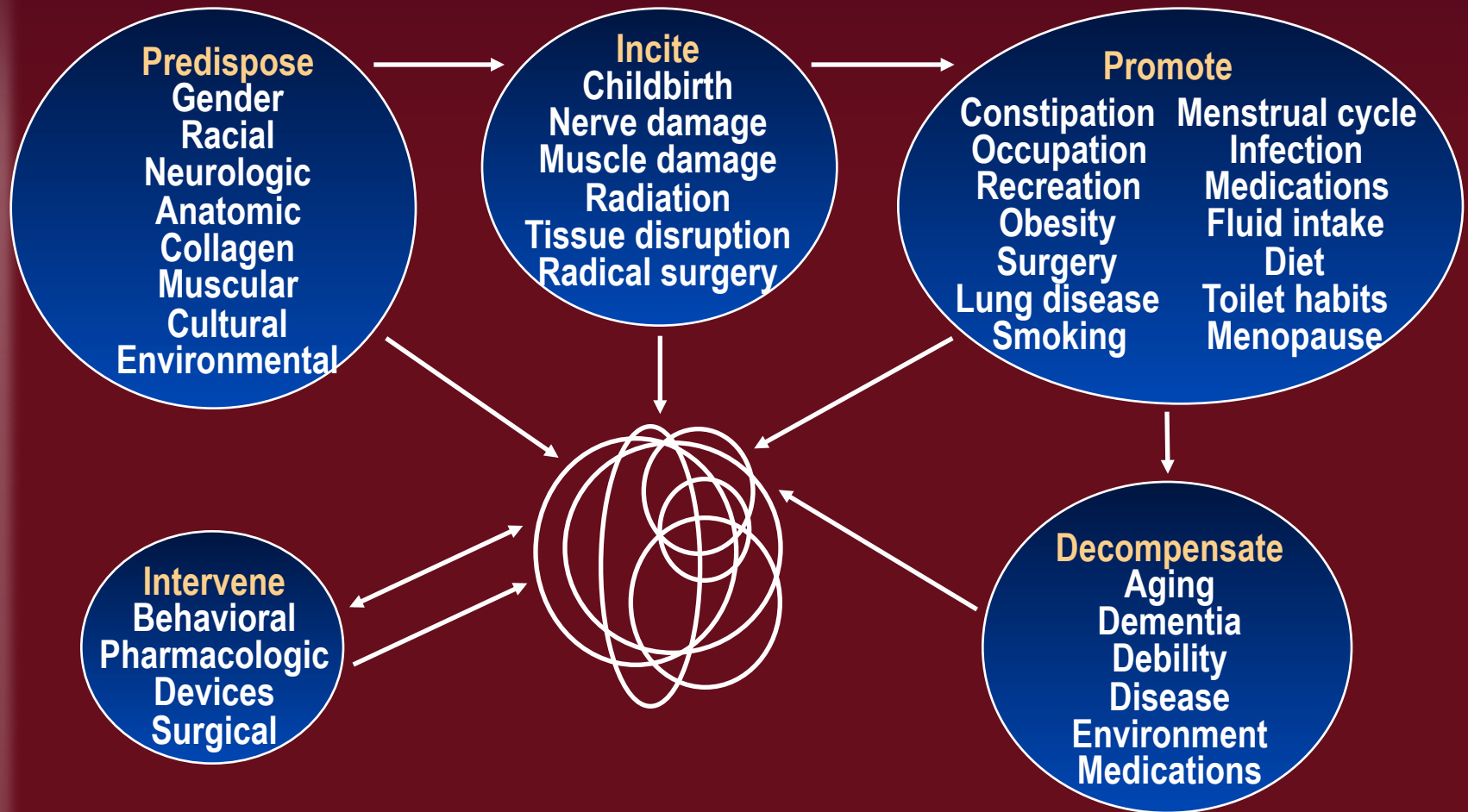
# Overactive bladder

N=1916



# 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<sup>1</sup>
- Symptoms can affect family, social and work life, as well as mental and physical wellbeing<sup>2</sup>
- **Emotional impact can include**
  - Reduced social and physical activities<sup>2,3</sup>
  - Embarrassment, shame, frustration and anxiety<sup>2,3</sup>
  - Seclusion, isolation and psychological stress<sup>3</sup>
  - Feeling ugly and undesirable<sup>3</sup>
  - 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<sup>2</sup>
  - Falls and fractures<sup>2</sup>
  - Urinary tract and skin infections<sup>2</sup>
  - Several common chronic conditions, such as depression, constipation, neurological conditions, and erectile dysfunction, have also been associated with OAB.<sup>4</sup>

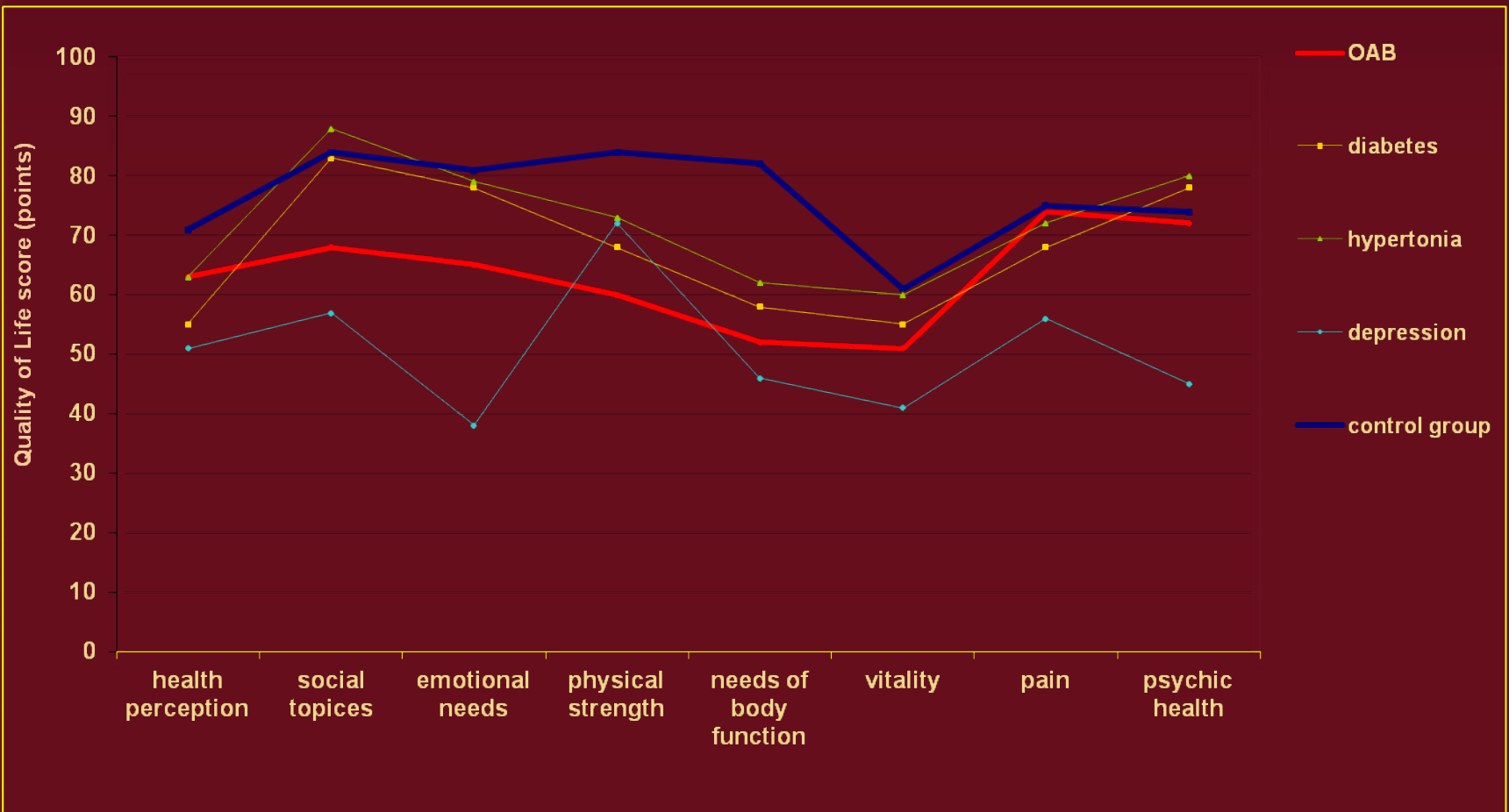
1. Milsom I. et al. *BJU Int* 2001; 87(9): 760-766

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



# **Elderly patients - specificities**

# Comorbidities – “DIPPERSA”

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

# Bladder's volume operating range

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

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**Measure total urine production per day!**

# Cognitive status

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- Urinary control represents in many ways a failure of integrative brain processes

