AŞIRI AKTİF MESANE FARMAKOTERAPİSİNDE YENİLİKLER

DR.M.MURAT DİNÇER,FECSM

Bağcılar Eğitim ve Araştırma hastanesi , Üroloji kln.

TÜAK İnkontinans topl.

14 mayıs 2016 Kayseri

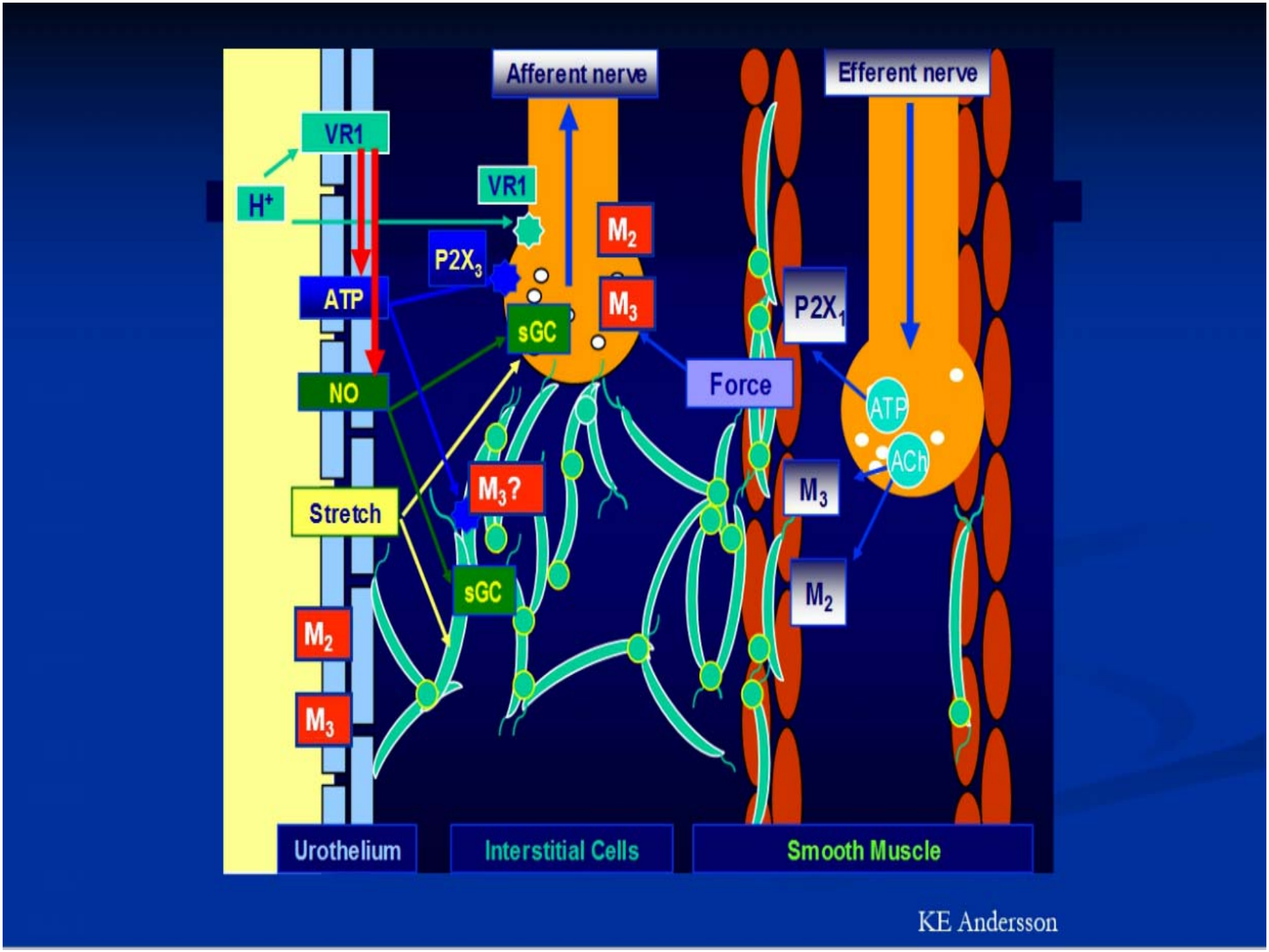
FORUMS

A Decade of Pharmacotherapy for Overactive Bladder: What Have We Learned?

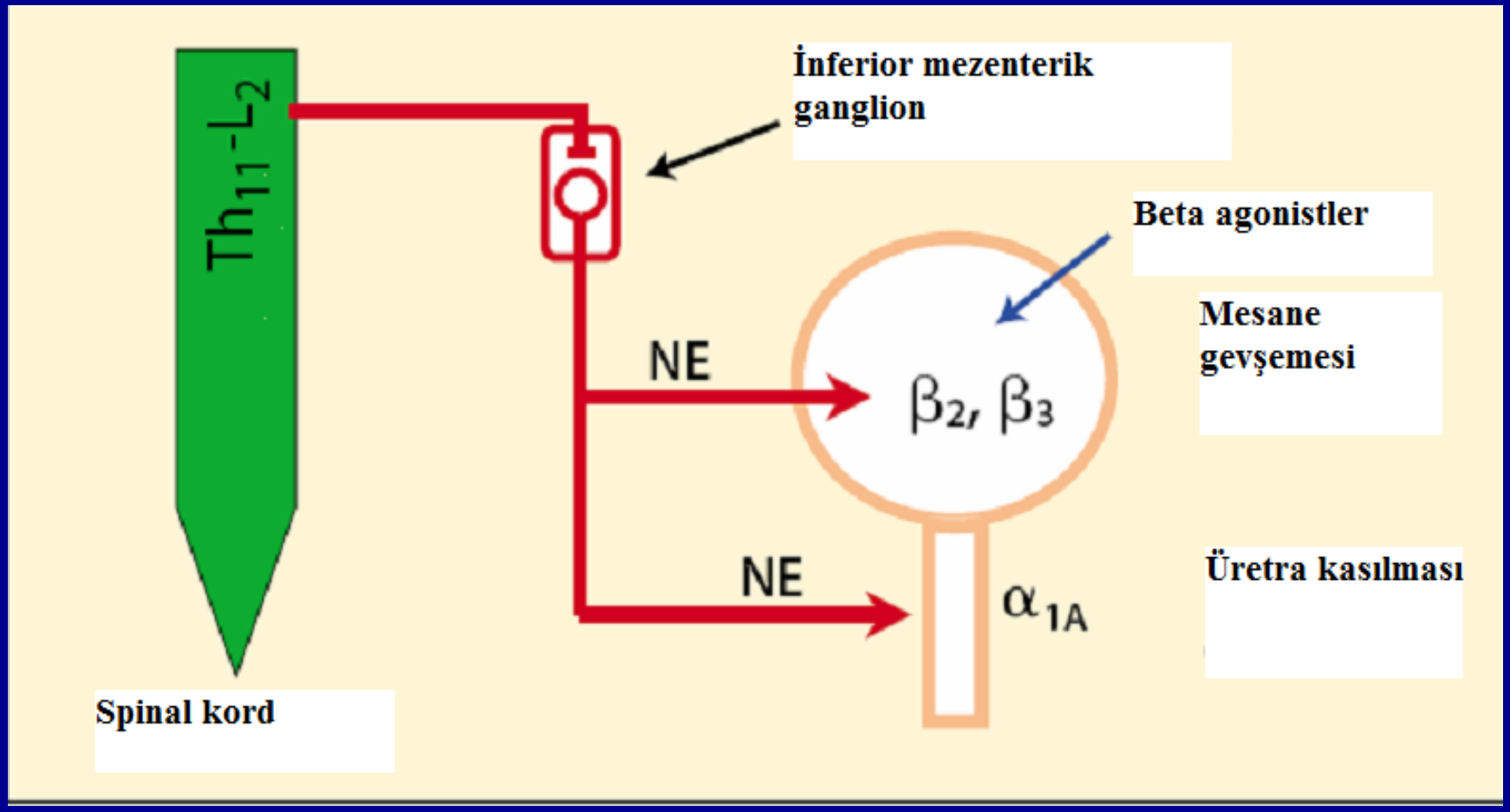
Alan J. Wein, MD, PhD (hon), FACS, Moderator

