MIPS Mediterranean Incontinence and Pelvic Floor Society

10-12 December 2015

III Annual Meeting

Ljubljana • Slovenia

Treatment of female OAB: techniques, results and follow up

"Pharmacotherapy (Antimuscarinics, B3 agonist)"

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Do We Need a New Definition of the Overactive Bladder Syndrome? ICI-RS 2013

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Aim and Methods: Overactive bladder syndrome (OAB) has a symptom-based definition. Following a presentation of issues, the definition was subjected to expert discussion at the International Consultation on Incontinence Research Society to identify key issues. **Results:** OAB is a widely used term; it is a pragmatic approach to categorizing a recognized group of patients, and is understood by the patients, however, expert opinion suggested several issues for which additional evidence should be sought. Naming an organ (bladder) in the condition may suggest underlying mechanism, when contributory aspects may lie outside the bladder. No severity thresholds are set, which can cause uncertainty. Urgency is prominent in the definition, but may not be prominent in patients whose adaptive behavior reduces their propensity to urgency. OAB can co-exist with other common conditions, such as benign prostate enlargement (BPE), stress incontinence or nocturnal polyuria. Consensus led by the International Continence Society can be attempted for aspects such as "fear of leakage." To develop a new definition, more substantive evidence is needed for key elements, and until such evidence is available, full redefinition is not appropriate. Thus, the medical profession should accept constructive compromise and work supportively. **Conclusions:** The ICI-RS proposes that the terminology is slightly rephrased as: "overactive bladder syndrome (OAB) is characterized by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology." More substantive changes would require additional scientific evidence. Strengths, limitations, and practicalities of the definition of OAB were discussed at the ICIRS meeting 2013. Following a presentation of issues, the definition was subjected to expert discussion. *Neurourol. Urodynam. 33:622–624, 2014.* © 2014 Wiley Periodicals, Inc.

URGENCY

WİTH OR W/O

URGENCY
URINARY
INCONTINENCE

NOCTURIA

INCREASED
DAY-TIME
FREQUENCY

Conditions That Can Cause or Contribute to OAB Symptoms

- Urinary tract infection
- Obstruction (POP)
- Impaired bladder contractility (urinary retension & decreased functional bladder capacity)
- Bladder abnormalities

  (tumors,calculi,mesh, interstisial cyctitis)
- Estrogen deficieny
- Sphincter weakness
- Neurologic conditions (Brain / Spinal cord / Peripheral innervation)

Prevalence

- The prevalence varies with the criteria used for diagnosis
- According to Irwin et al. using the ICS definition 2002, the overall prevalence of OAB, based on computer assisted telephone interviews (EPIC study)

11.8%

- The rates were similar in men and women and increased with age

Understanding the elements of overactive bladder: questions raised by the EPIC study

Debra E. Irwin, Paul Abrams*, Ian Milsom†, Zoe Kopp‡ and Kate Reilly‡ on behalf of the EPIC Study Group

*Department of Epidemiology, University of North Carolina, Chapel Hill, NC, ‡Pfizer Inc, New York, NY, USA, *Bristol Urological Institute, Southmead Hospital, Bristol, UK, and †Department of Obstetrics and Gynaecology, Sahlgrenska Academy at Goteborg University, Goteborg, Sweden*

Accepted for publication 15 November 2007

Study Type – Symptom prevalence study

defined using the current ICS definition (i.e.

urgency and nocturia. More than half of those

Symptom	Men (502)	Women (932)
Urgency	18.7	16.1
UUI	1.2	2.1
Urgency + frequency	3.8	2.3
Urgency + nocturia	38.2	31.7
Urgency + UUI	0.6	4.6
UUI + frequency	0	0.5
UUI + nocturia	3.8	7.4
UUI + frequency + nocturia	1.4	1.6
Urgency + UUI + nocturia	7.4	13.4
Urgency + UUI + frequency	0.4	0.9
Urgency + nocturia + frequency	19.3	12.2
All four	5.2	7.2

By ICS definition;
Apart from urgency;
the next most common storage symptom was

Nocturia

For both women (74%)
(once or more)
and men (75%)

followed by

UUI in women (38%)
and ICS-defined
frequency in men (30%).

ICS DEFINED LUTS

SUI

Intermittency

Slow stream

Straining

Terminal dribble

Incomplete emptying

Postmicturtion dribble

EPIC study also indicates that

most participants who reported urgency also had other LUTS, including voiding and postmicturition symptoms

in this sub-analysis,

59% of women with OAB symptoms reported

voiding and/or postmicturition symptoms

in addition to storage symptoms

.

Furthermore,

21% of the women with OAB symptoms

reported having **six or more LUTS**

Irvin DE et al, BJU Int. 2008; 101 , 1381-1387

DİAGNOSİS &TREATMENT OF OAB (NON-NEUROGENİC) İN ADULTS: AUA/SUFU GUİDELİNE

Panel Members:
E. Ann Gormley, Deborah J. Lightner, Kathryn L. Burgio, Toby C. Chai, J. Quentin Clemens, Daniel J. Culkin, Anurag Kumar Das, Harris Emilio Foster, Jr., Harriette Miles Scarpero, Christopher D. Tessier, Sandip Prasan Vasavada

Clinicians should offer oral anti-muscarinics or oral Beta 3-adrenoceptor agonists as second-line therapy
(Evidence Strength Grade B)