# Life with OAB

- Women (older than 50 yrs), incontinent or continent, with urgency<sup>1</sup>
- Comorbidity related to aging and lifestyle including:
  - Impaired cognitive functions<sup>2</sup>
  - CV symptoms<sup>3</sup>
- concomitant use of different drugs<sup>4</sup>
  - **31,6% of patients taking 6 or more drugs with prescription<sup>4</sup>**



1. Irwin DE. et al. *Eur Urol* 2008;53:1029–39
2. Crook TH. et al. *Dev Neuropsychol* 1993;9:103–13
3. Andersson K-E. et al. *Prezentirano na ICS-u 2007. (sažetak 40)*
4. Sharkey JR. et al. *Pharmacoepidemiol Drug Saf* 2005;14:715-23

# UI / OAB treatment

## “Step by step” therapy

**Nonpharmacological**



**Pharmacotherapy**



**Electro - / ExMi stimulation**



**Sacral blockade**



**Surgical therapy**

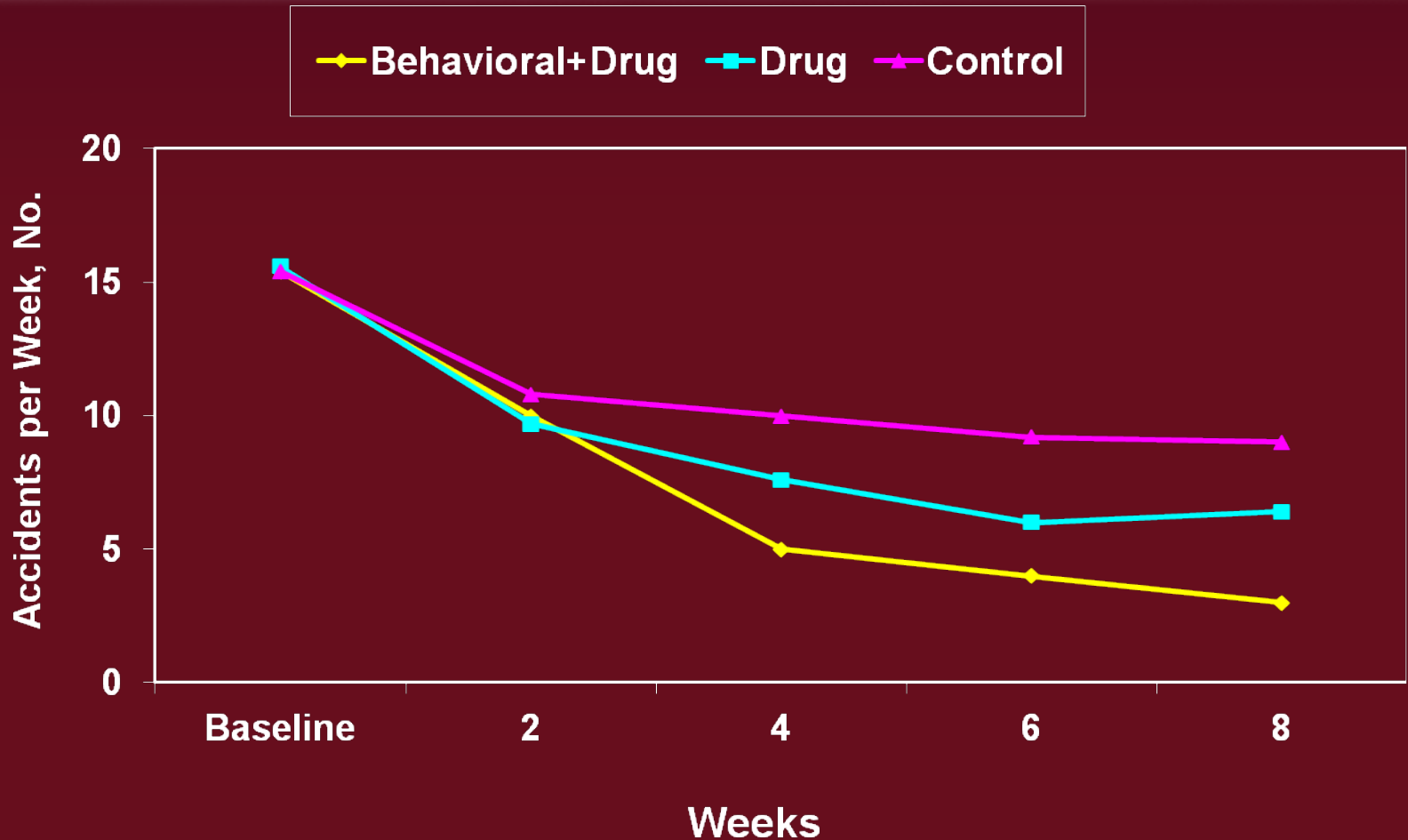


# Nonpharmacologic treatment

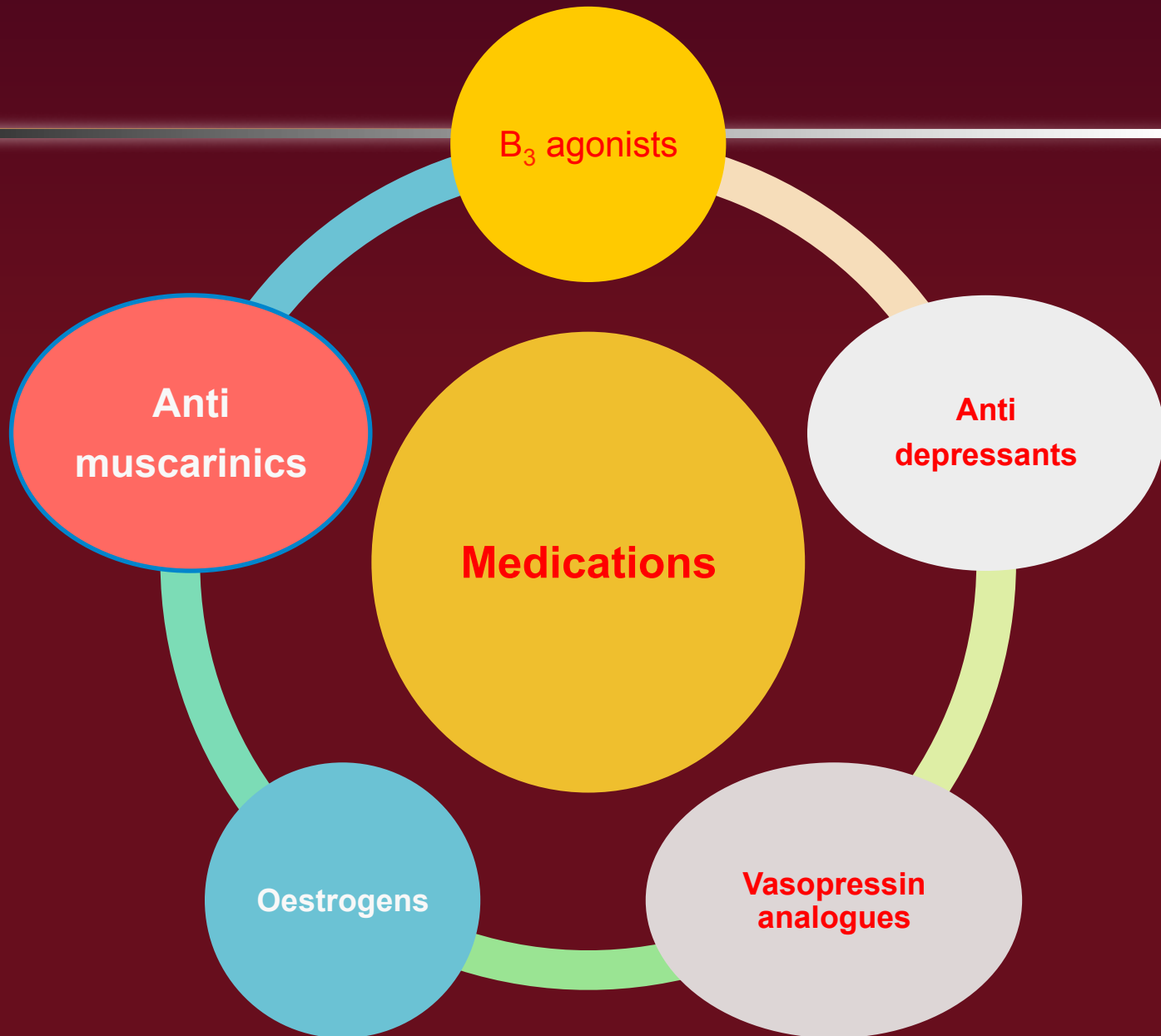
- Communication
- Diet modification
- behavior
  - bladder training
  - timed voiding
  - habit training
- training
  - PFMT
  - techniques for urge suppression
- supportive measures
  - physiotherapy, biofeedback or percutaneous tibial nerve stimulation