Origin of the Term Overactive Bladder

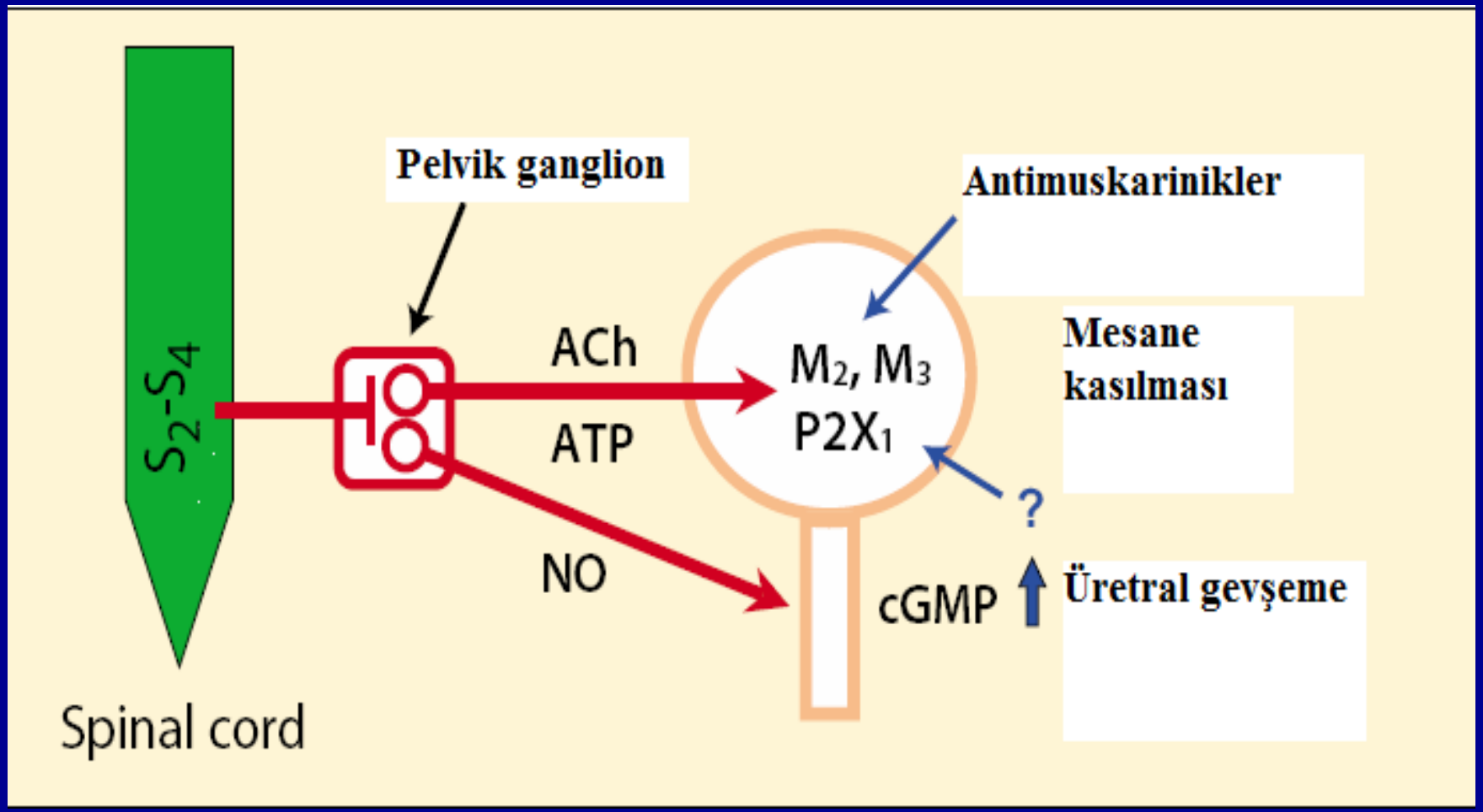
Dr. Paul Abrams pointed out that use of the term overactive bladder (OAB) originated in 1997 as an alternative to the term "unstable bladder." The term was first used in the title of a symposium in 1997, "Introduction to the Overactive Bladder: From Basic Science to Clinical Management." It was ultimately adopted in 2002 by the Standardization Subcommittee of the International Continence Society and officially defined as "urinary urgency usually accompanied by frequency and nocturia, with or without urge urinary incontinence, in the absence of urinary tract infection or other obvious cause."


Afferent nerve
Efferent nerve
VR1
H+
VR1
M2
P2X3
ATP
M3
sGC
P2X1
NO
Force
ATP
ACh
M3?
Stretch
M3
sGC
M2
M2
M3
Urothelium
Interstitial Cells
Smooth Muscle
KE Andersson

Depolama (Sempatetik sinir sistemi)



Boşaltma (Parasempatik sinir)



İDEAL İLAÇ ?

- Mesanenin istenmeyen kasılmalarını önlemeli
- Detrusor kasının amplütüdünü azaltmalı
- Mesane kapasitesini artırmalı
- İlk idrar hissini geciktirmeli
- Normal işemeyi engellememeli

- Sıkışma hissi (Urgency)
- Sık idrara gitme
- Noktüri
- Sıkışma (Urge) tip İnkontinans semptomlarını önlemeli ya da azaltmalı

COCHRANE REVIEW 2012

AKILCI İLAÇ KULLANIMI

- Akılcı İlaç Kullanımı tanımı ilk defa 1985 yılında Dünya Sağlık Örgütü tarafından yapılmıştır.

- Kişilerin klinik bulgularına ve bireysel özelliklerine göre; **uygun ilacı**, **uygun süre** ve **dozda**, **en düşük fiyata** ve **kolayca** sağlayabilmeleri olarak tanımlanmaktadır.

Conference of Experts on the Rational Use of Drugs, World Health Organization, Nairobi, Kenya, WHO/CONRAD/WP/RI, (25-29.12.1985).

ANTİKOLİNERJİK AJANLAR

Oxybutynin
Tolterodine
Propiverin
Trospium chloride
Solifenacin
Darifenacin
Fesoterodine

KANIT

Evidence summary	LE
All formulations of Fesoterodine, Oxybutynin, Propiverine, Solifenacin, Tolterodine, Darifenacin and Trospium, provide a significantly better rate of cure or improvement of UUI compared to placebo.	1a
All formulations of Fesoterodine, Oxybutynin, Propiverine, Solifenacin, Tolterodine, Darifenacin and Trospium, result in higher rates of dry mouth compared to placebo.	1b

Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline

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

From the American Urological Association Education and Research, Inc., Linthicum, Maryland, and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction

Diagnosis & Treatment Algorithm: AUA Guideline on Non-Neurogenic Overactive Bladder in Adults.

History and Physical; Urinalysis

Diagnosis unclear or additional information needed

+/- urine culture, post-void residual, bladder diary, and/or symptom questionnaires

Not OAB or Complicated OAB; treat or refer

Signs/symptoms of OAB, (-) urine microscopy

Signs/symptoms of OAB

Patient education:
- Normal urinary tract function
- Benefits/risks of treatment alternatives
- Agree on treatment goals

Patient desires treatment and/or treatment is in patient's best interests

Behavioral Treatments
(consider adding anti-muscarinic if partially effective)

Follow-up for efficacy and adverse events

Treatment goals met

In extremely rare cases, consider urinary diversion or augmentation cystoplasty

Treatment goals not met; Patient desires further treatment and/or further treatment in patient's best interests

Anti-muscarinics with active management of adverse events (e.g., dry mouth, constipation); consider dose modification or alternate anti-muscarinic if effective but adverse events are intolerable

Treatment goals not met; Patient desires further treatment and/or further treatment in patient's best interests

Reassess and/or refer; consider urine culture, post-void residual, bladder diary, symptom questionnaires, other diagnostic procedures as necessary for differentiation

Signs/symptoms consistent with OAB diagnosis

Consider in carefully-selected patients
(multiple therapies may be tried but they should not be combined):

FDA-Approved:
- Sacral neuromodulation (SNS) or
- Percutaneous tibial nerve stimulation (PTNS) or

Non-FDA-Approved:
- Intradetrusor onabotulinumtoxinA

The complete OAB Guideline is available at www.AUAnet.org/Guidelines.

This resource is supported by an educational grant from Astellas Scientific and Medical Affairs, Inc.

Antikolinerjiklerde Karşılaştırma: KANIT

Table 5: Comparison of antimuscarinic drugs as reviewed in the 2012 AHRQ review [180]

Experimental drug versus standard drug	No. of studies	Patients	Relative risk (95% CI) of curing UI
Efficacy			
Fesoterodine vs. tolterodine ER (continence)	2	3312	1.1 (1.04-1.16)
Oxybutynin ER vs. tolterodine ER (improvement)	3	947	1.11 (0.94-1.31)
Solifenacin vs. tolterodine ER	1	1177	1.2 (1.08-1.34)
Trospium vs. oxybutynin	1	357	1.1 (1.04-1.16)
Discontinuation due to adverse events			
			RR – 95% CI of discontinuation
Solifenacin vs. tolterodine ER	3	2755	1.28 (0.86-1.91)
Trospium vs. oxybutynin	2	2015	0.75 (0.52 -1.1)
Fesoterodine vs. tolterodine	4	4440	1.54 (1.21-1.97)

Which anticholinergic drug for overactive bladder symptoms in adults (Review)

Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJC

THE COCHRANE

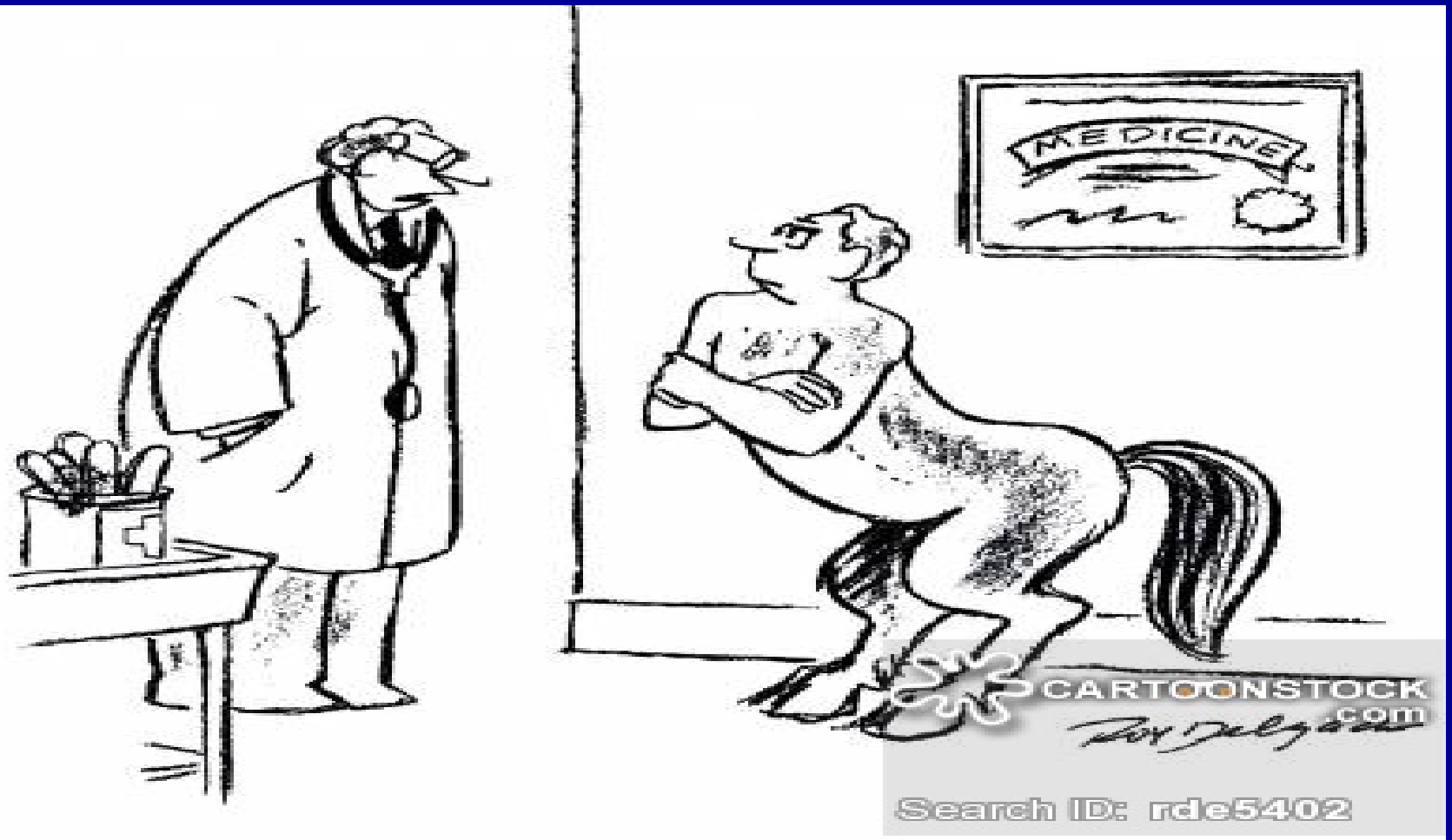
Cochrane Database Syst Rev. 2012 Jan 18;1:CD005429.

Which anticholinergic drug for overactive bladder symptoms in adults.

Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJ.
Obstetrics & Gynaecology, Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, UK.Priyamadhuvrata@nhs.net

- Trospium vs Oxybutynin
- Darifenacin versus oxybutynin
- Trospium versus Tolterodine
- Propiverine vs Tolterodine
- Solifenacin vs Propiverine

Yeterli veri yok!



"I told you there might be some side-effects from the medication."

Offer IR or ER formulations of antimuscarinic drugs for adults with urgency urinary incontinence.	A
If IR formulations of antimuscarinic drugs are unsuccessful for adults with urgency urinary incontinence, offer ER formulations or longer-acting antimuscarinic agents.	A

EAU guidelines 2015

Age and Ageing 2015; **44:** 745–755
doi: 10.1093/ageing/afv077
Published electronically 23 June 2015

Appropriateness of oral drugs for long-term treatment of lower urinary tract symptoms in older persons: results of a systematic literature review and international consensus validation process (LUTS-FORTA 2014)

Matthias Oelke[1], Klaus Becher[2], David Castro-Diaz[3], Emmanuel Chartier-Kastler[4], Mike Kirby[5,6], Adrian Wagg[7], Martin Wehling[8]

Fesoterodin yaşlılarda B kategori düzeyi ile ön

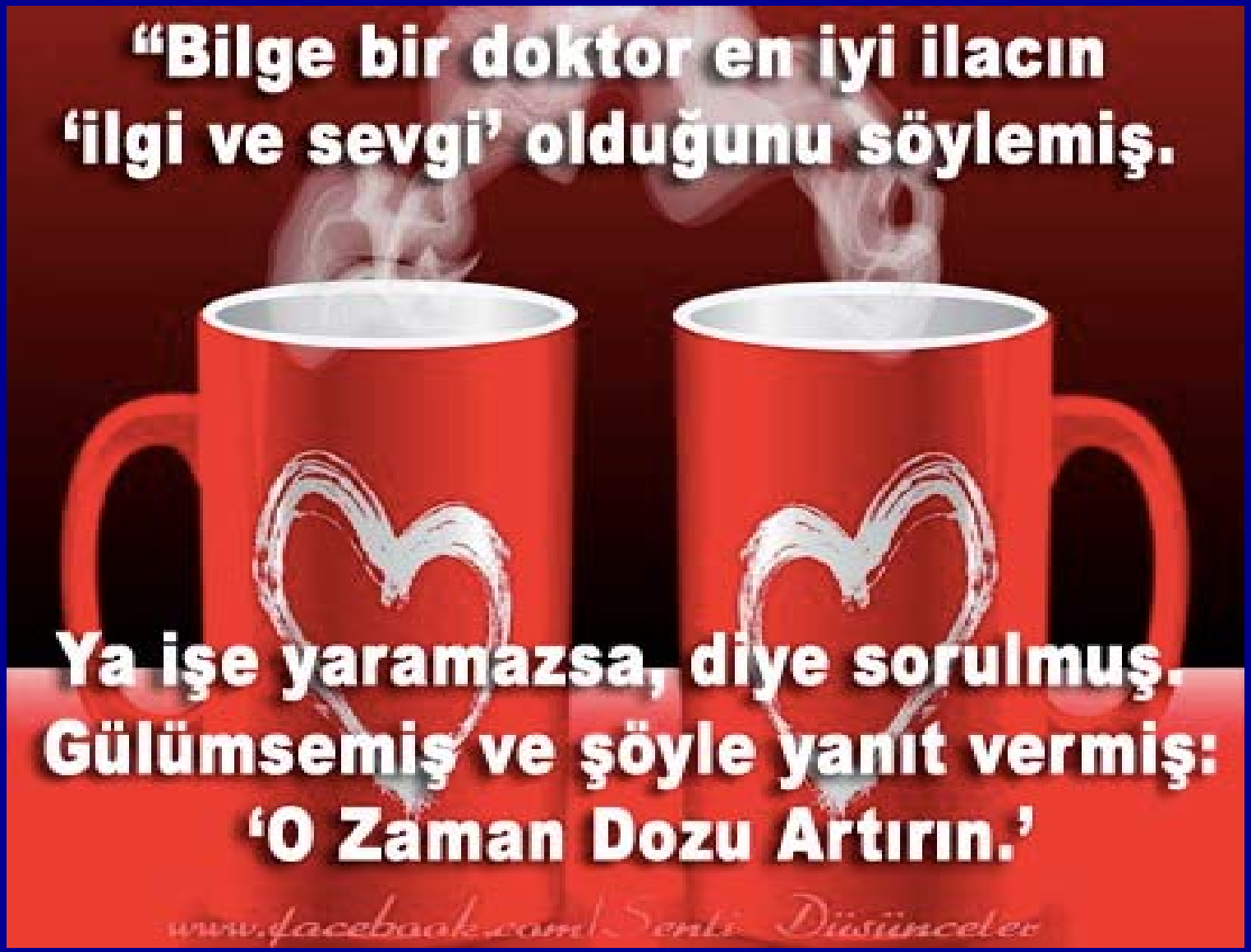
all different

all equal

Evidence summary	LE
All formulations of Fesoterodine, Oxybutynin, Propiverine, Solifenacin, Tolterodine, Darifenacin and Trospium, provide a significantly better rate of cure or improvement of UUI compared to placebo.	1a
All formulations of Fesoterodine, Oxybutynin, Propiverine, Solifenacin, Tolterodine, Darifenacin and Trospium, result in higher rates of dry mouth compared to placebo.	1b

EAU guidelines 2016


9½ 11
9½ 11
9 10½
9 10½
9 10½
10½ 12
10½ 12
11½ 13
11½ 13
10 11½
9½ 11
9½ 11
11 12½
11 12½


“Bilge bir doktor en iyi ilacın
‘ilgi ve sevgi’ olduğunu söylemiş.
Ya işe yaramazsa, diye sorulmuş.
Gülümsemiş ve şöyle yanıt vermiş:
‘O Zaman Dozu Artırın.’
www.facebook.com/Sonsuz Düşünceler

Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline

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

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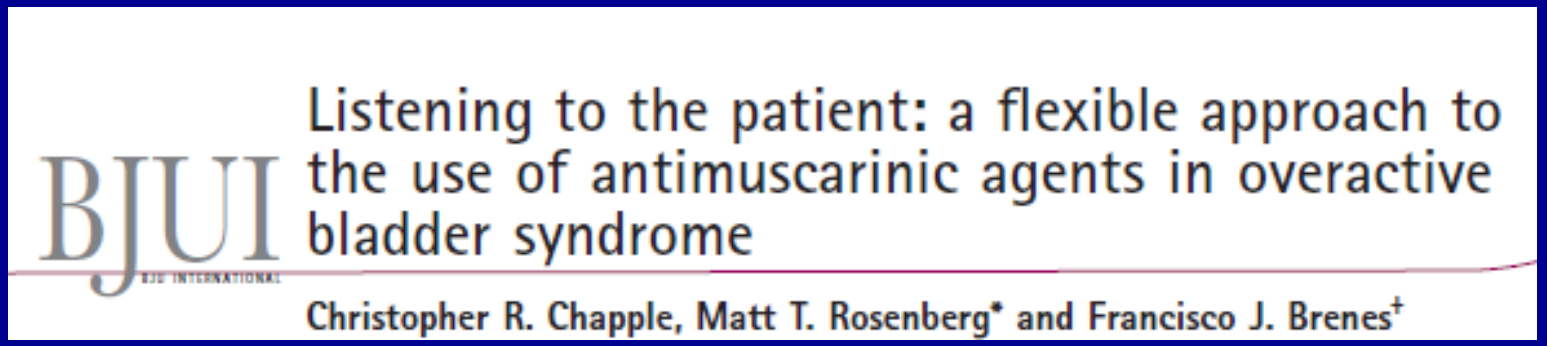
- **Guideline Statement 11.**

  If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one anti-muscarinic medication, then a dose modification or a different anti-muscarinic medication may be tried.

