SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

La Prostata nel Mirino

Napoli, 1 dicembre 2016

La vescica iperattiva: dalla diagnosi ai nuovi approcci terapeutici

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Definition of Overactive Bladder

Overactive bladder (OAB) is a symptom complex that is characterized by urinary urgency, with or without urgency-associated urinary incontinence. OAB is often associated with urinary frequency and nocturia in the absence of pathologic or metabolic conditions that may cause or mimic OAB, such as urinary tract infections, polyuria, transitional cell carcinoma of the bludder, and underlying neurologic abnormalities.

Urgency, the hallmark of OAB, is defined as the sudden compelling desire to urinate, a sensation that is difficult to defer. Urinary frequency is defined as voiding 8 or more times in a 24-hour period. Nocturia is defined as the need to wake 1 or more times per night to void.

The current definition of overactive bladder syndrome is a symptomatic diagnosis.

International Continence Society
Urology 2003;61:37-49

The prevalence of overactive bladder in conducted population-based survey

Variable	Korea [1]	Finland [2]	Europe and Canada [3]	United States [4]	Japan [5]
No. of respondents	2,000	3,727	19,165	5,204	4,570
Response rate (%)	22.1	62.4	33.0	44.3	45.3
Age distribution (y)	≥18	18–79	≥18	≥18	40–100
Survey method	Telephone survey	Postal survey	Telephone survey	Telephone survey	Postal survey
Prevalence of OAB (%)					
Men	10.0	6.5	10.8	16.0	14.0
Women	14.3	9.3	12.8	16.9	11.0
Overall	12.2	8.0	11.8	16.5	12.4

1) Korean EPIC study. World J Urol 2011;29:185-90
2) A population-based study in Finland. PLoS One 2007; 7:2:e195
3) EPIC study. Eur Urol 2006;50:1306-14
4) Prevalence and burden of overactive bladder in USt. World J Urol 2003;20:327-36
5) An epidemiological survey of overactive bladder symptoms in Japan. BJU Int 2005;96:1314-8

Real-world characteristics of elderly patients with overactive bladder in the United States

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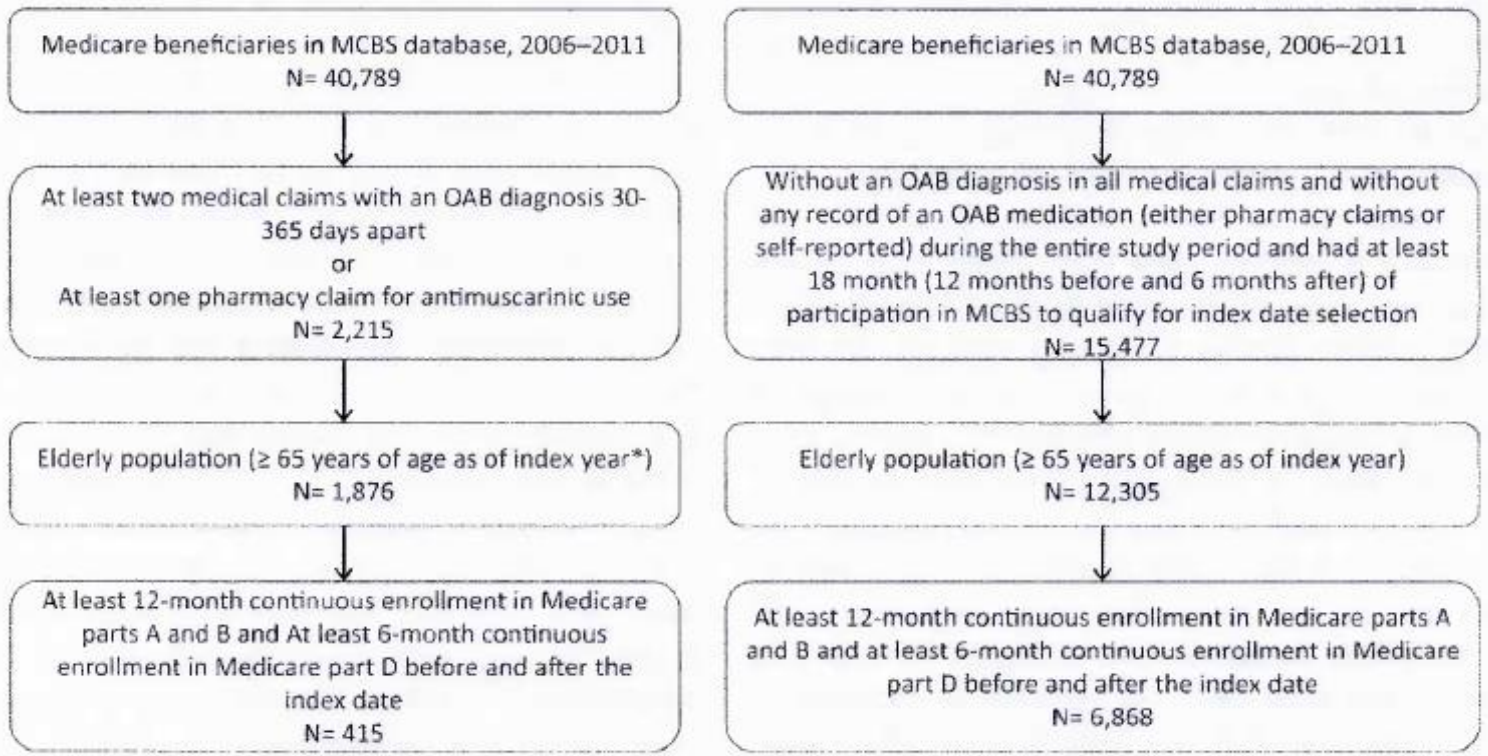
[a]Evidera, Waltham, MA, USA; [b]Pfizer Inc., New York, NY, USA

Methods: We used Medicare claims and the Medicare Current Beneficiary Surveys from 2006 to 2011 to identify patients with OAB. We describe the demographic characteristics, functional impairment and physical limitations, concurrent medical conditions, Charlson Comorbidity Index (CCI) scores, and concomitant medication use of patients with OAB; these characteristics are also described by sex and age group (65–74 vs. ≥75 years). We also compare the characteristics of OAB with non-OAB patients.