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AUTONOMIC EFFERENT INNERVATION OF BLADDER

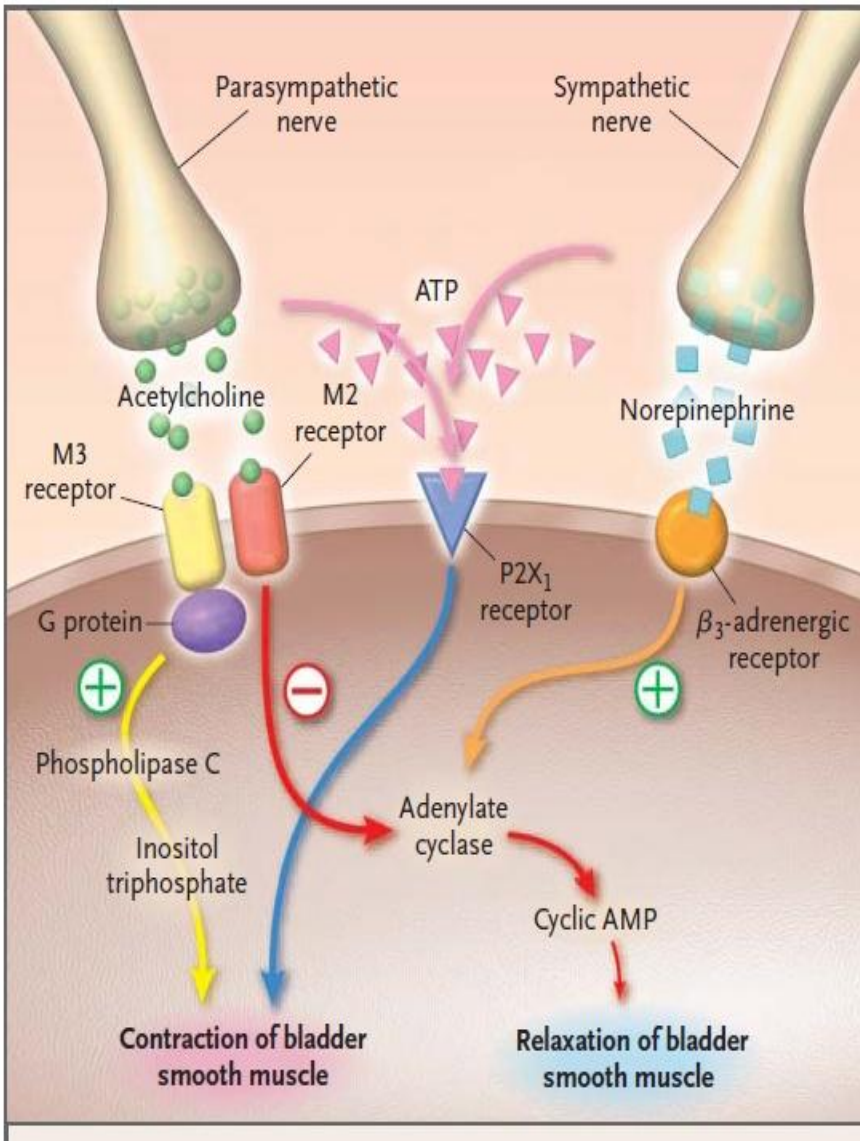
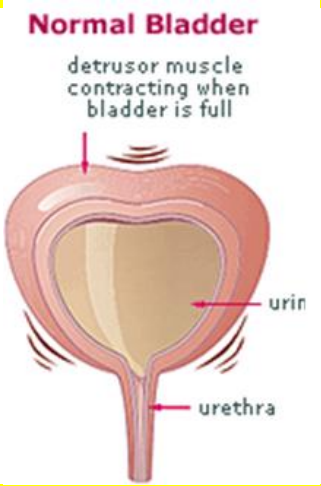


Figure 2. Current Concepts of Autonomic Efferent Innervation Contributing to Bladder Contraction and Urine Storage.

In the normal human bladder, acetylcholine is the predominant neurotransmitter that causes bladder contraction. Acetylcholine interacts with M3 muscarinic receptors and activates phospholipase C through coupling with G proteins, which generates inositol triphosphate, which in turn causes the release of calcium from the sarcoplasmic reticulum and the contraction of bladder smooth muscle. M2 receptors may contribute to bladder contraction by inhibiting adenylate cyclase activity and decreasing intracellular cyclic adenosine monophosphate (AMP) levels, which mediate bladder relaxation. In the normal human bladder, only a small proportion of muscle contraction is resistant to atropine. Resistance to atropine most likely results from the interaction of ATP with purinergic receptors, including $P2X_1$ receptors. ATP and other noncholinergically mediated processes may have a more important role in disorders that cause overactive bladder. Stimulation of β_3-adrenergic receptors may also lead to relaxation of bladder smooth muscle. Plus signs indicate activation, and minus signs inhibition. Data are from Morrison et al.,[20] Yoshimura and Chancellor,[21] and Andersson and Hedlund.[22]

Acetylcholine (ACh)

Predominant peripheral neurotransmitter responsible for bladder contraction



ACh receptors

- Nicotinic receptors
- Muscarinic receptors

Acetylcholine, interacts with the five known muscarinic receptors **(M1 through M5)** on the detrusor muscle