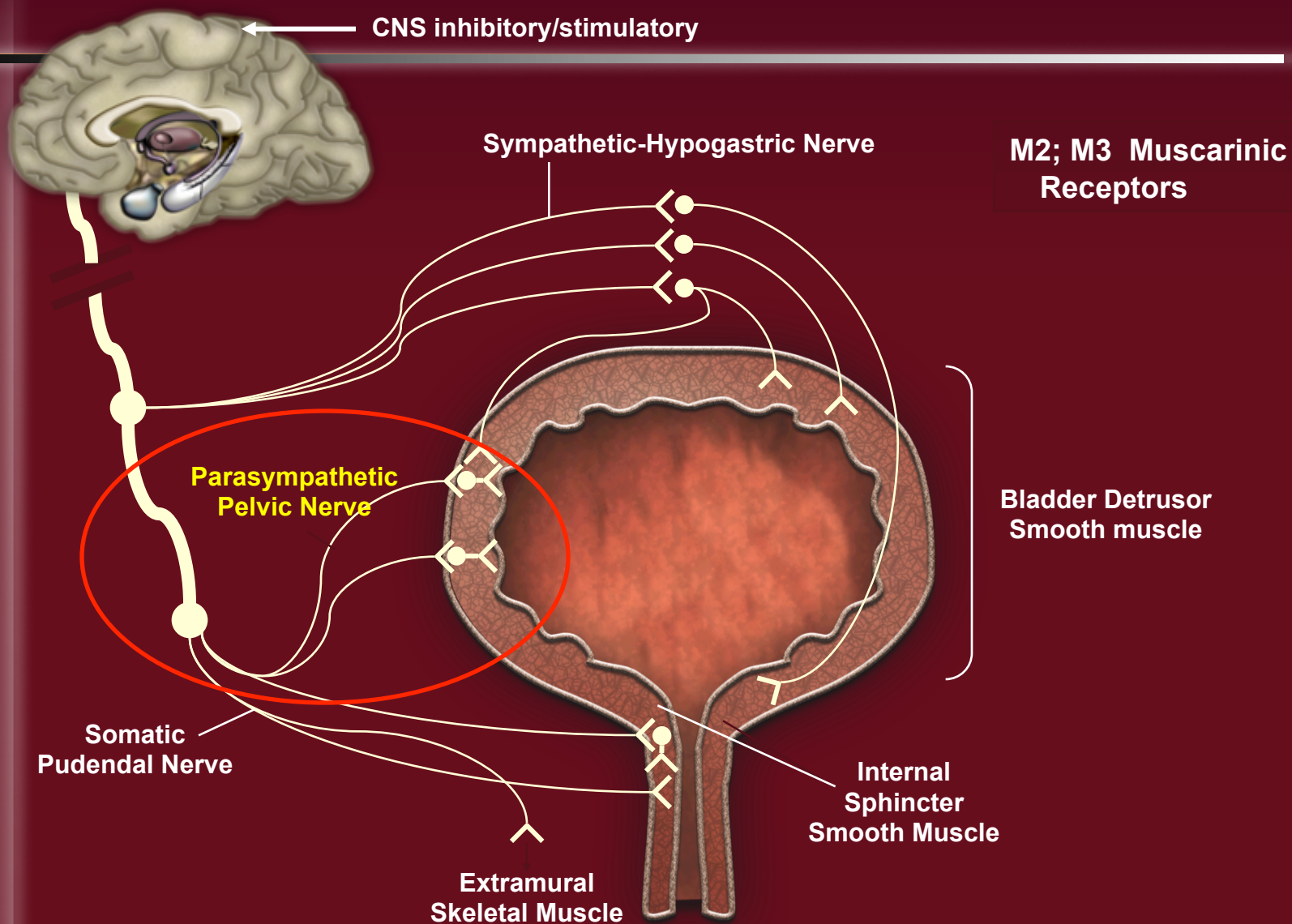


# Combined pharmacologic and behavioral therapy provides improved outcomes

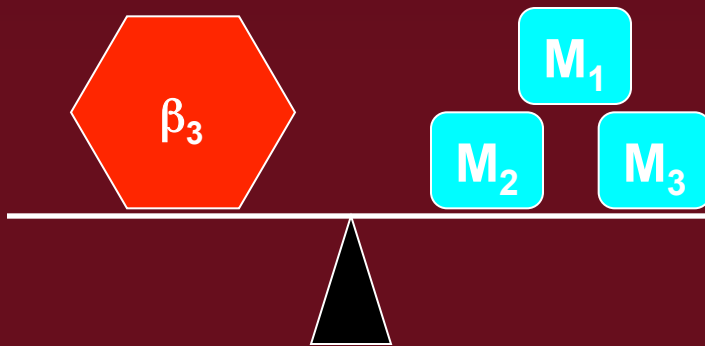


# Medications for overactive bladder

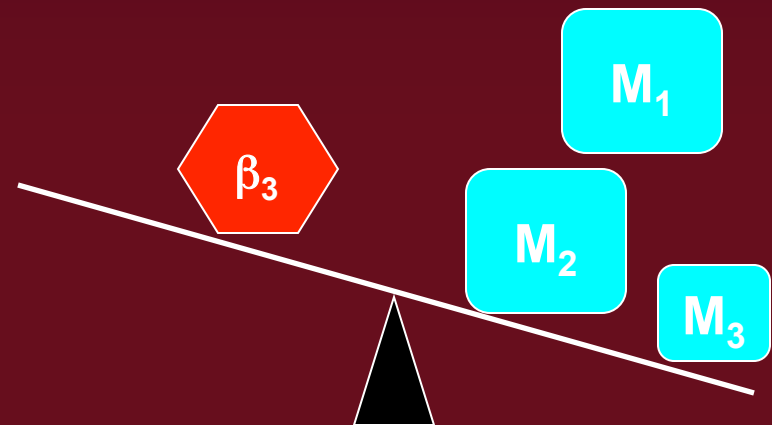




# Pharmacotherapy of OAB



**Normal bladder**



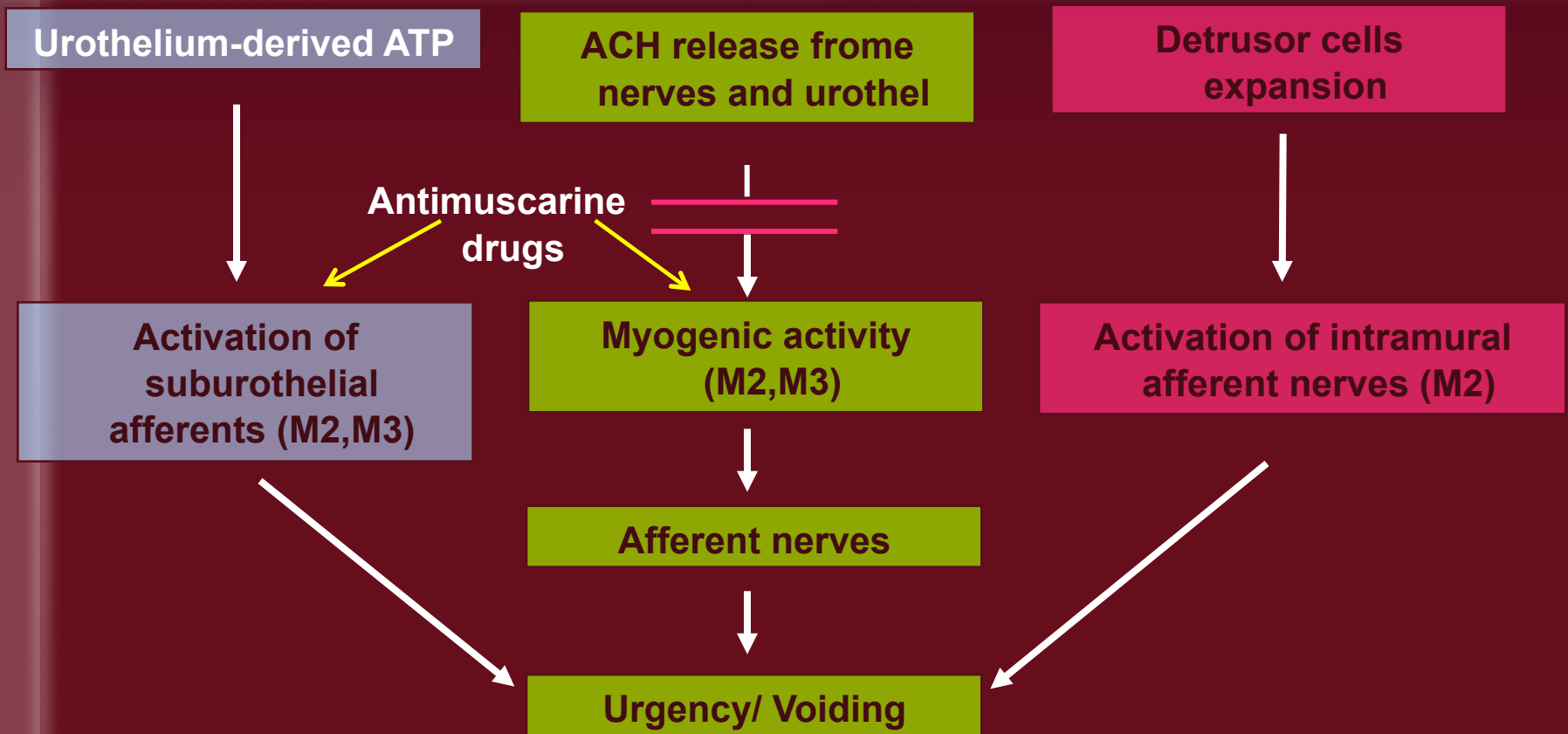
**Overactive bladder**

# Pharmacologic Therapy for the Treatment of OAB

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

# Inhibitory effect of antimuscarinics



# Ideal Muscarinic Receptor Antagonist

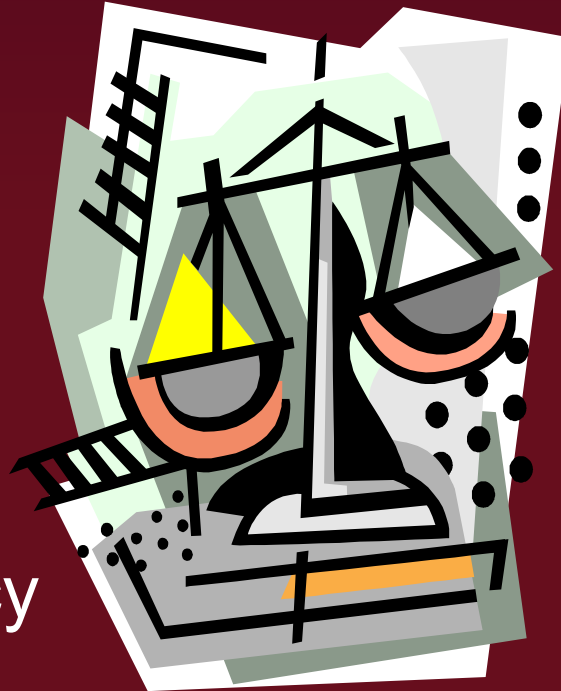