MEDICAL RESEARCH AND OPINION, 2016
doi.org/10.1080/03007995.2016.1226167

Baseline demographic characteristics and functional impairment measures, MCBS respondents, by OAB status.

	OAB Patients (Unweighted $N = 415$, Weighted $N = 1{,}019{,}946$)	Non-OAB patients (Unweighted $N = 6868$, Weighted $N = 17{,}768{,}956$)	*P* Value
Age, years	78.5 (0.4)	76.9 (0.1)	<.01
Age Group, %			<.01
<75 years	34.6	46.1	
≥75 years	65.4	53.9	
Sex, %			
Female	71.2	61.7	<.01
Male	28.9	38.3	
Race, %			
White	75.9	75.8	0.87
Black	8.2	9.0	
Hispanic	10.2	10.2	
Other/Unknown	5.8	5.0	
Activities of Daily Living Limitations, %			
0 items	56.0	67.4	<.01
1–2 items	20.5	18.7	
≥3 items	22.4	13.3	
Missing	1.0	0.7	
Instrumental Activities of Daily Living Limitations, %			
0 items	46.7	60.2	<.01
1–2 items	25.1	21.3	
≥3 items	16.0	11.9	
Missing	12.2	6.6	
Physical Functioning Limitations, %			
0 items	9.8	18.6	<.01
1–2 items	27.5	37.2	
≥3 items	50.4	37.4	
Missing	12.4	6.8	
VES-13 Score	5.9 (0.15)	4.7 (0.05)	<.01
VES-13 Score <3	22.7	37.4	<.01
VES-13 Score ≥3	77.3	62.6	

Economic Costs of Overactive Bladder in the United States

In 2007, average annual per capita costs of OAB were $1925 ($1433 in direct medical, $66 in direct nonmedical, and $426 in indirect costs). Applying these costs to the 34 million people in the United States with OAB results in total national costs of $65.9 billion (billion = 1000 million), ($49.1 billion direct medical, $2.3 billion direct nonmedical, and $14.6 billion indirect). Average annual per capita costs in 2015 and 2020 would be $1944 and $1969 and total national costs would be $76.2 billion and $82.6 billion, respectively.

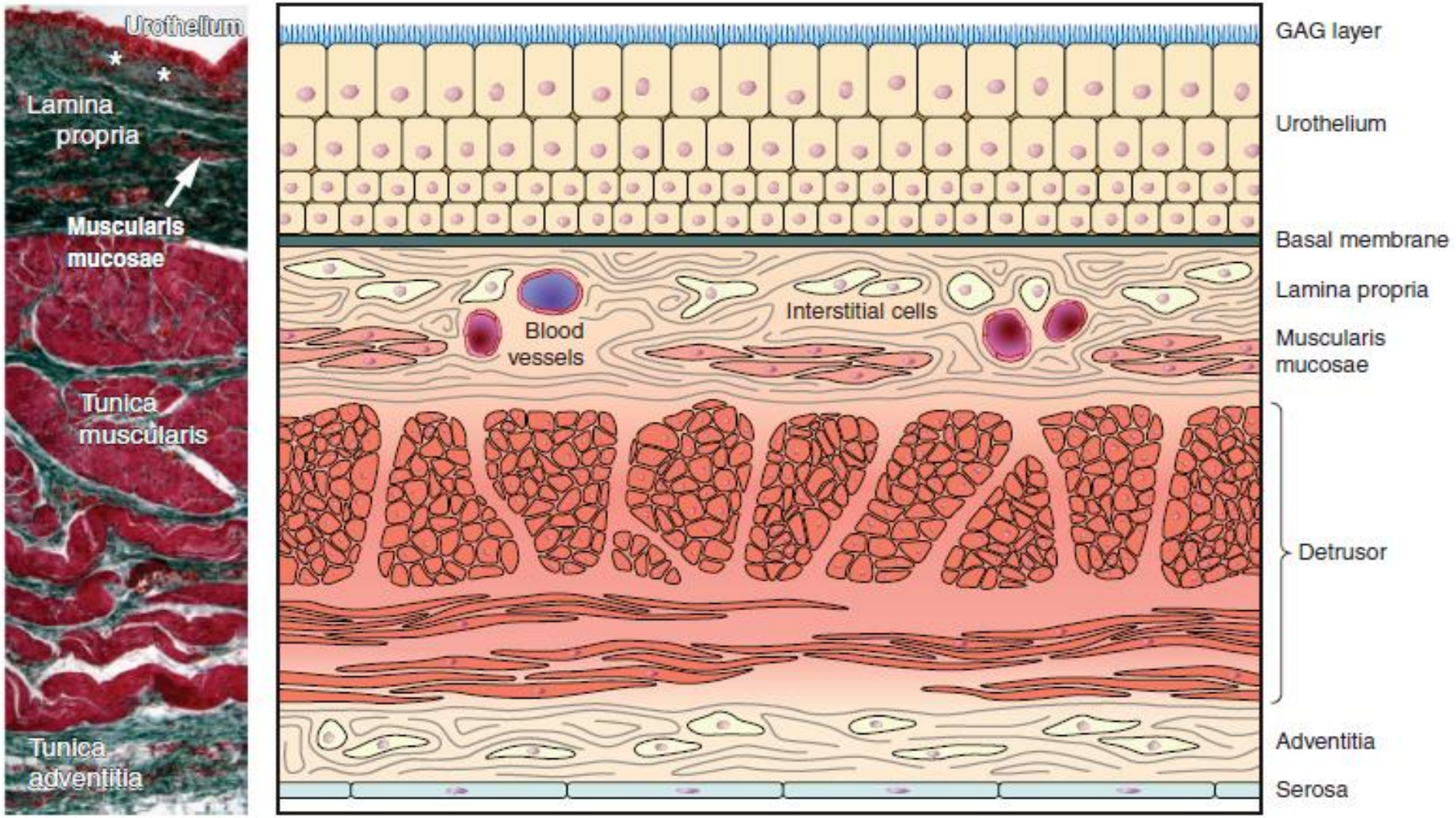
0090-4295/10/$34.00
doi:10.1016/j.urology.2009.06.096