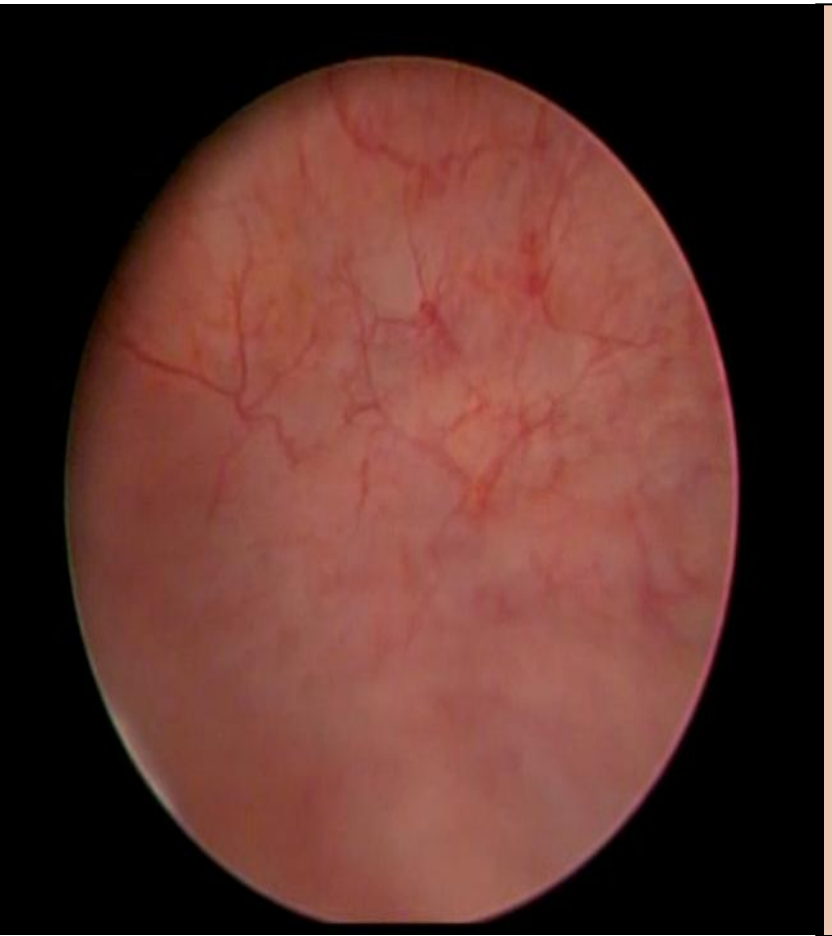
M3 appears to be the most clinically relevant in the human bladder,

The most important afferents for the micturition process are **myelinated A delta fibres** travelling in the pelvic nerve to the sacral spinal cord, conveying information from receptors in the bladder wall about bladder filling

PATHOGENESIS OF OAB

- Acetylcholine is not only released from parasympathetic nerve endings in the urinary bladder, but also, non-neuronally by the urothelium
- Pathologic conditions like bladder-outflow obstruction may enhance responsiveness to acetylcholine
- **C fibers** are relatively inactive during normal voiding due to high mechanical threshold but may have a critical role in symptoms of OAB in patients with neurologic and other disorders

PATHOGENESIS OF OAB



C-fibers respond primarily to chemical irritation of the bladder mucosa

&

exhibit spontaneous firing when the bladder is empty and increased firing during bladder distension