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- Efficacious
  - inhibits involuntary bladder contractions
  - does not adversely affect volitional detrusor activity
- Organ selective
  - preferentially affects the bladder over other organs
  - results in minimal side effects and improved tolerability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

# Anticholinergics

## A Delicate Balance

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### Efficacy

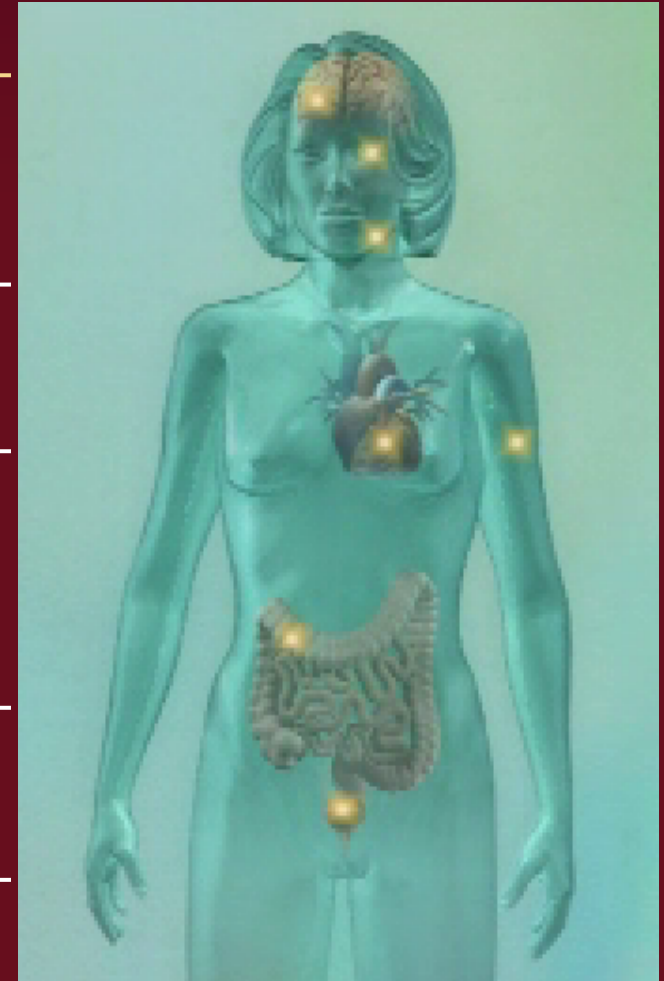
- Less frequency
- Less UUI
- Increased voided volume