Age-related changes in the lower urinary tract (LUT)

Decreased
Bladder capacity
Sensation of filling
Speed of detrusor contraction
Pelvic floor muscle bulk and tone
Sphincteric resistance
Urine flow rate

Increased
Urinary frequency
Post-void residual volumes
Outflow tract obstruction (in men)

Components of the bladder wall through normal human urinary bladder

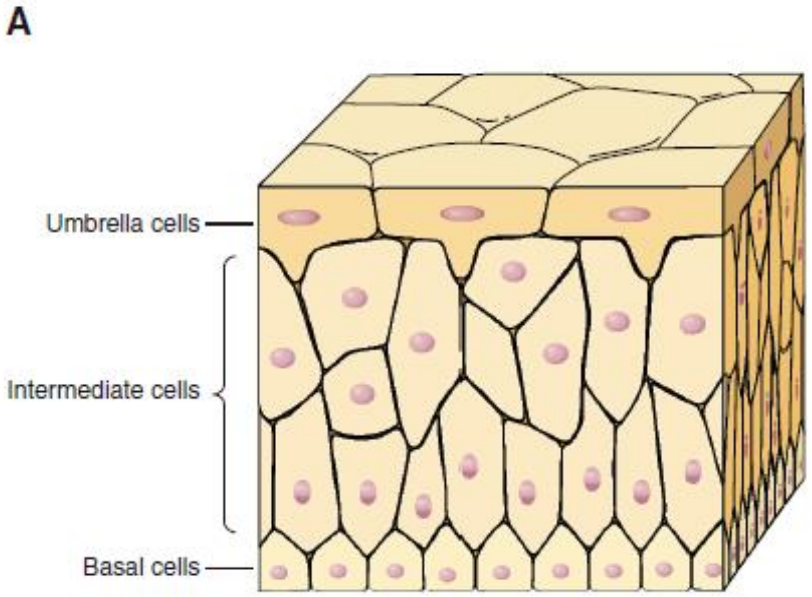


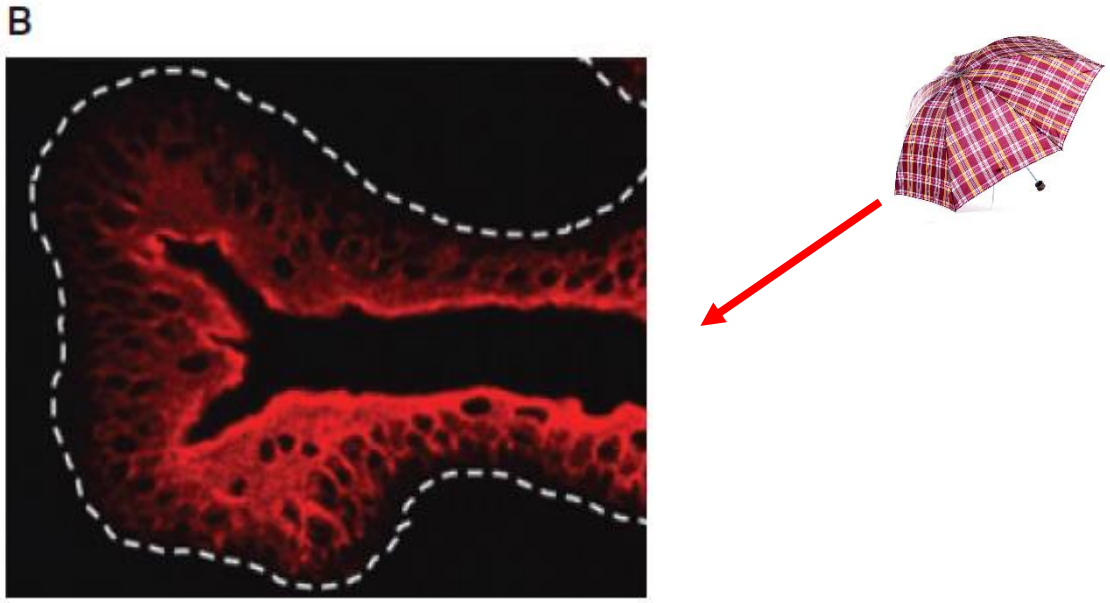
Physiol Rev 93: 653–680, 2013
doi:10.1152/physrev.00030.2012

Urinary bladder urothelium and associated tight junctions

A: multiple epithelial cell layers within the urothelium.