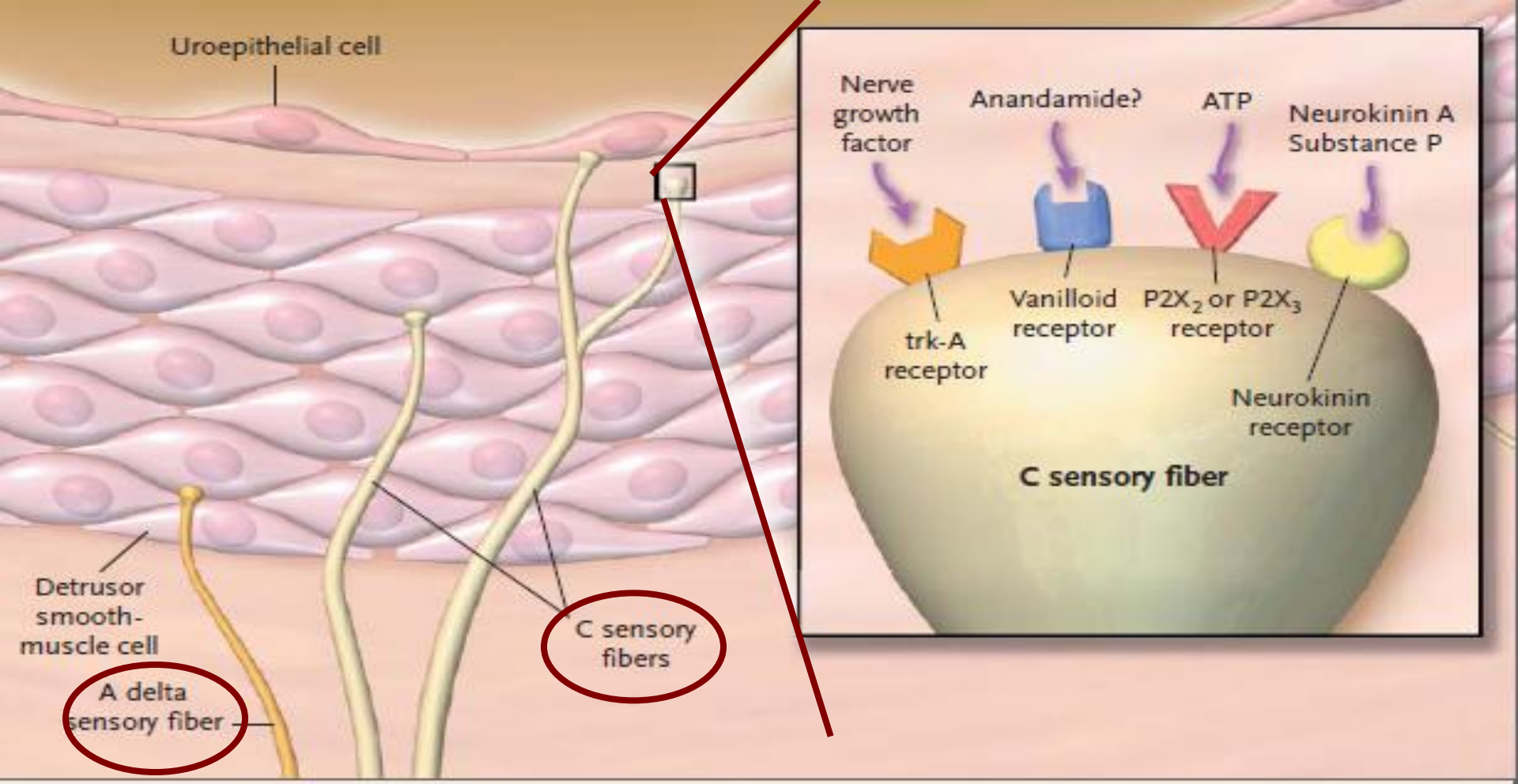
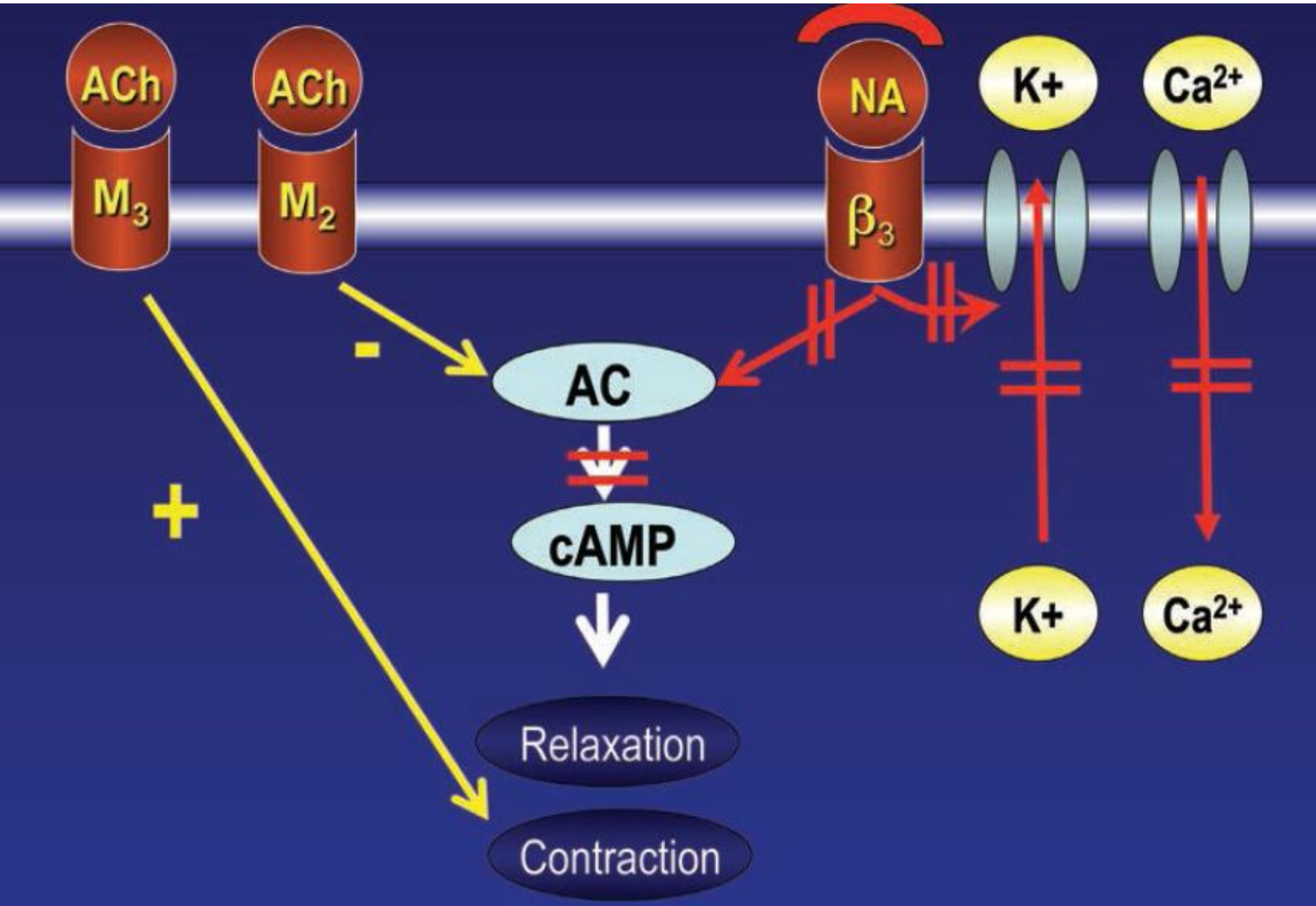


Figure 3. Current Concepts of Sensory Innervation of the Bladder.