### Adverse effects

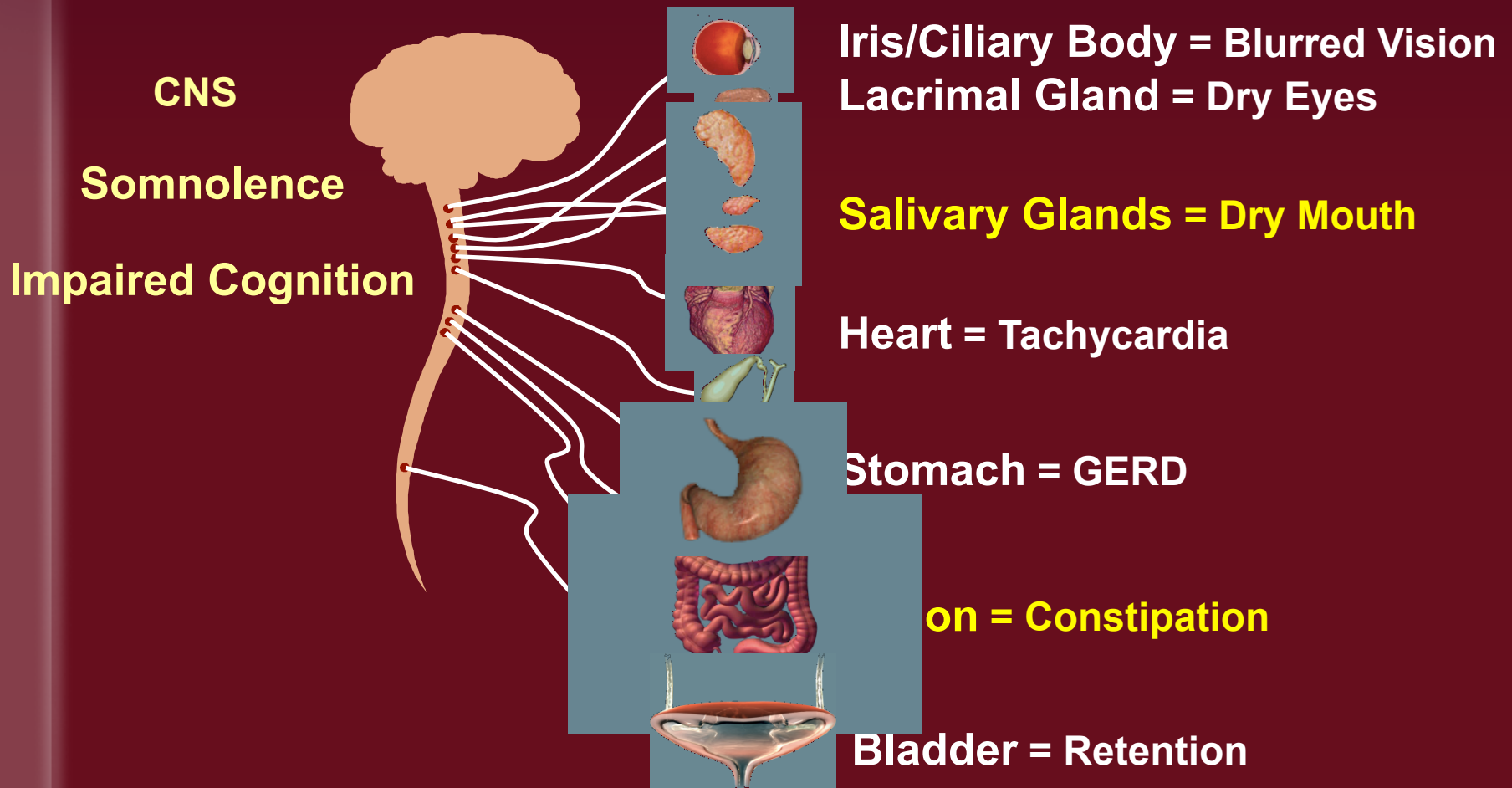
- Dry mouth
- Constipation
- CNS

# Distribution and function of muscarinic receptors

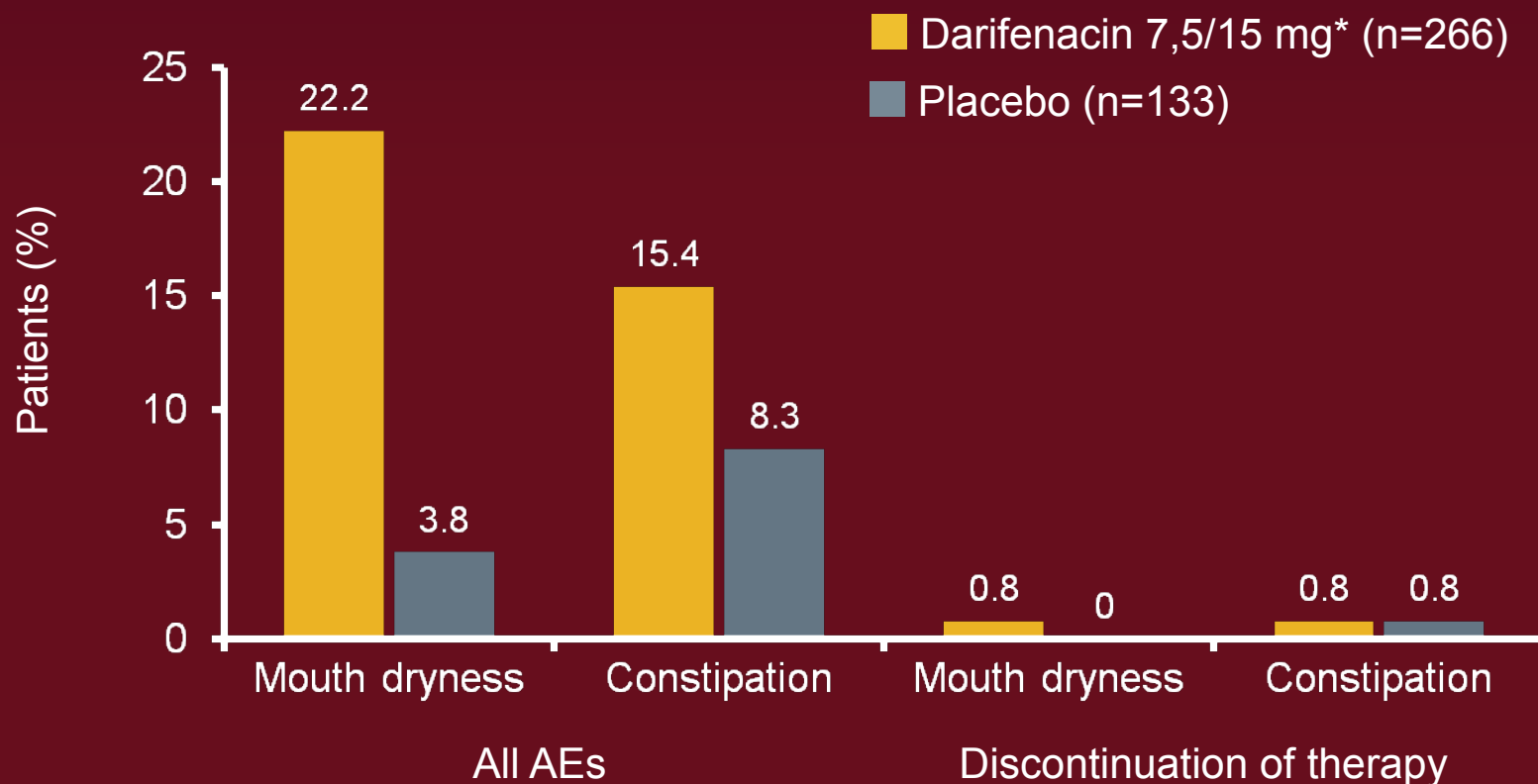
|    | Distribution   | Function  |
|----|--|---|
| M1 | Cortex, hippocampus, secretory organs, sympathetic ganglia | Cognitive functions, memory, secretion of saliva etc.   |
| M2 | Heart  | Heart frequency, pyloric tone   |
| M3 | Smooth muscles of secretory organs, eyes, bronchi          | Detrusor 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



## Patients older $\geq 65$ yrs – adverse events



# Almost 47% patients with OAB have concomitant CVD

- Incidence of OAB and CVD increased with age<sup>1,2</sup>
- 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**<sup>3</sup>
  - Study on 16833 patients included in database GE Healthcare -**38,8% patients with OAB have accelerated pulse** ( $\geq 80$  heart beats/min)<sup>4</sup>
- In those patients the risk of CV accidents can be increased<sup>5</sup>
- Introduction of antimuscarinics – take care of CV risks<sup>5</sup>
  - **Due to  $M_2$  receptors blockage some antimuscarinics could accelerate puls or prolong QT interval**<sup>5</sup>

1. Stewart WF. et al. *World J Urol* 2003;20:327–36

2. National Center for Health Statistics 2005

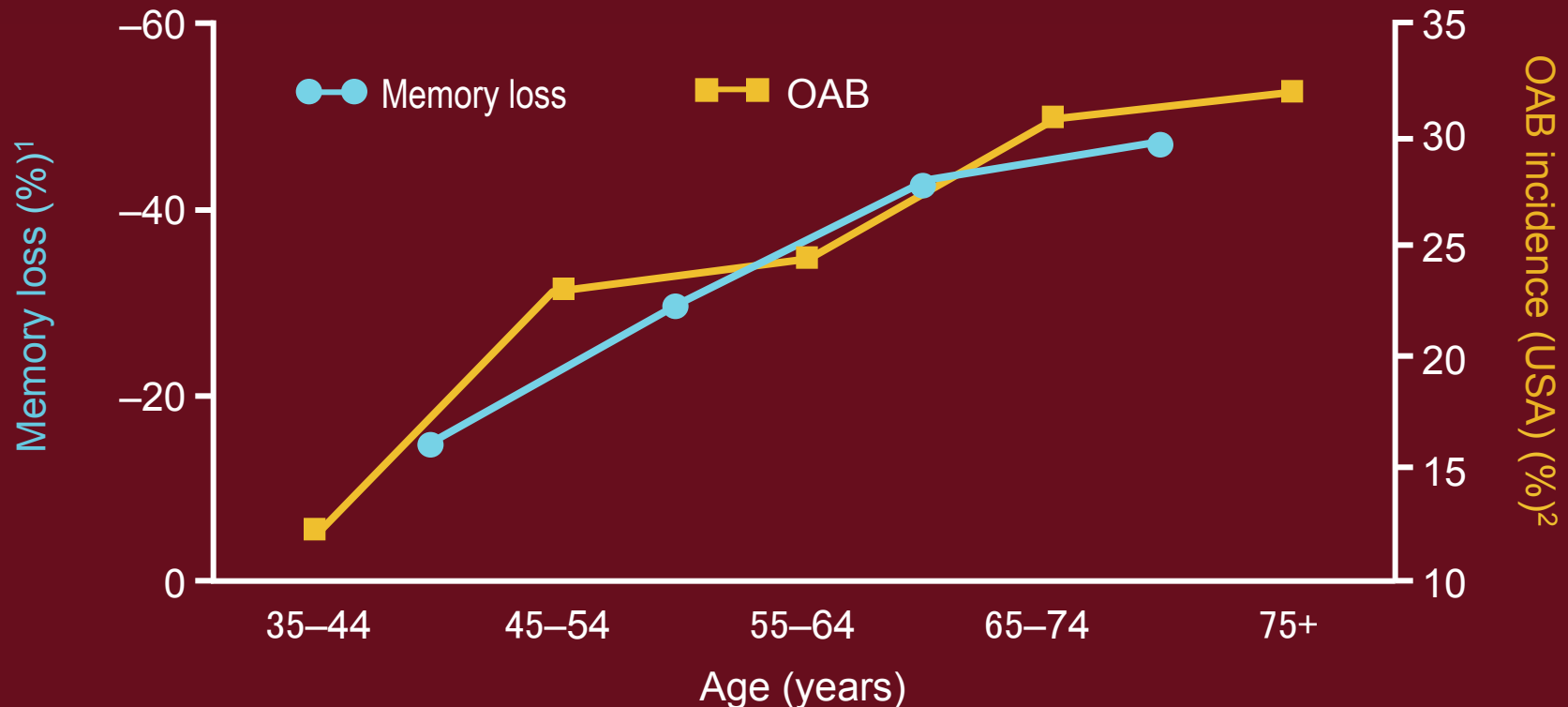
3. Andersson K-E. et al. *Prikazano na ICS-u* 2007. (Abstract 40)

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 <sup>1,2</sup>)