B: staining of urothelium with an antibody touroplakin III showing staining of superficial umbrella cells



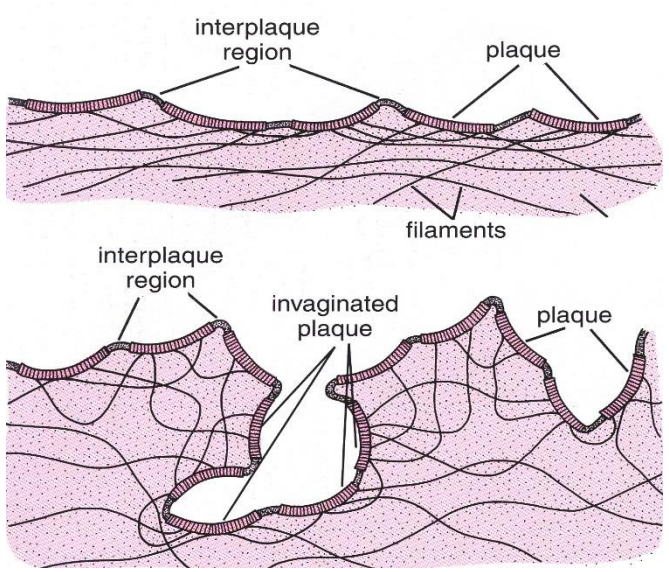


Urothelium a transitional epithelium

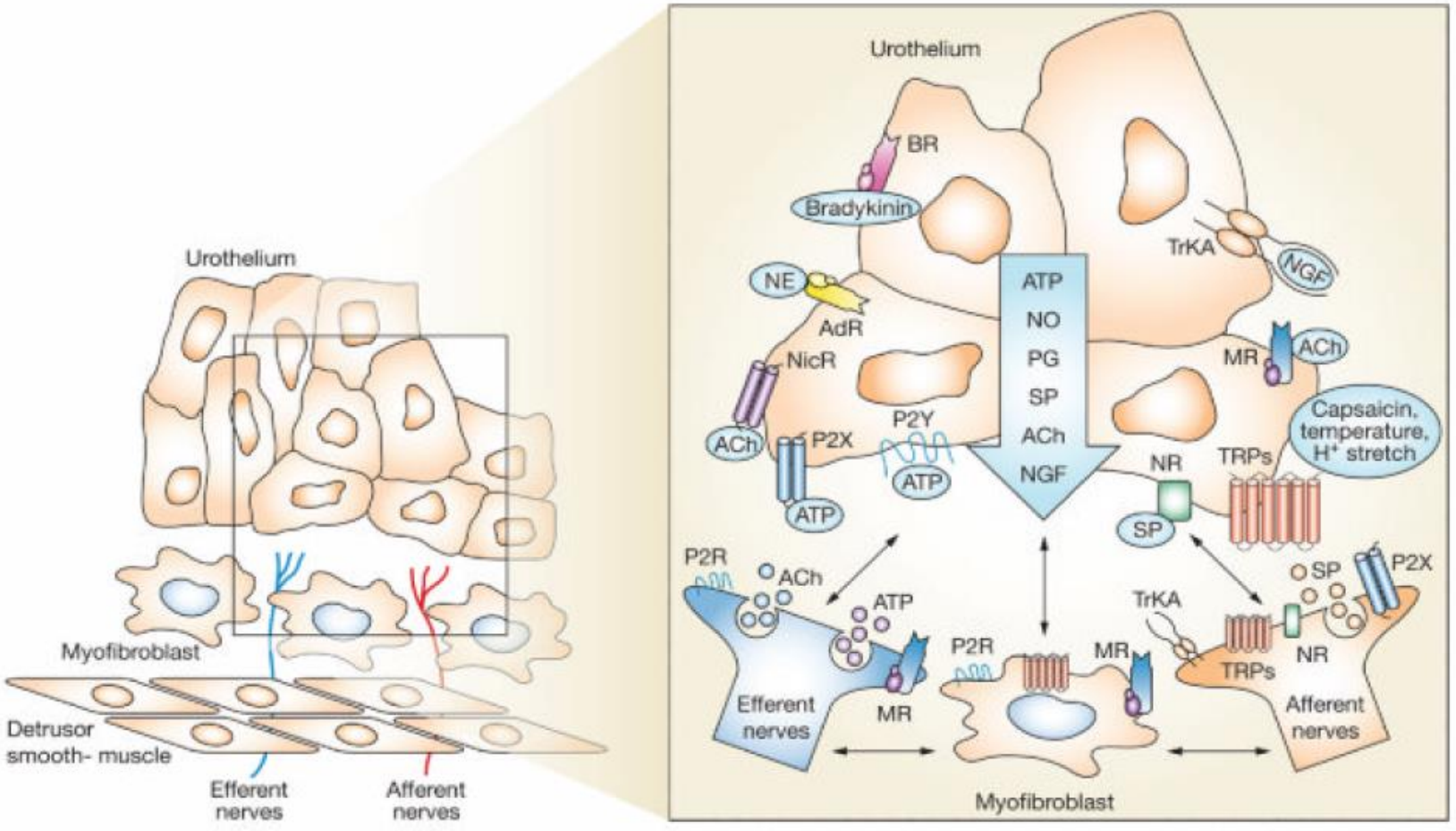
1. accommodate the fluctuation in volume
2. protect against the caustic effects of urine

Umbrella cells:

1. apical exocytosis of specialized fusiform vesicles (aka discoid vesicles) during distension of the bladder provides additional fragments (reserve) of cell membrane, which are incorporated into the cell membranes, allowing them to stretch in a full bladder;
2. the apical plasma membrane of umbrella cells, facing the urine, is covered with rigid-looking plaques, which, together with tight junctions, form a specialized membrane compartment that represents one of the tightest and most impermeable barriers in the body.