Myelinated A delta sensory fibers respond predominantly to mechanical stretching of detrusor muscle cells during bladder filling. Unmyelinated C sensory fibers may help trigger the symptoms of overactive bladder in pathologic conditions. C fibers have receptors for a variety of neurotransmitters and substances that can be released from afferent nerves, detrusor smooth muscle, and the uroepithelium. These receptors include vanilloid receptors, which can be stimulated by capsaicin and, possibly, endogenous anandamide; purinergic receptors ($P2X_2$ and $P2X_3$), which are activated by ATP; neurokinin receptors, which are activated by neurokinin A and substance P; and trk-A receptors for nerve growth factor. The nerve growth factor produced by muscle cells, as well as nitrous oxide produced by the uroepithelium, may play key roles in modulating the responsiveness of afferent innervation in the bladder. Data are from Morrison et al.,[20] Yoshimura and Chancellor,[21] and Andersson and Hedlund.[22]


ACh
ACh
NA
K+
Ca2+
M3
M2
β3
-
AC
+
cAMP
K+
Ca2+
Relaxation
Contraction

Oxybutynin – immediate release (FDA 1992)

- OXY-IR was the first drug used for OAB
- The short half-life of 2−3 hours necessitates frequent dosing, with a common regime of 2.5−5 mg administered every 8 hours
- Undergoes extensive first-pass metabolism in the liver
- The most common side effects at 5–20 mg/day; dry mouth (71.4%), constipation (15.1%), somnolence (14%) and nausea (11.6%)

Pagoria D et al. *Curr Urol Rep*. 2011;12(5):351–357

Oxybutynin – extended release (FDA 1999)

- Available as, 5 mg /10 mg /15 mg once daily formulation
- Following the first dose, plasma concentrations rise for 4−6 hours, and remain steady for up to 24 hours
- Similar efficacy for the ER and IR formulations but a reduced incidence of dry mouth with the ER formulation (68% ER vs 87% IR)
- Better tolerability than the IR formulation

Kennelly MJ et al. *Rev Urol*. 2010;12(1):12–19

Oxybutynin- controlled release transdermal patch (OXYTROL) FDA (2013)

- After initial application of (OXY-TDS), plasma concentrations increase for 24−48 hours and remain steady for up to 96 hours
- By-pass gastrointestinal and hepatic metabolism
- Most common adverse reactions; application site pruritus (16.1%), application site erythema (7.0%), dry mouth (7.0%), constipation (2.1%)
- Efficacy and safety of OXY-TDS, compared with tolterodine-ER, demonstrated similar improvements, with less systemic adverse effects
- The first over-the-counter treatment for OAB in women aged 18 or older

Dmochowski RR et al. *World J Urol*. 2005;23(4):263–270

Oxybutynin – topical gel (FDA 2009)

- Steady state concentrations are achieved within 3 days of continuous dosing, applied once daily to clean, dry skin
- The most common adverse event, dry mouth, occurred in 6.1%, 73.1%, and 7.8% of participants receiving OXY-OTG, OXY-IR, and placebo, respectively
- Compared with OXY-IR, OXY-OTG has equivalent efficacy, with reduced anticholinergic side effects
- Not associated with the skin irritation of the patch

Staskin DR, et al. *J Urol*. 2009;181(4):1764–1772
Kay GG, et al. *Clin Drug Investig*. 2012;32(10):707–714.

Tolterodine tartarate (FDA 1997)

- Available in IR (1−2 mg twice daily) & ER formulations (2 mg or 4 mg daily dose)
- Undergoes hepatic metabolism forming an active metabolite; 5-hydroxymethyl (5-HMT)
- Tolterodine and 5-HMT are highly selective for muscarinic receptors
- Hepatic and renal insufficiency can significantly alter the metabolism of tolterodine
- Increases the cardiac QT interval at doses of 8 mg/day or higher
- Should not be preferred in patients with a known prolongation of QT interval, or who are taking class IA or III antiarrhythmic medications
- A Cochrane review found that compared with OXY, tolterodine had equivalent effects on QOL, patient-reported cure or improvement, leakage episodes, and voids in 24 hours

Cochrane Database Syst Rev. 2012

Solifenacin succinate (FDA 2004)

- Solifenacin (YM-905) is a long-acting muscarinic receptor antagonist (Mean terminal half-life is approximately 50 hours)
- Tertiary amine with some selectivity for M3 receptors (10–20-fold)
- Well absorbed from the gastrointestinal tract (absolute bioavailability 90%)
- Hepatic metabolism involving the cytochrome P450 enzyme system (CYP3A4)
- The efficacy, safety, and tolerability in OAB have been documented in large-scale early trials
- Recommended dosages are 5mg/d and 10mg/d

Madhuvrata P. Et al. *Cochrane Database Syst Rev*.2012;1:CD005429

Trospium chloride (FDA 2004)

- Quaternary ammonium compound
- No selectivity for muscarinic receptor subtypes
- Cross the blood-brain barrier to a limited extent
- Plasma half-life of approximately 20 hours
- Mainly (60%) eliminated unchanged in the urine by tubular secretion
- Not metabolized by the cytochrome P450 enzyme system
- Well documented effect in OAB/DO and seems to be well tolerated
- Recommended dose for adults is 20mg twice-daily

Ginsberg DA et al. *Neurourol Urodyn*. 2011;30(4): 563–567

Darifenacin HBr (FDA 2004)

- Selective muscarinic M3 receptor antagonist
- Tertiary amine with moderate lipophilicity
- Well absorbed from the gastrointestinal tract
- Metabolised in the liver by the cytochrome P450 isoforms CYP3A4 and CYP2D6
- Controlled-release formulation (once-daily dosing of 7.5mg/d and 15mg/d)
- Reported rates of constipation are comparatively higher than with equivalent alternative antimuscarinics (14.8% with 7.5 mg daily and 21.3% with 15 mg/daily)

Enablex (darifenacin) extended-release tablets [prescribing information]. Stein, Switzerland: Novartis Pharma Stein AG; 20008

Fesoterodine fumarate (FDA 2008)