Vol. 188, 2455-2463, December 2012 THE JOURNAL OF UROLOGY®



- Solifenasin, Darifenasin ve Oksibutinin'in uzun etkili formları değerlendirilmiş

- Doz artırımı gereken hastalar genellikle başlangıçta yoğun semptomları olan hastalar ve doz artırımı yakınmalarda azalma sağlamış

BJU İnternational, 104, 960-967, 2009.


ABCDEFGH
IJK
LMN
OPQ
RST
UV
YZ
NrlStyle.blogspot.com
Eğer A planı işe yaramazsa Alfabede 28 harf daha olduğunu hatırlayın!:)

What Treatment Should We Use If Drugs Fail for OAB; and, What Really Works After Drugs?

J.L.H.R. Bosch,[1*] C. Kelleher,[2] P.E.V. van Kerrebroeck,[3] and B. Schurch[4]

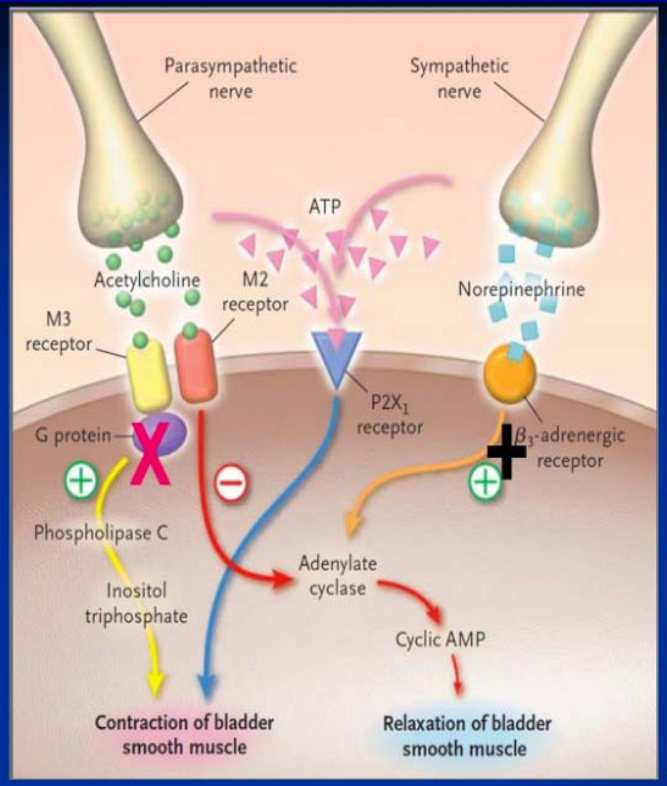
- Hastayı tekrar değerlendir
- İlaç kombinasyonları
  - Davranış tedavileri
  - Beta 3 agonistler ve/veya antikolinerjik
  - Antikolinerjik + Alfabloker
  - Antkolinerjik + Desmopressin
- Eksperimental ilaçlar

Neurourology and Urodynamics 29:658–661 (2010)

BETA 3 AGONİSTLER

Antimuscarinics

Decrease contraction contracción vesical



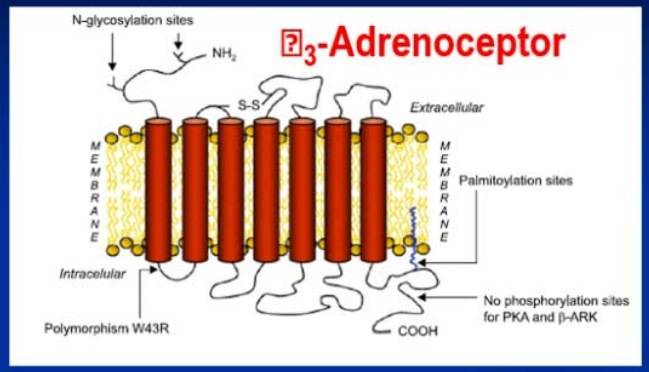
β3 Agonists

Produce bladder relaxation

Stimulation of β3 receptors inhibits involuntary detrusor contractions during filling phase improving OAB symptoms

Ouslander NEJM 2004

Beta$_3$-Adrenoceptor Agonists



Solabegron

Mirabegron

Beta 3 agonist (Mirabegron)

- ß-adrenoreceptor agonist, detrusor kasını gevşetir.
- 50-100 mg ER formu UUI tedavisinde orta düzeyde fayda sağlıyor.
- Kalpte 2 atım/dk da artışa neden oluyor.
- Amerika , Japonya ve Avrupa 25 ve 50 mg dozlarında AAM kullanımı için onay verilmiş.
- Hipertansiyon (%9.9), nasofarenjit (%4.1), İYE (%3.1%), başağrısı, ağız kuruluğu, ekstremite ağrısı

Wagg et al. Age Ageing, 2014

EUROPEAN UROLOGY 67 (2015) 11–14

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

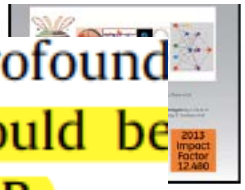
European Association of Urology

Platinum Priority – Brief Correspondence

Editorial by Maurizio Serati and Fabio Ghezzi on pp. 15–16 of this issue

Efficacy of the β3-adrenoceptor Agonist Mirabegron for the Treatment of Overactive Bladder by Severity of Incontinence at Baseline: A Post Hoc Analysis of Pooled Data from Three Randomised Phase 3 Trials

Christopher Chapple [a,], Vik Khullar [b], Victor W. Nitti [c], Jeffrey Frankel [d], Sender Herschorn [e], Mathilde Kaper [f], Mary Beth Blauwet [g], Emad Siddiqui [h]*



profound truth." In this case, we could have two profound truths and one encouraging hope: Mirabegron could be highly effective in women with severe forms of OAB.

Platinum Priority – Editorial

Referring to the article published on pp. 11–14 of this issue

Severity of Symptoms of Overactive Bladder: A Predictor of Success and of Failure

Maurizio Serati [*], Fabio Ghezzi

Department of Obstetrics and Gynecology, University of Insubria, Varese, Italy

PDE 5 İNHİBİTÖRLERİ

EUROPEAN UROLOGY 59 (2011) 272–279

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Neuro-urology

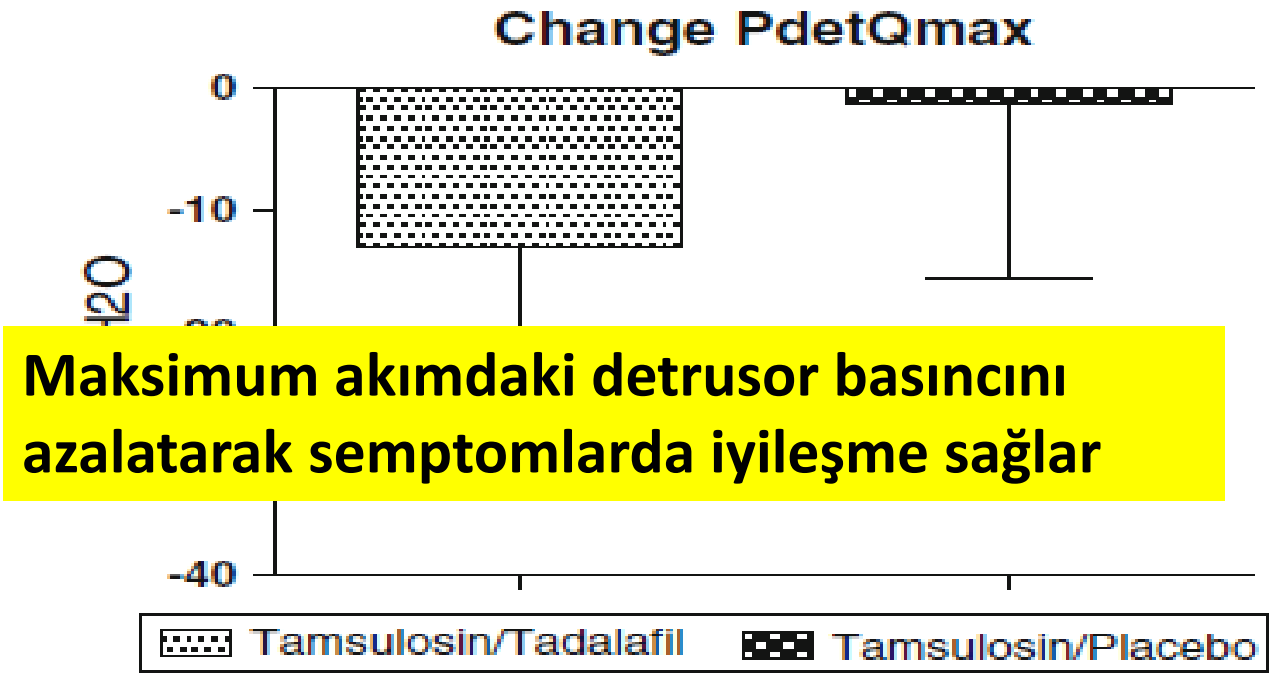
Vardenafil Decreases Bladder Afferent Nerve Activity in Unanesthetized, Decerebrate, Spinal Cord–Injured Rats

Delphine Behr-Roussel [a,d], *Stephanie Oger* [a,d], *Stéphanie Caisey* [a,d], *Peter Sandner* [b], *Jacques Bernabé* [a,d], *Laurent Alexandre* [a], *Francois Giuliano* [c,d,*]

Conclusions: Systemic vardenafil reduced both NVCs and BANF in unanesthetized, decerebrate, SCI rats. These findings provide new insights into the mechanism of action by which PDE5-Is improve storage symptoms in SCI patients.