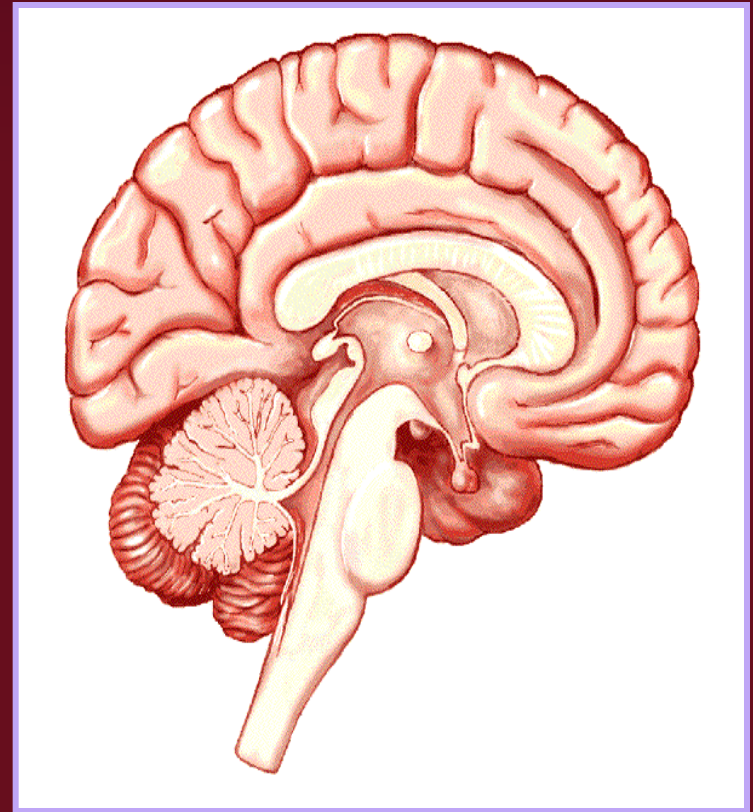


1. Crook TH. et al. Dev Neuropsychol 1993;9:103-13

2. Stewart WF. et al. World J Urol 2003;20:327-36

# Antimuscarinics and Cognition

- Antimuscarinic drugs used for the bladder can theoretically cause cognitive impairment
- ACh is a pivotal mediator of short-term memory and cognition
- Cholinergic system involvement in Alzheimer's disease has been clearly established
- Of the 5 muscarinic receptors  $M_1$  appears most involved in memory and learning



# The degree of cognitive risk with antimuscarinics

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- 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

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

| Antimuscarinic           | pKi for M <sub>1</sub> receptors | pKi for M <sub>3</sub> 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                              |

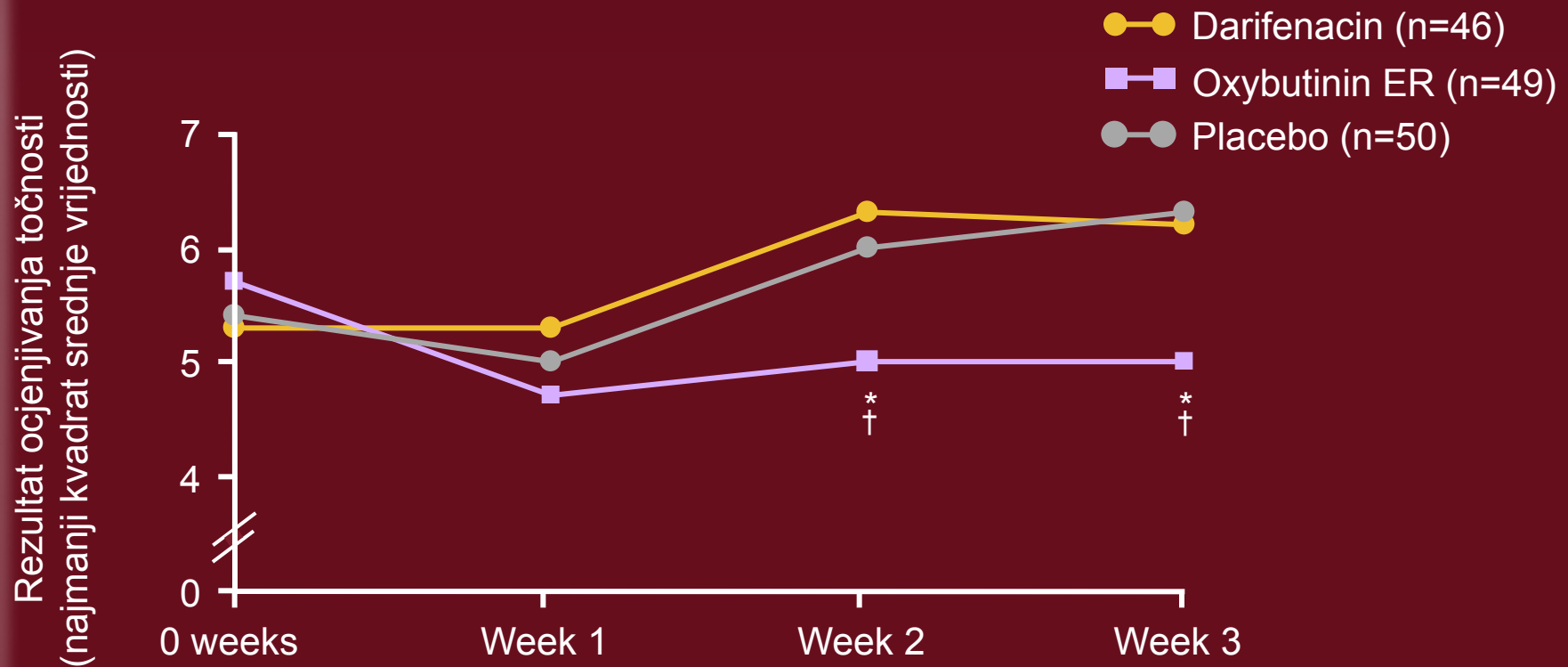
# Molecular weight of antimuscarinics

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

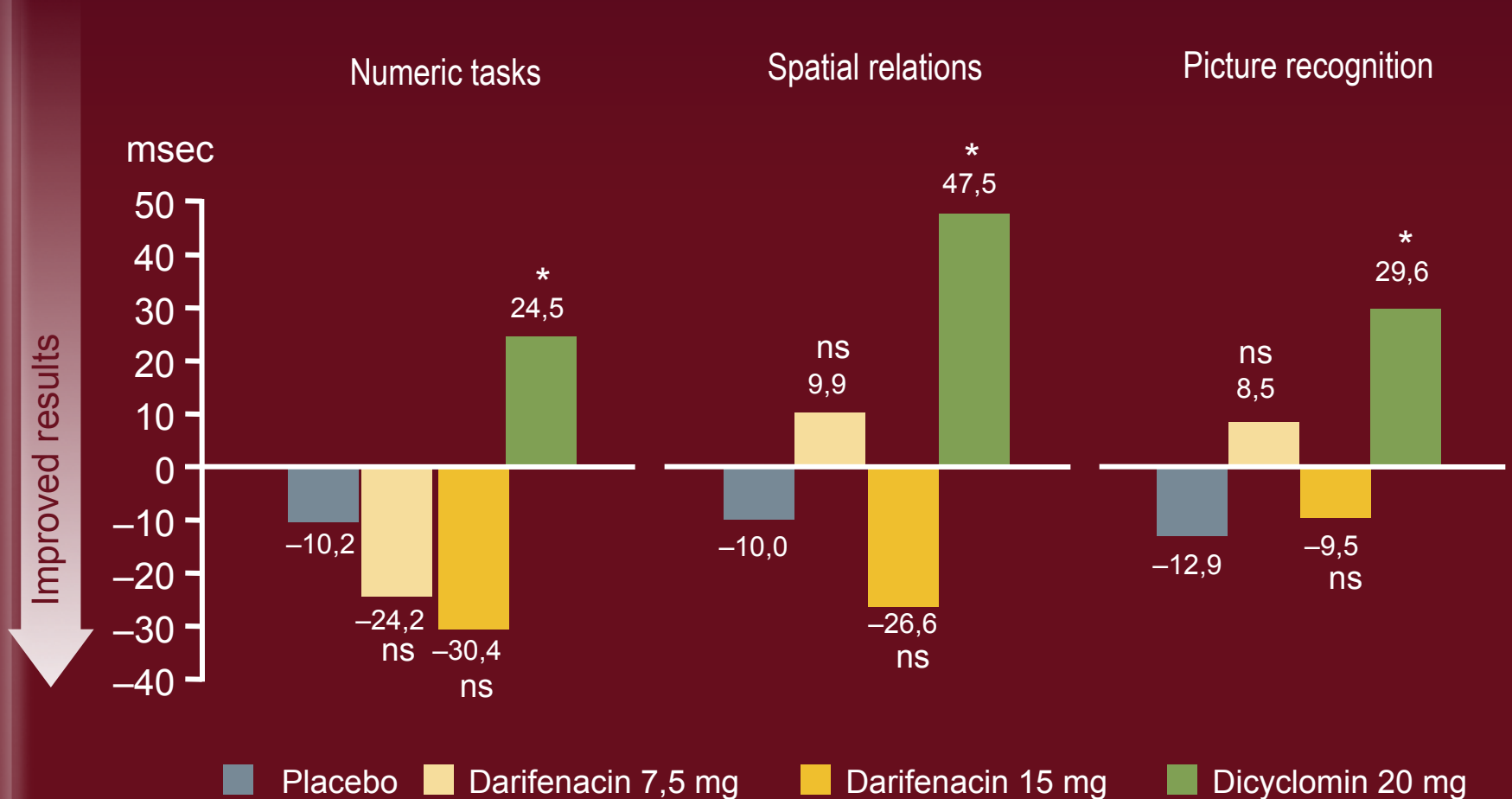
| Antimuscarinic               | Chemical structure (type of amine) | Molecular weight of the base compound (kDa) (the MW of the conjugated salt is given in parenthesis) | Lipophilicity          |
|------------------------------|------------------------------------|---|------------------------|
| Oxybutynin                   | 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 oxybutinin, darifenacin has no influence on memory processes