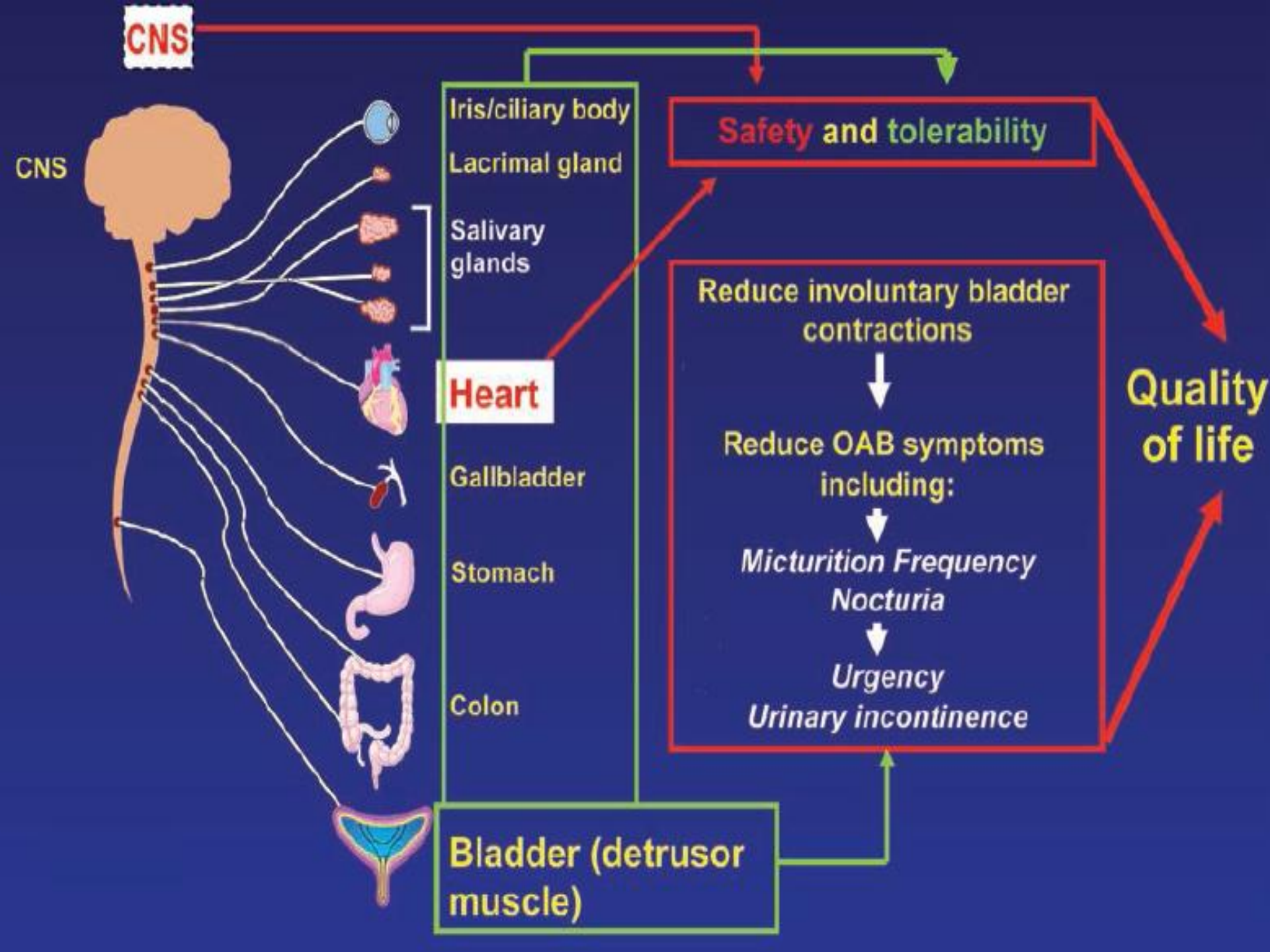
- Available as ER 4 mg or 8 mg once-daily oral doses
- Rapid and extensive hydrolyse by serum esterases to 5-HMT, results in more consistent and predictable drug levels compared with tolterodine
- The rapid metabolism and the low−moderate lipophilic nature contribute to its minimal effect on cognition
- ECG measures showed no prolongation of QT interval with a therapeutic dose (4 mg) and supratherapeutic dose (28 mg) in a double-blind, randomized, placebo-and positive-controlled (moxifloxacin 400 mg) parallel trial
- Superior to tolterodine across multiple outcome measures, including patient-reported cure or improvement in leakage episodes, frequency, and urgency episodes in 24 hours

Kay GG et al. *Postgrad Med*. 2012;124(3):7–15

Propiverine HCL

- Mixed-action drug with a nonselective antimuscarinic component & calcium channel−blocking effects
- The usual starting dose of propiverine-IR is 15 mg bid and 30 mg once daily for the ER formulation
- Several placebo-controlled studies demonstrated significant reduction in average micturition volume, frequency, number of incontinence episodes with propiverine IR and ER formulations with a higher rate of dry mouth, blurred vision and constipation

Asimakopoulos AD et al. *Urol Int*. 2012;89(3):259–269


CNS
CNS
Iris/ciliary body
Lacrimal gland
Salivary glands
Heart
Gallbladder
Stomach
Colon
Bladder (detrusor muscle)
Safety and tolerability
Reduce involuntary bladder contractions
Reduce OAB symptoms including:
Micturition Frequency
Nocturia
Urgency
Urinary incontinence
Quality of life

ADVERSE EFFECTS OF ANTIMUSCARINICS

- Angioedema of the face, lips, tongue, and/or pharynx has been noted in several of these agents in postmarketing surveillance, including solifenacin, darifenacin, trospium chloride, and fesoterodine

- Frequent side effects;
  dry mouth, constipation, blurred vision, and drowsiness, may also produce confusion, especially in elderly patients