Sistemik vardenafil enjeksiyonu sipinal kord hasarı oluşturulan ratlarda mesane afferent sinir uyarımını ve dolum fazı kasılmalarını engeller.

Tadalafil

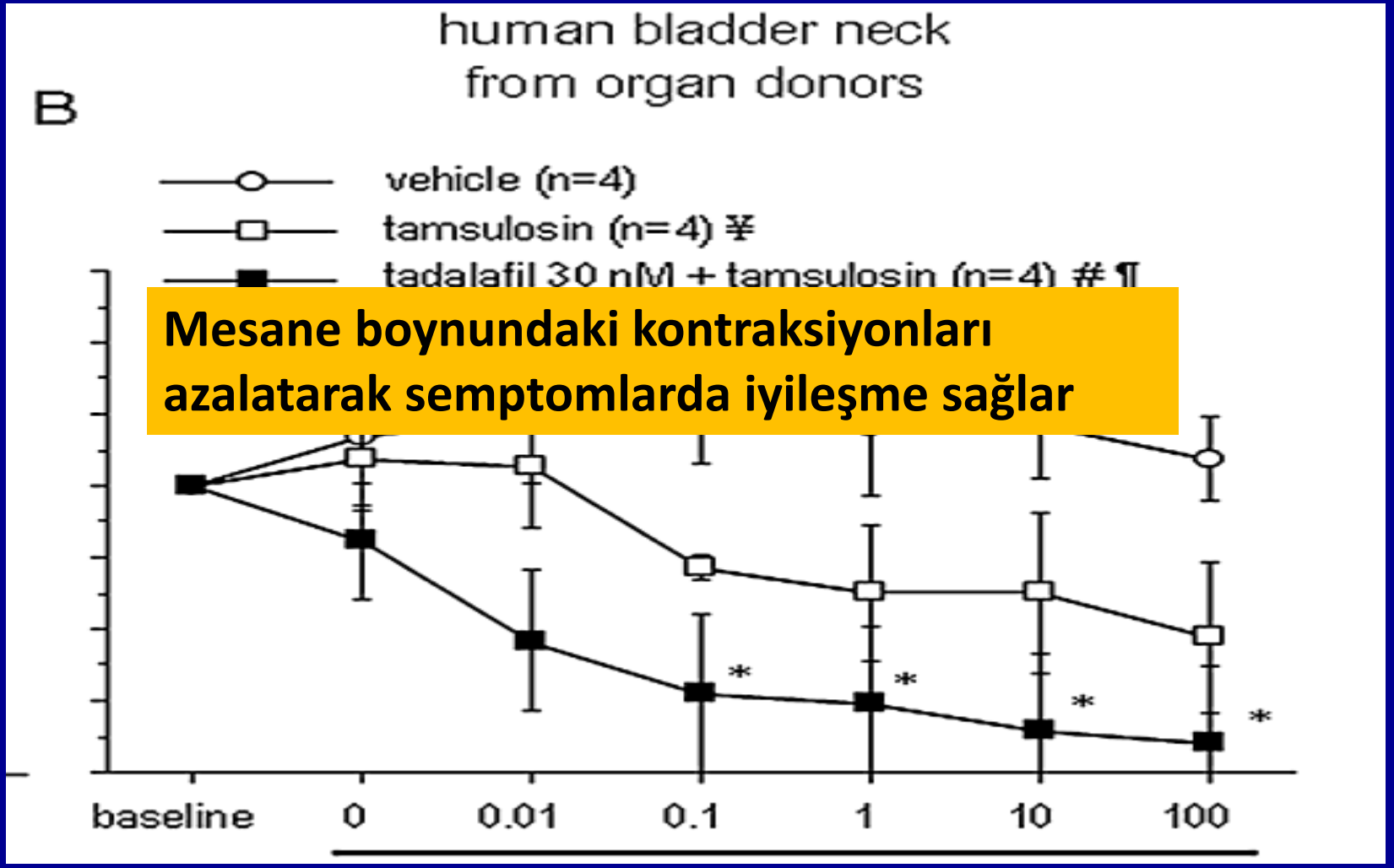


Maksimum akımdaki detrusor basıncını azalatarak semptomlarda iyileşme sağlar

Fig. 1 Changes in the detrusor pressure at maximum flow (PdetQmax) after 4 weeks treatment. Results are expressed as mean ± SD ($n = 20$). *$P = 0.03$ compared with tamsulosin/placebo group

RP, Regadas, Int Urol Nephrol (2013) 45:39–43

Tadalafil



Mesane boynundaki kontraksiyonları azalatarak semptomlarda iyileşme sağlar

Angulo et al.-J Sex Med 2012;9:2293–2306

PDE 5

- Uzun dönem sonuçlar
- Kadınlarda etkinlik !

ÖSTROJENLER

Östrojen Kullanımı

Recommendations	GR
Women using systemic oestrogen should be counselled that they have an increased risk for developing urinary incontinence or worsening of their existing incontinence.	A
Offer post-menopausal women with urinary incontinence local oestrogen therapy, although the ideal duration of therapy and best delivery method are unknown.	A
Advise post-menopausal women who are taking oral oestrogens that they have an increased risk for developing urinary incontinence or worsening of their existing urinary incontinence.	A

- Postmenapozal kadınlarda sistemik östrojen tedavisi yakınmaları daha da bozarken, lokal östrojen tedavisi faydalı olabilir.

- Ancak uzun döneme ait veriler bulunmamaktadır.

EAU Guidelines, 2016

Maturitas 71 (2012) 188–193

Contents lists available at SciVerse ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Mini review

Overactive bladder: Diagnosis and management

Dudley Robinson*, Linda Cardozo

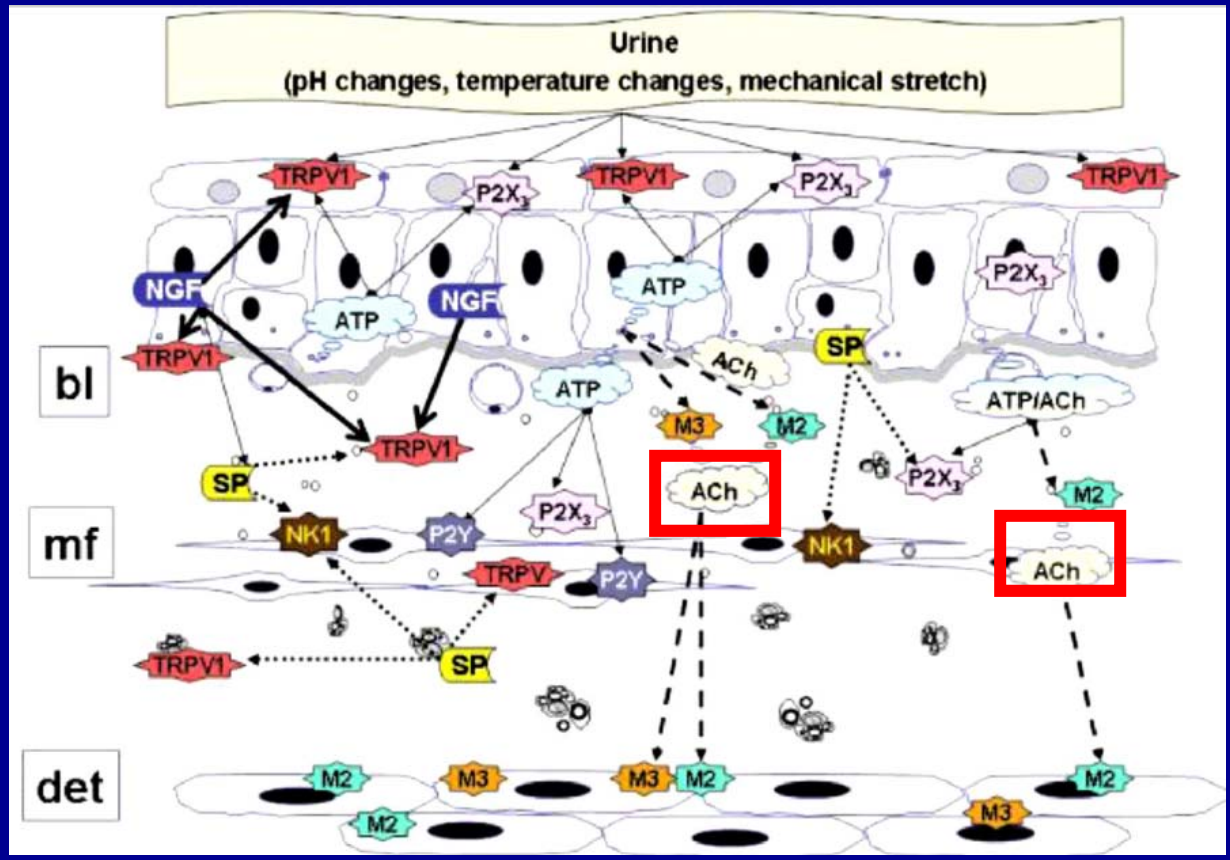
- Antikolinerjik tedavi ile birlikte lokal östrojen tedavisi kullanımı ile etkinliğin artabileceği tartışmalıdır.