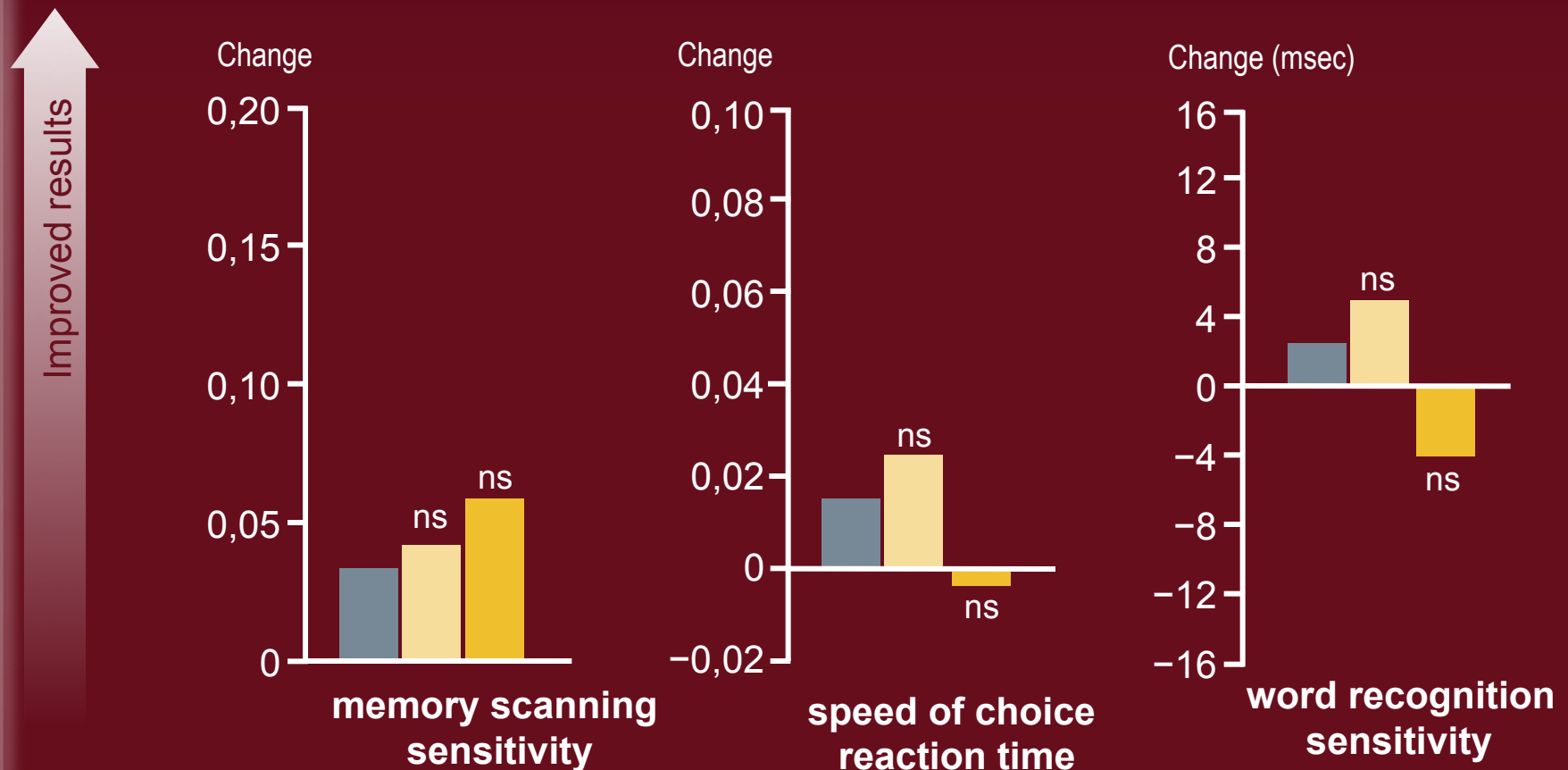
# Selective M3 antimuscarinics - no influence on memory process (Age 28 yrs)



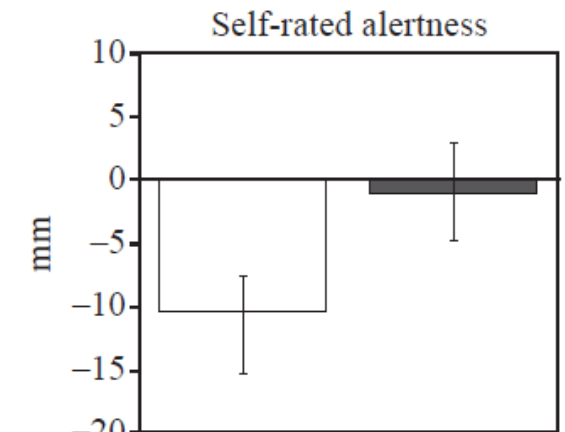
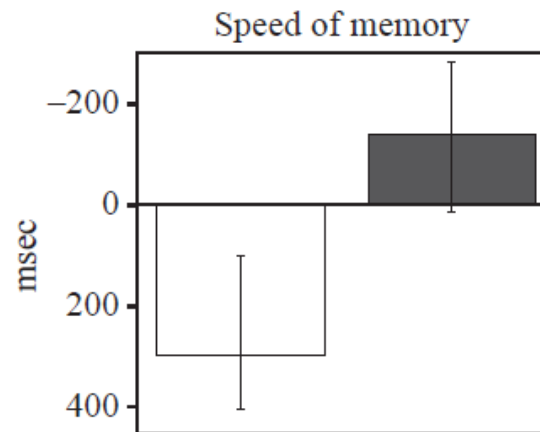
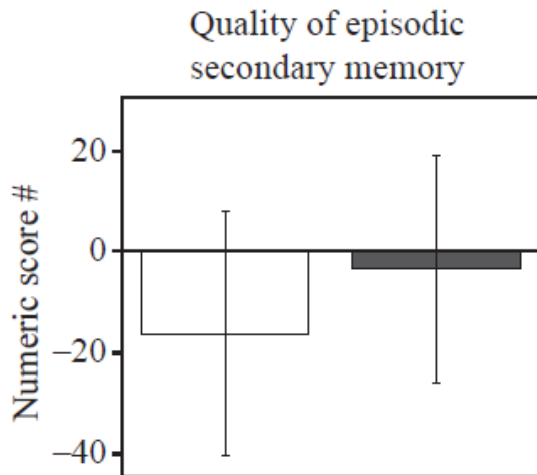
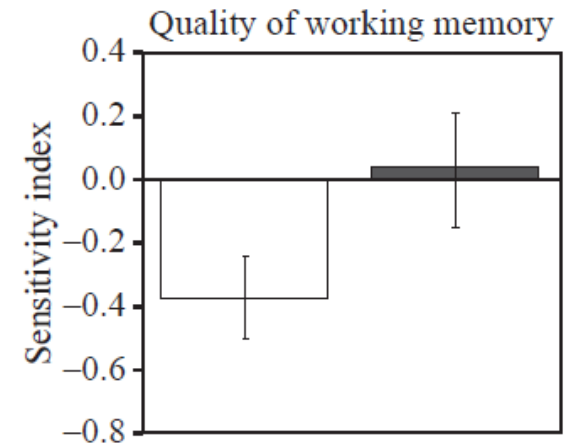
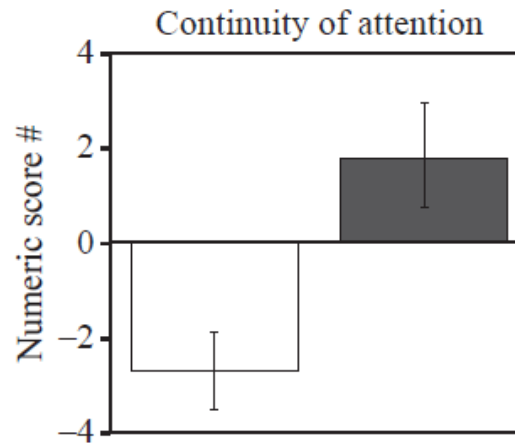
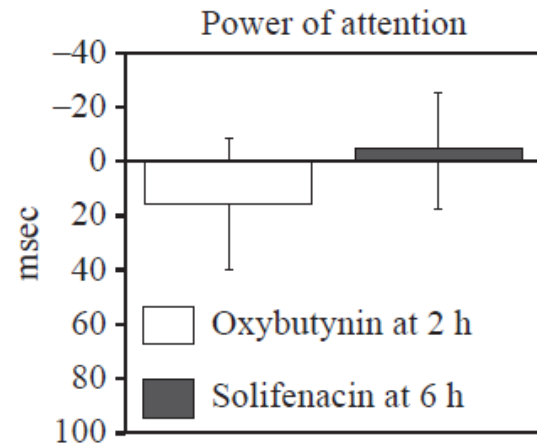
ns = not statistically significant, \* $p < 0,05$  Vs placebo