Hypothetical model of the possible autocrine (i.e. autoregulation) or paracrine (release from nearby nerves or other cells) interactions between bladder afferent and efferent nerves, urothelial cells, smooth muscle and myofibroblasts.



ACh,acetylcholine; AdR, adrenergic receptor; BR, bradykinin receptor; H+, proton; MR,muscarinic receptor; NE, norepinephrine; NGF, nerve growth factor; NR, neurokinin receptor; NicR, nicotinic receptor; NO, nitric oxide; P2R, purinergic 2 receptor; P2X and P2Y, purinergic receptors; PG, prostaglandin; SP, substance P; Trk-A, receptor tyrosine kinase A, high affinity receptor for nerve growth factor; TRPs, transient receptor potential channels.

Mechanisms of Disease: involvement of the urothelium in bladder dysfunction

KEY POINTS

- The urothelium, a specialized lining of the urinary tract, has historically been viewed as a passive barrier to ions and solutes
- There is evidence that the urothelium responds to both physiological and chemical stimuli and can release a number of signaling molecules
- Release of chemical mediators from urothelial cells indicates that these cells have specialized sensory and signaling properties that could allow reciprocal communication with neighboring urothelial cells, as well as afferent and efferent nerves or other cells (i.e. myofibroblasts and immune or inflammatory cells) within the bladder wall
- Various types of transient receptor potential channels including TRPV1 are expressed in the urothelium as well as in bladder afferent nerves
- Results from TRPV1-null mice demonstrate that TRPV1 receptors are essential for normal mechanically evoked purinergic signaling by the urothelium, and indicate that the function of these receptors extends beyond pain sensation to include participation in normal bladder function

Clinical assessment

Careful history:

Symptoms such as urgency, urgency incontinence, nocturia, increased frequency, dysuria, haematuria, and lower urinary tract pain (symptom based questionnaire);

General examination:

General examination, abdominal and pelvic examination, and a basic neurological examination;

Instrumental evaluation:

Urodynamics, cystoscopy, and diagnostic urinary tract ultrasound should not generally be used in initial workup of the uncomplicated patient.

American Urological Associaton reccommendations for overactive bladder therapy

Level of therapy	Type of therapy	Examples of therapy
First-line therapy	Behavioral therapy	Bladder diet, bladder training, pelvic floor physical therapy, and biofeedback
Second-line therapy	Medical therapy	Anticholinergic medication and β3 agonist medication
Third-line therapy[a]	Neuromodulation	PTNS®, InterStim®, and Botox®

Abbreviation: PTNS, percutaneous tibial nerve stimulation.

Research and Reports in Urology
27 July 2016

OAB Therapy: First-Line

Non-pharmacologic and -surgical Intervention

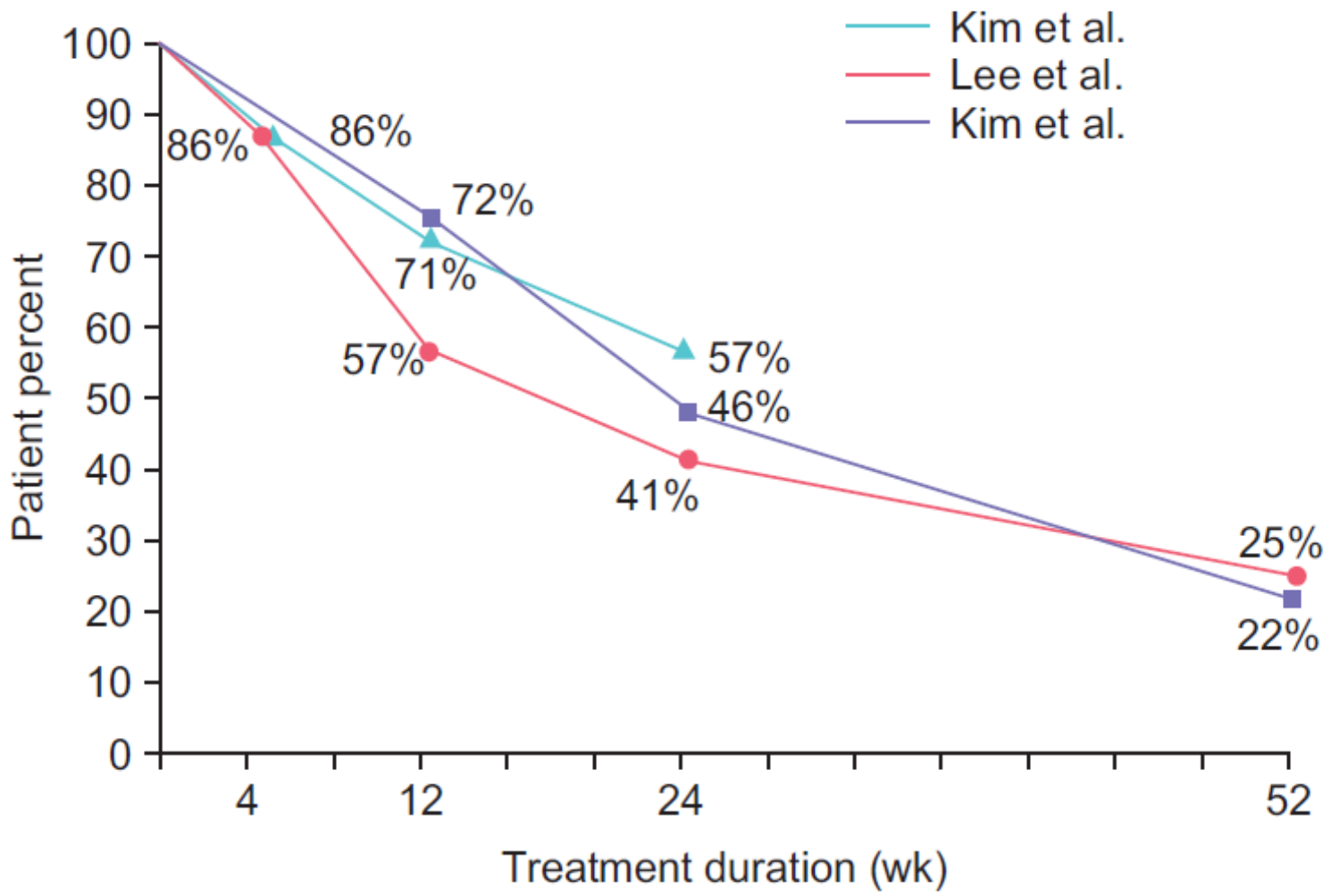
Behavioral therapy is a treatment approach that aims to alter an individual's actions or environment to improve bladder control. Components of behavioral therapy include:
(1) education,
(2) dietary and lifestyle modification,
(3) bladder training,
(4) pelvic floor muscle therapy (PFMT),
(5) self-monitoring with bladder or voiding diaries.