Desmopressin

- Urge ve sık işemede fayda sağlıyor ancak UI da etkinliği tartışmalı.
- Nokturi vakalarında tercih ediliyor.
- Uzun süreli kullanım önerilmiyor.
- Hiponatremi riski var.
- Antikolinerjiklerle kullanımı sözkonusu

  (Solifenasın+Vasopressin, Han YK et al. Korean J Urol. 2011)

İlaç Tedavileri



Gelecekte Kullanılabilecek İlaçlar

- **Mukozal uyarıları engellemeyi hedefleyenler**
  - NGF inhibitörleri
  - P2X3- purinergic receptor antagonists
  - K kanal açıcılar
  - Prostanoid reseptör blokerleri
  - TRP- transient receptor potential
- **Miyosit uyarılarını engellemeyi hedefleyenler**
  - Beta 3 adrenoreseptör agonistleri
  - PDE 5 inhibitörleri
  - Roa-kinaz inhibitörleri
- **MSS etkileyen ilaçlar**

AUA
2016
san diego

Abstract: MP74-01

Introduction and Objectives

Introduction and Objective: Nocturia is a multi-factorial condition characterized by 2 or more voids per night interrupting sleep, with no currently approved treatments available in the US. This condition can be associated with BPH and OAB but can also occur independently of these conditions. SER120 is a novel formulation of low dose desmopressin (peptide analogue of the human anti-diuretic hormone) nasal spray designed to achieve low blood concentrations limiting the anti-diuretic effect to the hours of sleep, while decreasing the risk of hyponatremia. The objectives of this Phase 3 clinical study were to evaluate the efficacy and safety of 2 doses of SER120 for nocturia.

Methods

Methods: Patients greater or equal to 50 years old with a history of 2 or more nocturic episodes per night were screened for 2 weeks. After a double-blind 2-week placebo lead-in to define placebo responders, patients were randomized to one of 2 doses of SER120 (1.5 or 0.75 mcg) or placebo and treated for 12 weeks. Patients completed 3-day voiding diaries and serum sodium was monitored every two weeks throughout the study. A new validated QoL questionnaire (INTU, impact of nighttime urination) was completed by patients during screening and at Weeks 6 and 12 of treatment. The co-primary efficacy endpoints were the mean change in number of nocturic voids and the percentage of patients with greater or equal to 50% decrease in the mean number of nocturic voids.

Results

Results: 806 patients were randomized and 782 were included in the ITT population, while the mITT population excluded placebo responders and had 586 patients. Efficacy results appear in Table 1. The INTU questionnaire total score and nighttime domain score showed a statistically significant improvement in QoL compared to placebo for the 1.5 mcg dose in the ITT population. Overall, the treatment was well tolerated. There were 2 patients in the 1.5 mcg group (0.76%), 1 in the placebo group (0.37%) and none in the 0.75 mcg group with hyponatremia (less than 125 mmol/L serum sodium or less than 130 with symptoms).

Conclusions

Conclusions: SER120 was well tolerated and resulted in statistically significant efficacy compared to placebo for adult patients with nocturia. In addition, statistically significant improvements in patients quality of life were demonstrated based on a new, validated PRO instrument.

Date & Time: May 9, 2016 1:00 PM-3:00 PM

Session Title: Urodynamics/Lower Urinary Tract Dysfunction/Female Pelvic Medicine: Non-neurogenic Voiding Dysfunction I

Sources of Funding: Serenity Pharmaceuticals

Abstract: MP74-16

Introduction and Objectives

Protein kinase C (PKC)-potentiated inhibitory protein of 17 kDa (CPI-17) inhibits myosin light chain phosphatase and induces detrusor smooth muscle contraction by maintaining the levels of myosin light chain (MLC) phosphorylation. Dysregulation of CPI-17 expression and phosphorylation has been linked to pathological conditions associated with detrusor smooth muscle contractile dysfunction in bladder outlet obstruction (BOO)-induced bladder smooth muscle (BSM) hypertrophy. Overexpression of CPI-17 is associated with the increased basal MLC phosphorylation and the high degree of force maintenance, and slow relaxation of BSM in BOO. These studies suggest that CPI-17 expression and activation may contribute to bladder overactivity in BPH patients. However, the mechanism by which the transcriptional regulation of CPI-17 in BSM is not known. In the present study, we sought to identify the transcription machinery critical for CPI-17 expression and PKC mediated smooth muscle contraction during BSM hypertrophy in partial bladder outlet obstruction (PBOO) using murine models

Methods

We used DNA affinity column chromatography and chromatin immunoprecipitation to identify the binding of transcription factors to the murine CPI-17 promoter in BSM tissues from normal and obstructed bladders of mouse. Bladder sections prepared from sham-operated and PBOO mice were subjected to immunofluorescence and confocal microscopy to localize the specific transcription factor within the muscle bundles. Functional studies were carried out using muscle strips stimulated with PDBu (Phorbol 12,13-dibutyrate).

Results

Findings from a combination of DNA affinity chromatography, and chromatin immunoprecipitation studies demonstrated that the transcription factor, MEF-2D binds to AT-rich motif of the promoter and regulates CPI-17 gene expression. The DNA binding activity of MEF-2D and expression of CPI-17 was higher in BSM tissues from PBOO mice bladder compared to controls. Overexpression of MEF-2D in murine BSM cells and strips resulted in up-regulation of CPI-17. MEF-2D overexpression in BSM strips significantly increased the forces in response to PDBu compared to vector controls.

Conclusions

Our data identify MEF-2D as a critical regulator of CPI-17 expression in BSM and contribute to BSM contractility. This study provides the mechanism mediating CPI-17 overexpression during pathological BSM hypertrophy and implicates MEF-2D as a therapeutic target for the treatment of bladder overactivity in BPH patients.

Date & Time: May 9, 2016 1:00 PM-3:00 PM
Session Title: Urodynamics/Lower Urinary Tract Dysfunction/Female Pelvic Medicine: Non-neurogenic Voiding Dysfunction I
Sources of Funding: None

Poster # 65-16

May 9, 2016 10:30 AM-12:30PM

Predictive Factors for Successful Treatment of Solifenacin in Patients with Overactive Bladder

Chung Cheng Wang, Hueih-Ling Ong, Hann-Chorng Kuo

Department of Urology, En Chu Kong Hospital, New Taipei City, Taiwan and Department of Urology , Buddhist Tzu Chi General Hospital, Tzu Chi University, Hualien, Taiwan

Objective: It is important to identify the factors potentially affecting the efficacy of the pharmacologic treatment of overactive bladder (OAB). If we can predict which patients will not benefit from antimuscarinic agents before treatment, we can avoid giving these p reduce potentia the aim of the therapeutic succ

Methods: This study was approved by the institutional review board and ethics committee of this hospital. Informed consent was obtained from all subjective before study. Between Jan 2008 and Dec 2011, consecutive OAB patients who visited the urological outpatient clinics of Buddhist Tzu Chi General hospital were prospectively enrolled in this post-marketing study. Inclusion criteria were patients' age > 18 years old, with at least a 1-month history of OAB symptoms. Patients with predominant symptoms of stress urinary incontinence, UTI, previous bladder or urethral surgery or possible neurogenic lesions were excluded.

After screening visit, Patients received 5mg solifenacin QD and were followed up at 1 month, 3 months, 6 months and 12 months.

All patients were evaluated with International Prostate Symptom Score (IPSS), quality of life (QOL), Indevus Urgency Severity Scale (USS), Overactive Bladder Symptom Score (OABSS), uroflowmetry at baseline, 2 weeks, 1 month, 3 months and 6 months, respectively. The successful treatment was defined as a reduction of USS of 2 or greater

that compared with baseline, IPSS-S, IPSS-T, QOL, OABSS, USS value were significantly improved and the therapeutic effects persisted up to 12 months.

Table 2 shows that compared with failure group, patients with successful treatment had statistically significantly higher baseline Qmax, higher USS score and higher percentage of OAB wet. However, gender, male with BPH, medial diseases or diabetes mellitus had no significant effects o the efficacy of solifenacin. 34.7% patients had dry month and 23% had constipation at 3 months.

Conclusion: Solifenacin is effective and safe for patients with OAB up to 12 months. Baseline high Qmax, high USS value and OAB wet patients are predictive factors for successful treatment.

Table 2: Comparison of OAB patients with successful treatment and failed treatment by solifenacin

	baseline	1M	3M	6M	12M
Patient number	365	325	245	199	175
Qmax (ml/sec)	12.8±7.4	13.4±7.5	12.5±7.6	13.9±8.0	13.4±9.4
Voided Volume (mL)	182±120	213±128	185±122	179±102	189±119
PVR (mL)	48±56	67±75	57±57	76±60**	60±85
IPSS-V	6.7±5.0	6.1±5.5	6.3±5.4	5.9±4.4	4.7±4.5**
IPSS-S	6.9±3.4	4.4±3.2***	4.7±3.0***	4.6±3.3***	4.2±2.8***
IPSS-T	13.5±6.6	10.5±7.1***	11.0±7.4*	10.4±6.1	8.9±6.0***

	Successful treatment	Failed treatment	P-value
Qmax (ml/sec)	14.4±6.5	11.7±6.7	0.01
Void volume(ml)	203±133	174±121	0.15
PVR (mL)	33±45	53±57	0.06
Bladder capacity (mL)	233±151	220±141	0.77
IPSS-V	6.6±5.4	7.2±5.1	0.53
IPSS-S	6.9±3.5	7.0±3.5	0.86
IPSS-T	13.5±7.0	14.3±6.7	0.59
OABSS	6.3±3.2	7.0±4.2	0.63
USS	3.4±1.2	2.9±1.3	0.02
QOL	3.8±1.2	3.9±1.2	0.72
Gender (M v.s F)	69.5% v.s. 30.5%	72.8% v.s 27.2%	0.71
BPH (only male)	43.9%	44.1%	1
OAB type	wet 81.4%	wet 58.0%	0.004
Medical diseases (%)	28.80%	30.80%	0.85
DM (%)	16.90%	21.00%	0.67

Conclusion: Solifenacin is effective and safe for patients with OAB up to 12 months. Baseline high Qmax, high USS value and OAB wet patients are predictive factors for successful treatment.