- Severe side effects; CNS & CVS
  sedation, inability to concentrate, memory impairment, delirium

- **CONTRAINDICATED IN PATIENTS** with urinary retention, gastric retention, and untreated narrow-angle glaucoma

- Should be used with caution in patients with clinically significant bladder outlet obstruction, decreased gastrointestinal motility, treated narrow angle glaucoma and myasthenia gravis

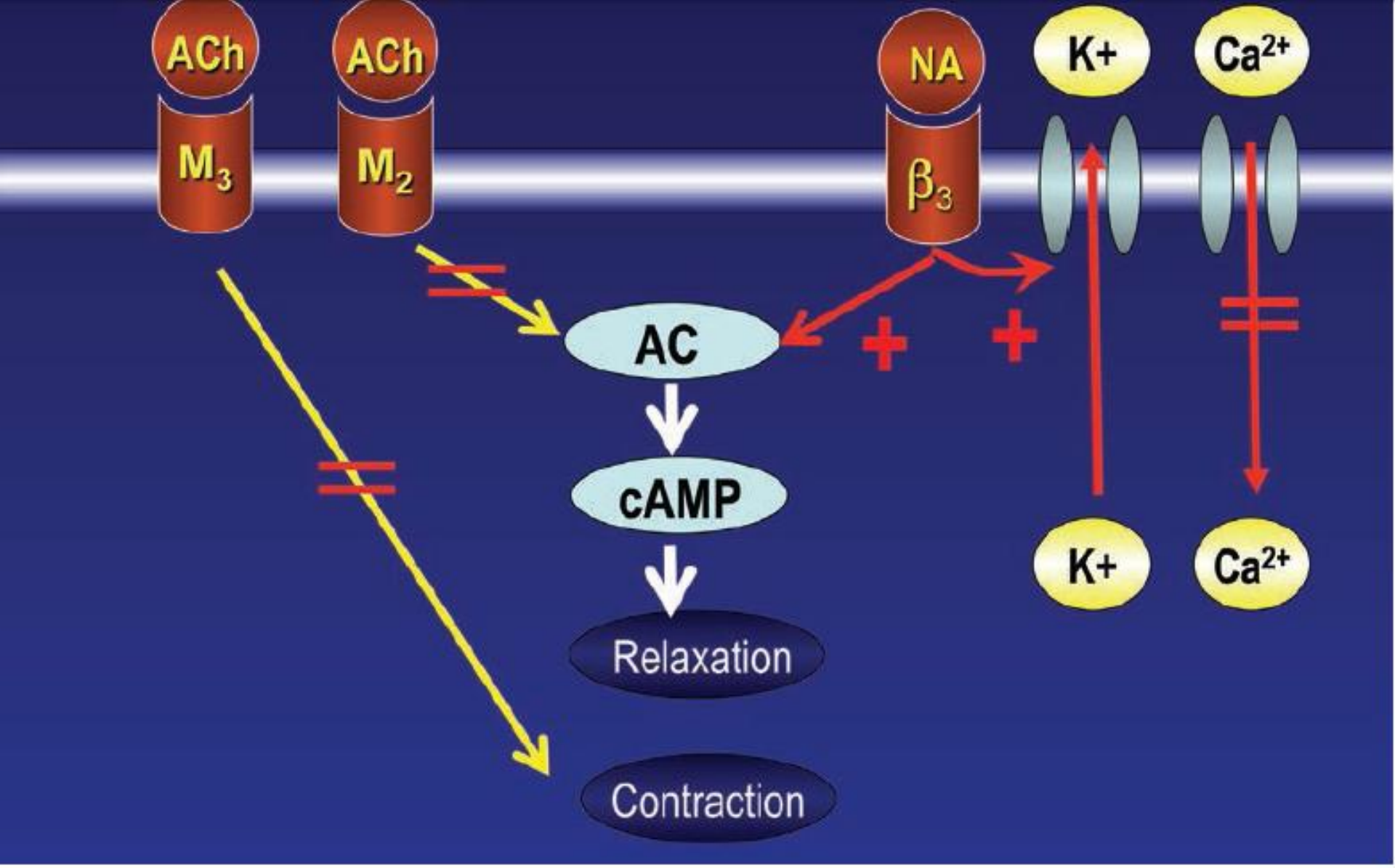


Figure 12 : During bladder filling, there is normally no parasympathetic nervous outflow to the bladder and no release of acetylcholine (ACh). The sympathetic nervous system is active and releases noradrenaline (NA) that via β3 adrenoceptors stimulates adenylyl cyclase (AC) and generation of cyclic AMP (cAMP) which mediates relaxation of the bladder. In addition, β3-adrenoceptor stimulation activate K+ channels,

Mirabegron

- First β3-AR agonist approved for the treatment of OAB
- Main sites of action are the β3-ARs on detrusor smooth muscle with a dose-dependent relaxation during bladder filling and inhibit detrusor overactivity
- Avoids the side effect profile typical of anticholinergic agents
- The recommended starting dose of mirabegron is 50 mg once daily in Japan and Europe; 25 mg once-daily in the USA & can be increased to 50 mg on an individual basis

Takasu T et al. *J Pharmacol Exp Ther*. 2007;321(2):642–647

AUA/SUFU GUİDELİNE RECOMMENDATIONS

- Extended release (ER) formulations should preferentially be prescribed over IR formulations because of lower rates of dry mouth *(Evidence Strength Grade B)*

- Transdermal (TDS) oxybutynin (patch or gel [available to women ages >/=18 years without a prescription] may be offered *(Evidence Strength Grade C)*

- *In the case of inadequate symptom control or unacceptable adverse effect drug with one anti-muscarinic medication;*