Second-Line Therapy: Medications

Medication brand (generic)	Dosage	Route	$t_{1/2}$ (hours)
Detrol[a] (tolterodine tartrate)	2 mg or 4 mg bid vs daily	Oral	8
Ditropan[a] (oxybutynin chloride)	5 mg, 10 mg, or 15 mg bid, tid, or daily	Oral	12–13[b]
Oxytrol (oxybutynin)	3.9 mg/d patch twice weekly	Transdermal patch	7–8[b]
Gelnique (oxybutynin)	3% three pumps (84 mg) daily and 10% one sachet (100 mg) daily	Transdermal gel	NA
Toviaz (fesoterodine)	4 mg or 8 mg daily	Oral	7–8[b]
Enablex (darifenacin hydrobromide)	7.5 mg or 15 mg daily	Oral	12
Vesicare (solifenacin succinate)	5 mg or 10 mg daily	Oral	45–68[b]
Sanctura (trospium chloride)	20 mg bid	Oral	18.3
Sanctura XR (trospium chloride)	60 mg daily	Oral	36
Myrbetriq (mirabegron)	25 mg or 50 mg daily	Oral	50

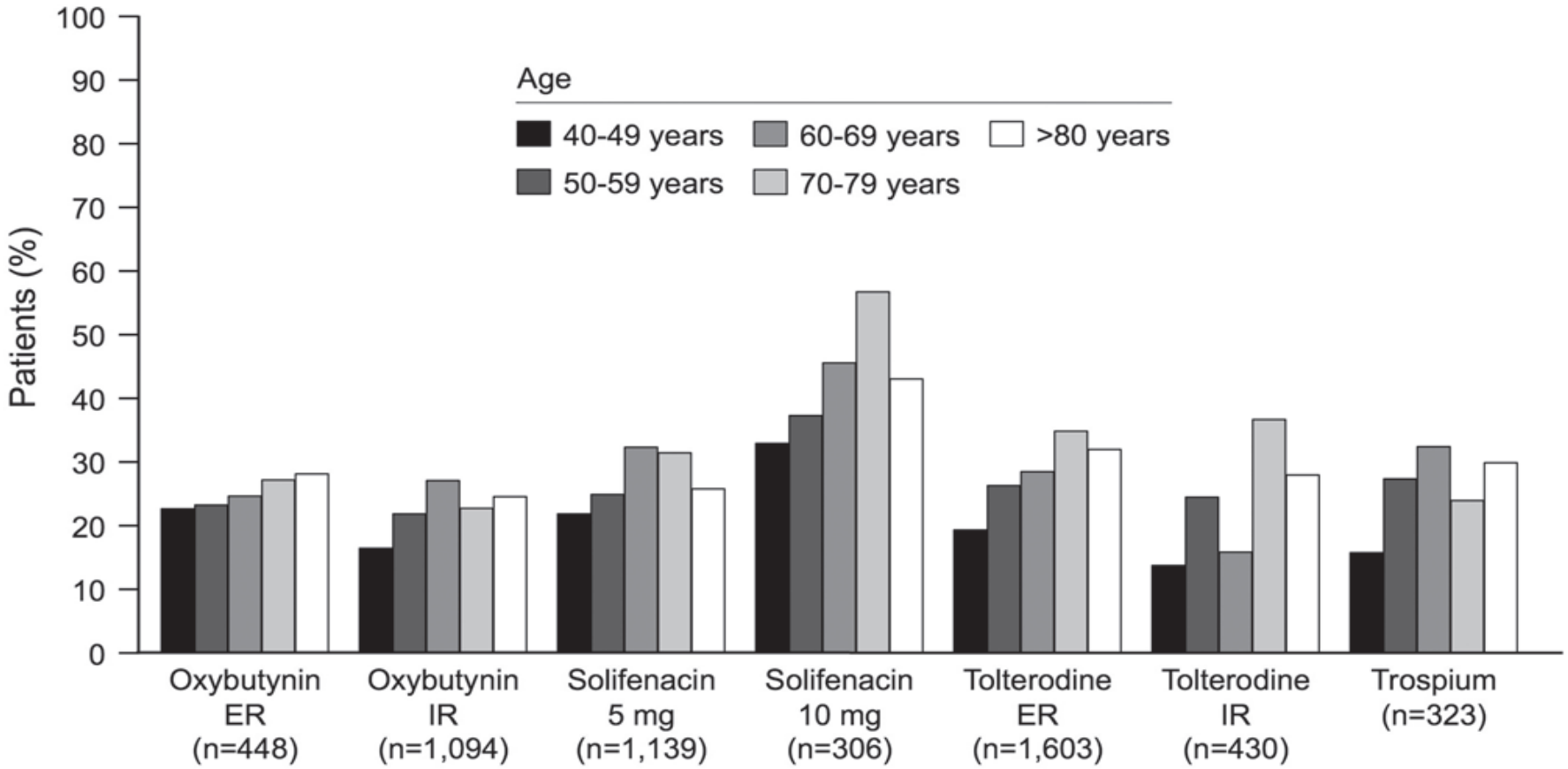
Research and Reports in Urology 2016:8

Trend of persistence of antimuscarinics in observational studies



ICUrology 2016;57:84-93.
http://dx.doi.org/10.4111/icu.2016.57.2.84
pISSN 2466-0493 • eISSN 2466-054X