Abstract: PD36-02

Introduction and Objectives

Incontinence is detrimental to health-related quality of life (HRQoL) in patients with OAB. This study (NCT01908829) assessed responder rates for efficacy and patient-reported outcomes (PROs), after treatment with a combination (COMBN) of the β3-adrenoceptor agonist, mirabegron (MIRA) and the antimuscarinic, solifenacin (SOLI), in incontinent patients with OAB and an inadequate response to SOLI 5mg monotherapy.

Methods

In this pre-specified analysis, incontinent adults with OAB symptoms for ≥3 mo entered a 2-wk wash-out period followed by 4 wks single-blind daily SOLI 5mg. Patients still reporting ≥1 incontinence episodes during a 3-day micturition diary were randomized (1:1:1) to daily double-blind treatment with COMBN (SOLI 5mg + MIRA 25mg, increasing to MIRA 50mg at 4 wks), SOLI 5mg, or SOLI 10mg for 12 wks. At end of treatment, responder rates for incontinence (zero incontinence episodes post-Baseline ['dry rate'] and ≥50% decrease in incontinence episodes/24 h); micturition reduction to <8 micturitions/24h; and PROs (exceeding threshold of minimally important differences [MID] in Patient Perception of Bladder Condition [PPBC], and OAB-questionnaire [OAB-q] Symptom Bother and total HRQoL scores) were evaluated individually or as double/triple responder analyses (50% reduction in incontinence plus OAB-q and/or PPBC).

Results

Baseline characteristics were similar between groups (COMBN, n=707; SOLI 5mg, n=705; SOLI 10mg, n=698). The odds for achieving full continence were 47% and 28% higher for COMBN vs SOLI 5mg or 10mg respectively; improvements in OAB-q outcomes were statistically significant (**Table**). Responder rates for ≥50% decrease in incontinence, micturition reduction and PPBC were also improved for COMBN vs SOLI 5mg. Significant improvements in favor of COMBN vs SOLI 5mg were found for all 5 double/triple responder analyses ($p<0.001$), and 3 of 5 variables for COMBN vs SOLI 10mg ($p<0.05$).

Conclusions

Mirabegron add-on treatment to solifenacin significantly improved responder rates, particularly the 'dry rate', and PROs, and may therefore be beneficial for incontinent OAB patients with an inadequate response to solifenacin monotherapy.

Date & Time: May 9, 2016 8:00 AM-10:00 AM

Session Title: Urodynamics/Lower Urinary Tract Dysfunction/Female Pelvic Medicine: Female Incontinence: Therapy I

Sources of Funding: Funding was provided by Astellas.

Abstract: MP68-08

Introduction and Objectives

Male lower urinary tract symptoms include storage symptoms, which are mostly caused by an overactive bladder (OAB) due to spontaneous detrusor contractions. Anticholinergic treatment represents the goldstandard of medical therapy, but discontinuation rates are high, due to disappointing efficacy and side effects. In addition to muscarinic receptors, detrusor contraction may be induced by thromboxane A2 (TXA2) and α1-adrenoceptors. Here, we studied effects of the TXA2 receptor (TXA2R) antagonist picotamide on detrusor contraction in the male human bladder.

Methods

Tissues were obtained from trigones of male patients (n=55) undergoing radical cystectomy. Contractility was studied in an organ bath. Expression of the TXA2 system was examined by RT-PCR, Western blot, immunofluorescence staining, and enzyme immunoassay (EIA).

Results

Carbachol, the α1-selective adrenoceptor agonist phenylephrine, and the TXA2 analogue U46619 induced concentration-dependent contractions of trigone tissues. Electric field stimulation (EFS) induced frequency-dependent contractions. Picotamide (300 µM) inhibited carbachol-, phenylephrine-, U46619-, and EFS-induced contractions. Inhibition was significant at 0.1-3 µM carbachol, 1-3 µM phenylephrine, 10-30 µM U46619, and at EFS with 32 Hz. TXA2R and TXA2 synthase (TXS) were detectable by RT-PCR and Western blot analysis. Immunoreactivity for TXA2R and TXS colocalized with calponin, indicating expression in smooth muscle. TXB2 was detectable by EIA in each sample, with most values ranging between 50-150 pg/mg trigone protein.

Conclusions

Picotamide inhibits different contractile systems in the human detrusor at once, including cholinergic, adrenergic, TXA2-induced, and neurogenic contractions. This distinguishes picotamide from available medications for OAB treatment. Because picotamide is well tolerated even under long-term administration, clinical studies and urodynamic effects appear possible.

Date & Time: May 9, 2016 10:30 AM-12:30 PM

Session Title: Urodynamics/Lower Urinary Tract Dysfunction/Female Pelvic Medicine: Basic Research & Pathophysiology II

Sources of Funding: none

Abstract: MP68-12

Introduction and Objectives

It is known that the β3-adrenoceptor (β3-AR) agonists relax the detrusor smooth muscle (DSM) by the adenylate cyclase pathway and the phosphodiesterase-5 inhibitors (PDE-5i) by the nitric oxide/cyclic guanosine monophosphate pathway. Therefore it has been hypothesized that these two drugs may cause synergic DSM relaxation. The goal of this study was to evaluate *in vitro* if the combination of PDE-5i (tadalafil) and β3-AR agonists (BRL 37344) produces greater relaxation than either compound alone. We also investigated the effect of a phosphodiesterase-4 inhibitor (rolipram).

Methods

Experiments were performed on bladder strips of mice. At first, after a potassium-induced contraction, increasing concentrations of tadalafil, rolipram and BRL 37344 were added in the bathing fluid. In another series of experiments, prior to potassium-induced contraction, strips were incubated with either tadalafil or rolipram and then increasing concentrations of BRL 37344 were added.

Results

Cumulative concentration-response curves were constructed for each drug. Tadalafil relaxed the detrusor only at the end of their concentration range. BRL 37344 had greater relaxing effect than rolipram at 1nM to 1μM ($p<0.05$) (Figure 1). Preincubation with tadalafil significantly increased the relaxation when compared to the experiments without preincubation (Figure 2) and pre-treatment with rolipram (Figure 3).

Conclusions

Pre-treatment with tadalafil increased the relaxing response of BRL 37344. Activation of both adenylate cyclase (β3-AR agonist) and nitric oxide/cyclic guanosine monophosphate (PDE-5i) pathways causes more significant relaxation of the DSM.

Date & Time: May 9, 2016 10:30 AM-12:30 PM

Session Title: Urodynamics/Lower Urinary Tract Dysfunction/Female Pelvic Medicine: Basic Research & Pathophysiology II

Sources of Funding: none

AUA2016

MP30-15

Pharmacological profile of DA-8010, a novel bladder selective muscarinic receptor 3 antagonist for treatment of overactive bladder

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Abstract

Objectives: Several antimuscarinics have been commonly used for overactive bladder patients, but dry mouth as a major anticholinergic side effect remains a shortcoming to limit long-term use. DA-8010 is a novel muscarinic receptor 3 antagonist being developed for the treatment of overactive bladder. The objectives of this study were to characterize the pharmacological profile of DA-8010 and to compare its bladder selectivity over salivary gland with those of currently used antimuscarinic agents.

Methods: The binding affinity of DA-8010 for various receptors was assessed in competitive radioligand binding assays. The antagonistic potency for muscarinic receptors was measured using human M3-overexpressing cells and rat bladder tissues. To assess the functional tissue selectivity *in vitro*, inhibition on carbachol-induced intracellular calcium increase was measured in bladder smooth muscle cells and salivary gland cells isolated from mice. Inhibitory effects on rhythmic urinary bladder contraction and carbachol-induced salivary secretion were evaluated for solifenacin and darifenacin, respectively.

Conclusions: DA-8010, a novel and potent muscarinic receptor 3 antagonist exerts the superior selectivity for urinary bladder over salivary gland to solifenacin, tolterodine, darifenacin and oxybutynin in preclinical studies. These findings suggest that DA-8010 may be a therapeutic agent having favorable properties with less dry mouth in the treatment of overactive bladder.

Introduction

Muscarinic receptor antagonists are currently the first-line pharmacotherapy for overactive bladder (OAB). They act during the storage phase, decrease involuntary contraction, increase bladder capacity, and delay the initial urge to void. Despite of the proven efficacy, the currently available antimuscarinics continued to make adverse effects related to tissue distribution of muscarinic receptors. Dry mouth is the most frequent adverse event, which often leads to discontinuation of treatment. Therefore, there is a need for new OAB treatments with high efficacy and fewer side effects. DA-8010 is a novel muscarinic receptor 3 antagonist being developed for the treatment of OAB. Here we describe the pharmacological profile of DA-8010 and elucidate its bladder selectivity over salivary gland.

Methods

Muscarinic receptor binding assay

Binding assays for human muscarinic receptors were performed with increasing concentrations (1 nM-10 μM) of test compounds and [^{3}H]N-methyl scopolamine in membrane preparations. Binding data were analyzed by non-linear regression analysis and Ki values were calculated using the Cheng-Prusoff equation (Cheng and Prusoff, 1973): $K_i=IC_{50}/(1+[L]/K_d)$ where [L]=radioligand concentration.

Isolation of bladder smooth muscle cells and salivary gland cells

Bladder smooth muscle cells and submandibular gland cells were prepared in male ICR mice (aged 16 weeks) according to previously reported methods (Ikeda et al., 2002; Ohtake et al., 2004) with minor modifications.