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

■ Placebo (n=66) ■ Darifenacin 7,5 mg (n=70) ■ Darifenacin 15 mg (n=61)



# Solifenacin Vs Oxybutynin



# = numeric score based on results of individual test scores

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

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

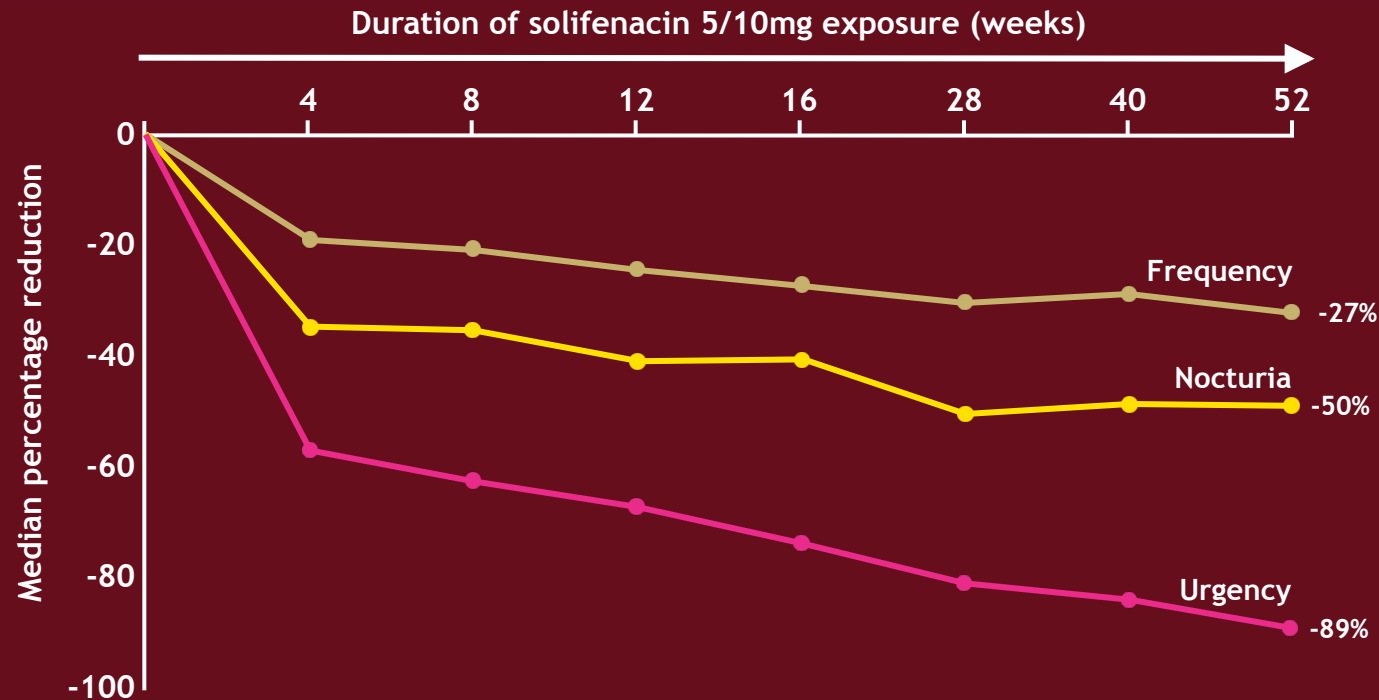
*From the University of Massachusetts Medical School and UMass Memorial Medical Center, Worcester, Massachusetts (CED), University of Texas Health Science Center at San Antonio, San Antonio, Texas (SRK), University of Kansas, Kansas City, Kansas (TLG), University of Pennsylvania, Philadelphia, Pennsylvania (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

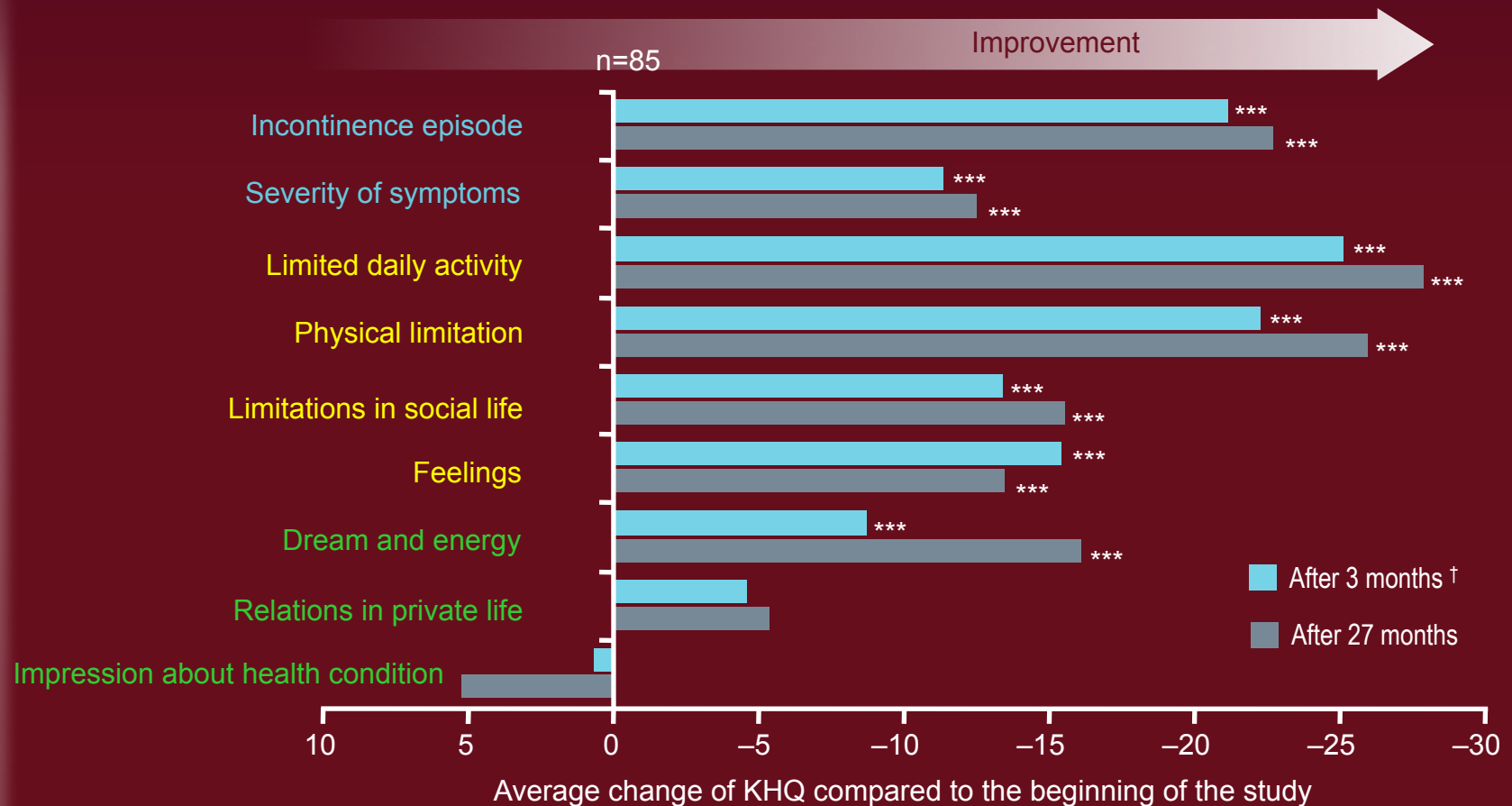
|                              | No. Placebo (%) | No. Fesoterodine (%) | RD (95% CI)            | p Value |
|------------------------------|-----------------|----------------------|------------------------|---------|
| AEs of special interest:     |                 |                      |                        |         |
| 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



# High HRQoL\* in patients older $\geq 65$ years with long-term treatment with M3 antagonists



\*KHQ = King's Health Questionnaire

\*\*\*  $p < 0.001$

# Take Home Messages

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- 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 pharmacokinetics 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 !