  Dose modification

  Different anti-muscarinic medication

  β3-adrenoceptor agonist may be tried (Clinical Principle)

AUA/SUFU GUİDELİNE RECOMMENDATIONS

- Anti-muscarinics shoud not be used in patients with narrow-angle glaucoma
- Should be used with extreme caution in patients with impaired gastric emptying or a history of urinary retention *(Clinical Principle)*
- Clinicians should manage constipation and dry mouth before abandoning effective anti-muscarinic therapy *(Clinical Principle)*
- Clinicians should use caution in prescribing anti-muscarinics or β3-adrenoceptor agonists in the frail OAB patient *(Clinical Principle)*

GUIDELINES & RECOMMENDATIONS

AUA

ER formulations should be

preferred over IR, because of the lower rates of dry mouth

EUA

Either IR or ER preparations may be used initially

ER preparations should be used if Initial trials of IR fail

NICE

Oxybutynin IR, tolterodine IR, or darifenacin should be used as firstline drugs

based mainly on cost factors

GUIDELINES & RECOMMENDATIONS

AUA

Do not mention **mirabegron** specifically

EUA

Recommends using **mirabegron** in patients with urgency

urinary incontinence (UUI)

NICE

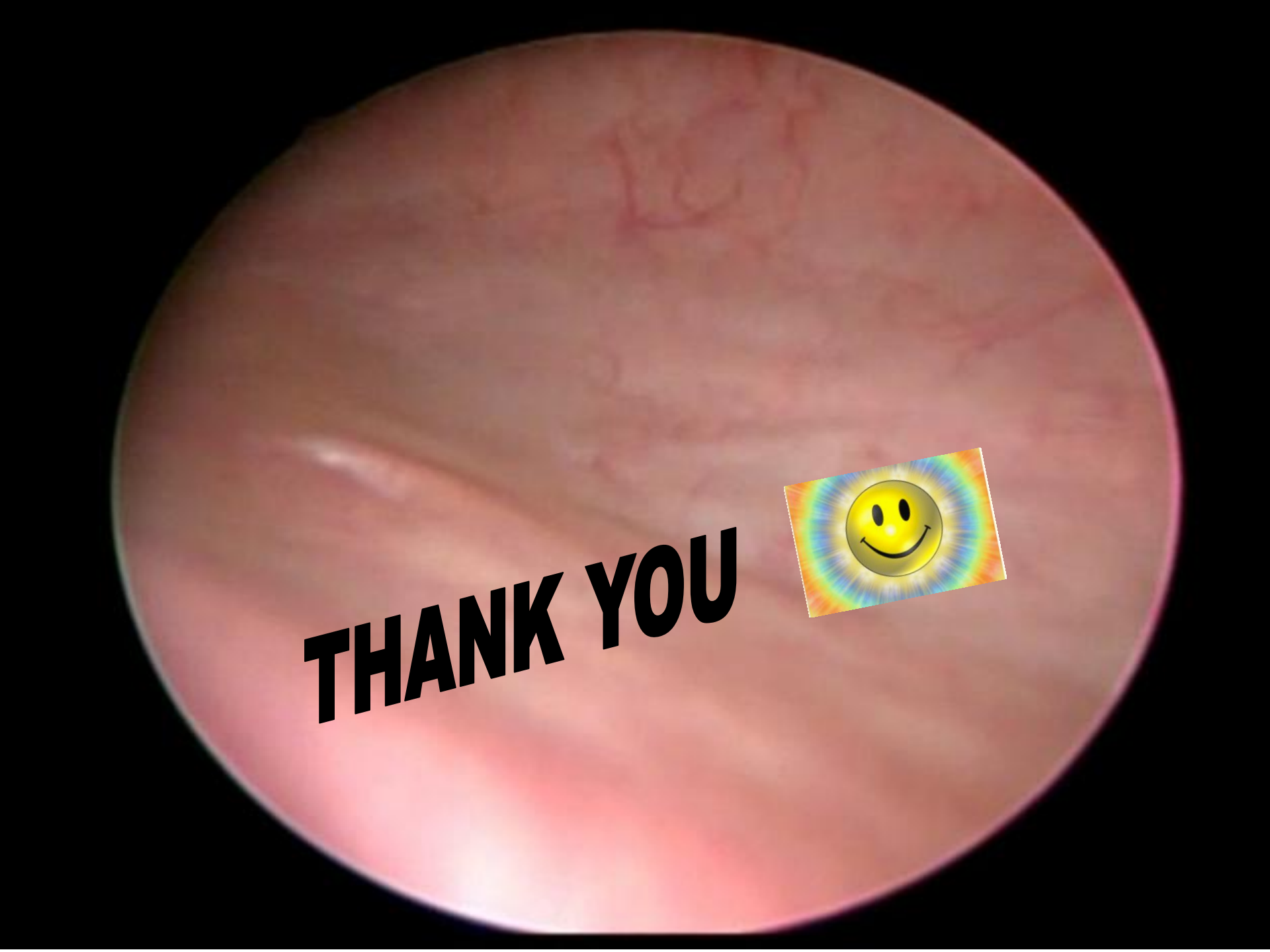
Recommends that **mirabegron** be used as a

third-line oral therapy option in patients who have failed a trial of at least two anticholinergics

THE FUTURE DEVELOPMENT OF DRUG THERAPY

- K+ channel openers
- 5-HT modulators
- Neurokinin receptor antagonists
- Alpha-adrenoceptor antagonists
- Nerve growth factor inhibitors
- Gene therapy
- Stem cell–based therapies

Future innovative therapies are aimed at novel mechanisms of action, all are of considerable interest and appears promising


THANK YOU