Elderly patients are more likely to be persistent with therapy



Age Ageing 2010; 39(suppl 1):i37.

Third-Line Therapy

Posterior Tibial Nerve Stimulation (PTNS)

- Treatment sessions usually last about 30 min;

- The evidence base for PTNS is composed of observational studies in patients with OAB in whom drug therapy had failed;

- The main limitations of this approach are the need for repeated sessions to sustain efficacy, and the attendant expense that this incurs.

Third-Line Therapy

Sacral Neuromodulation (SNM)

- A two stages implantation procedure of a device that generates electrical impulses transmitted to the sacral nerves. The lead that transmits the impulses is placed through the third sacral foramen;
- These impulses are thought to modulate the neural reflexes that control bladder function;
- There was a symptomatic improvement of >90% in about half of the patients, which was maintained at 3-5 years;
- Main limitations of SNM are the risk of complications, such as migration of the lead, infection and failure of the device, as well as the need for revision in 30% of patients.

Third-Line Therapy

Botulinum toxin A (BTxA)

.Approved by FDA BTxA exerts its effect upon the detrusor muscle by binding to membrane receptors on cholinergic neurons. The toxin is then internalized where it inhibits release of acetylcholine at the presynaptic cholinergic terminals. It is thought to inhibit striated and smooth muscle contraction and to suppress bladder afferent activity;

.Paucity of evidence supporting the use of BTxA for OAB in the vulnerable elderly;

.Some important issues for further investigation are the injection site, volume and number of injections.

Take home message

- OAB is a common problem with a significant personal burden for affected individuals, as well as bearing high healthcare costs;
- Despite extensive research, the pathophysiological basis of OAB is incompletely understood;
- Although new therapeutic targets are emerging(Beta-3 agonists), the mainstay

  of pharmacotherapy continues to be AMs: However, it is clear that the therapeutic plateau forAMs has now been reached;
- BTXhas provided an effective option for patients in whom oral pharmacotherapy

  has failed, whilst the optimal parameters in terms of dosing, injection, number and site are yet to be fully established.

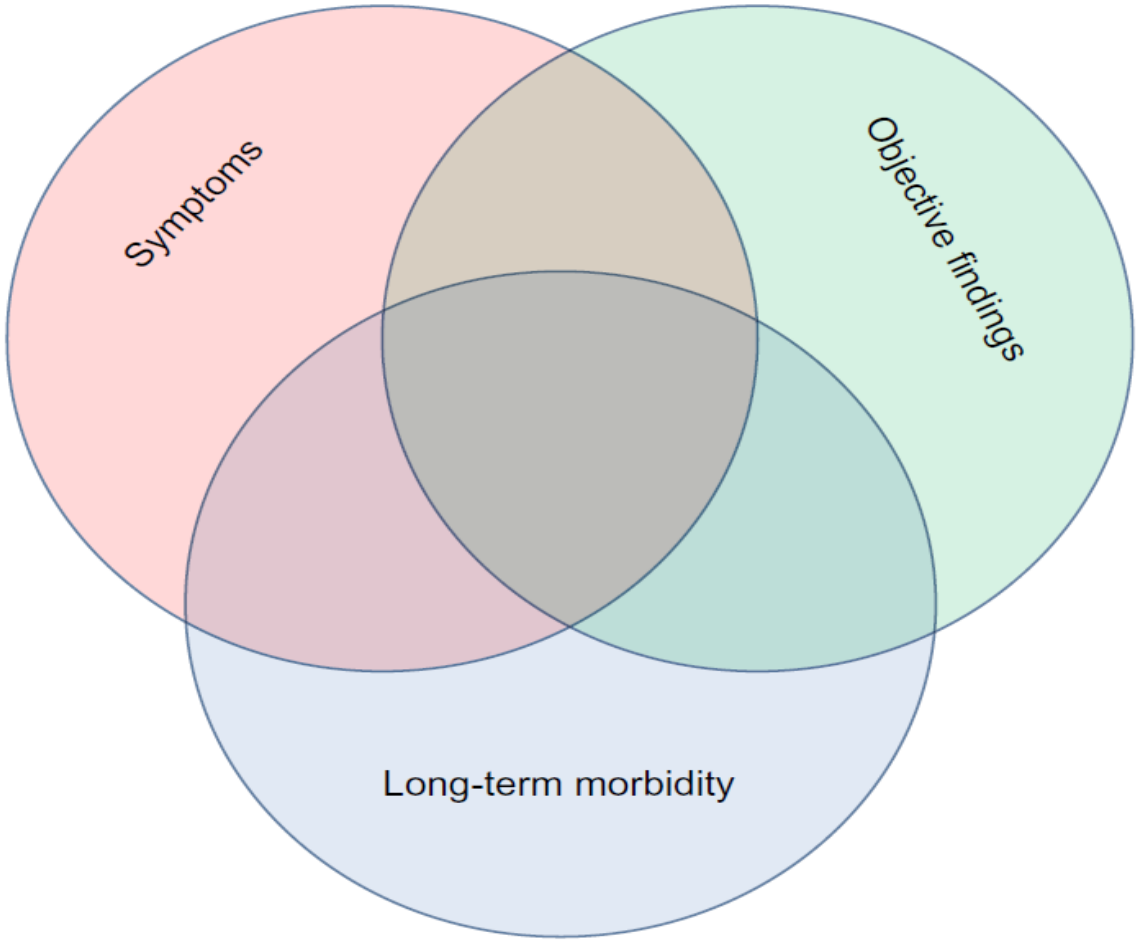
Drugs and targets of potential interest

Nerve growth factor – Inhibitor
Prostanoid receptors – Antagonists
Rho-kinase – Inhibitors
Vitamin D3 receptor – Agonists
K^+ channels – K^+ channel openers
Centrally acting drugs
Purinergic system – P2X3 receptor antagonists
Cannabinoid system – exocannabinoids; FAAH inhibitors
TRP channel family – TRP channel antagonists

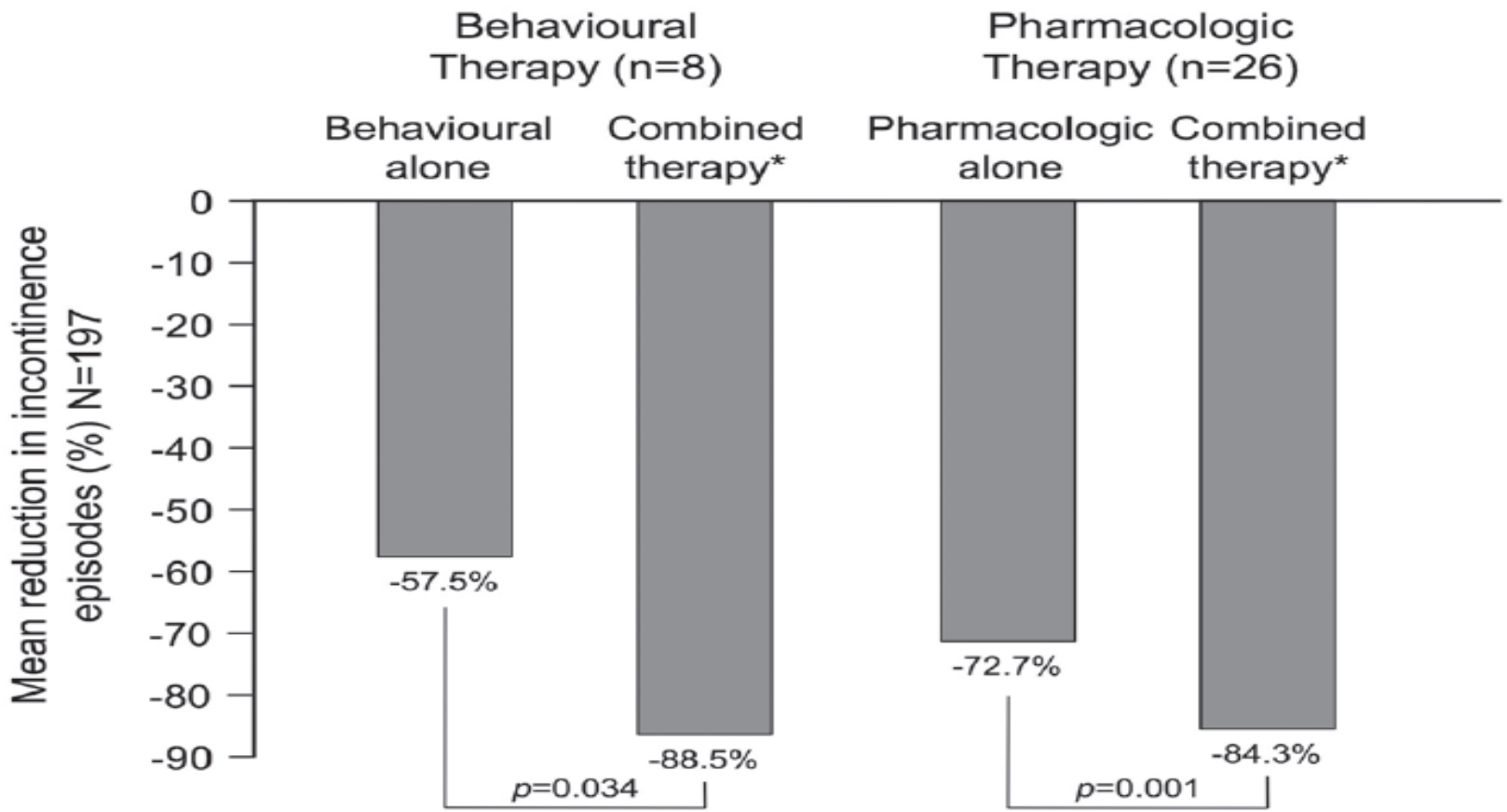
FAAH, fatty acid amide hydrolase; TRP, transient receptor potential.

http://dx.doi.org/10.4111/kju.2015.56.10.673

Evaluating OAB in the vulnerable elderly: conceptual relationship of clinical factors



Benefits of combined pharmacologic (oxybutynin) and behavioural therapy in older people



Burgio KL, et al. J Am Geriatr Soc 2000; 48:370-4.

PERCORSO DIAGNOSTICO TERAPEUTICO ASSISTENZIALE PER I PAZIENTI GERIATRICI DI SESSO MASCHILE CON SINTOMI DELLE BASSE VIE URINARIE

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