Measurement of intracellular Ca^{2+} mobilization

Antagonistic effects in primary cells and hM3-overexpressing Cos-7 cells were evaluated using Fluo-4 AM and calcium 5 assay reagent, respectively. The changes in fluorescence were recorded in a fluorometric imaging plate reader. Test compounds were pretreated for 2 min, and 3 μM of carbachol was treated. The responses were expressed as percentages of the maximum response to carbachol only.

Antagonistic effect on muscarinic receptors of rat bladder strips

The bladder s of female SD rats was cut into longitudinal sections and mounted in the organ bath system. The contractile responses by carbachol were recorded. Response curves to cumulative concentration of carbachol were obtained, and then antagonistic effects of test compounds were expressed as percentages of the maximum curve in oral cavity, and saliva was collected for 10 min after the carbachol injection.

Results

- DA-8010 showed the highest binding affinity for the hM3 receptor (K_i=1.55 nM) responsible for the control of bladder contraction. Furthermore, DA-8010 exhibited a great selectivity for the hM3 receptor (30.7-fold) over hM2 receptor and was similar to solifenacin in selectivity. DA-8010 was found to be a highly potent and competitive antagonist of hM3, showing the highest potency (K_i=0.25 nM) among all the antimuscarinics tested (Table 1).

Table 1. Binding affinity of DA-8010 for human muscarinic receptors

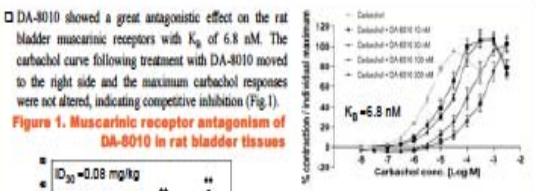
Compound	Affinity (K_i, nM)			Potency (K_i, nM)
	hM1	hM2	hM3	hM3
DA-8010	**5.52 ± 2.45**	**47.62 ± 22.44**	**1.55 ± 0.18**	**0.25 ± 0.07**
Solifenacin	126.79 ± 18.81	923.03 ± 73.04	39.35 ± 7.92	2.58 ± 0.39
Oxybutynin	19.59 ± 2.95	147.37 ± 15.82	7.48 ± 2.12	1.67 ± 0.81
Darifenacin	66.22 ± 10.75	347.73 ± 85.29	3.24 ± 1.1	1.26 ± 0.18
Tolterodine	14.02 ± 1.7	77.44 ± 21.91	18.00 ± 5.23	0.74 ± 0.07

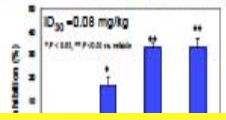
Each value represents the mean ± S.E.M. of 2-5 experiments performed in duplicate

- DA-8010 did not show significant affinity for non-muscarinic receptors. The binding affinities for the 5-HT_{2B} receptor, 5-HT_{3C} receptor, dopamine transporter and norepinephrine transporter were 390-, 60-, 80- and 600-fold lower than that of the hM3 receptor, respectively. The K_i values for other non-muscarinic receptors, ion channels and transporters were over 1 μM (data not shown).

- DA-8010 showed a great antagonistic effect on the rat bladder muscarinic receptors with K_B of 6.8 nM. The carbachol curve following treatment with DA-8010 moved to the right side and the maximum carbachol responses were not altered, indicating competitive inhibition (Fig.1).

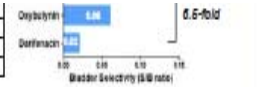
Figure 1. Muscarinic receptor antagonism of DA-8010 in rat bladder tissues





- DA-8010 significantly and dose-dependently inhibited the amplitude of the rhythmic urinary bladder contractions induced by distension in rats, suggesting the most effective

DA-8010	**0.08**	**0.010**
Solifenacin	1.79	0.096
Oxybutynin	0.44	0.027
Darifenacin	0.28	0.006

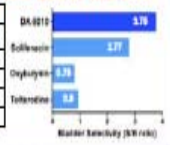


- The inhibitory effect of DA-8010 for native muscarinic receptors in bladder smooth muscle cells (K_i=0.23 nM) was 3.75-fold more potent than that in salivary gland cells (K_i=0.86 nM) (Table 3).

Table 3. Antagonistic effects on native muscarinic receptors in bladder smooth muscle cells and salivary gland cells isolated from mice

Compound	Potency (pK_B)	
	bladder smooth muscle cells (B)	Submandibular gland cells (S)
DA-8010	**9.64 ± 0.11***	**9.06 ± 0.09**
Solifenacin	8.55 ± 0.21***	8.11 ± 0.11
Oxybutynin	8.16 ± 0.12***	8.26 ± 0.18
Tolterodine	8.37 ± 0.14**	8.40 ± 0.31

*P < 0.05, **P < 0.01, ***P < 0.005 vs. pK$_i$ in submandibular gland cells (S), paired t test



Conclusions

DA-8010 may exert favorable properties for the treatment of overactive bladder.

- Highly selective and potent muscarinic receptor 3 antagonist
- Most effective in inhibition of distension-induced rhythmic bladder contraction among all the antimuscarinics tested
- Highly selective for bladder over salivary gland, *in vitro* and *in vivo* compared to other antimuscarinics, suggesting a lower possibilities of dry mouth adverse effect

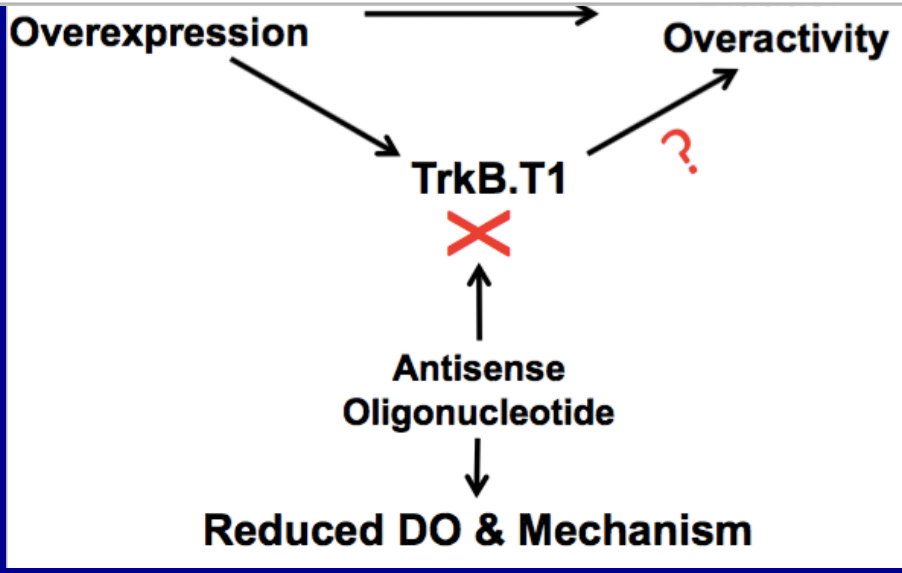
Conclusions: DA-8010, a novel and potent muscarinic receptor 3 antagonist exerts the superior selectivity f urinary bladder over salivary gland to solifenacin, tolterodine, darifenacin and oxybutynin in preclinical studie These findings suggest that DA-8010 may be a therapeutic agent having favorable properties with less dry mouth the treatment of overactive bladder.

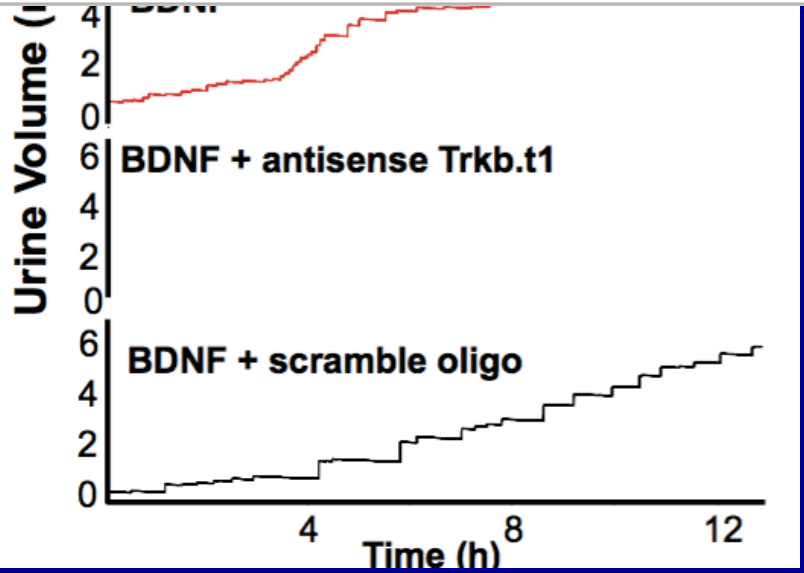
BDNF Enhances Detrusor Excitability through TrkB.T1 Mediated Activation of Calcium channels

Mahendra Kashyap, William Chet Degroat[1], Naoki Yoshimura, Pradeep Tyagi

Conclusion:

- TrkB.T1 augments smooth muscle excitability and contractility via L-type Ca^{+2} channels suggested by attenuation of neuronal resistance intrinsic muscular activity by TrkB.T1 antisense and Nimodipine
- Overall, TrkB.T1 in detrusor is a suitable drug target for OAB





Abstract: MP68-13

Introduction and Objectives

One of pathogenesis of diabetic cystopathy is the disturbance of bladder microcirculation. We examined the effect of eicosapentaenoic acid (EPA) on bladder microcirculation and bladder overactivity using a diabetes rat model.

Methods

Twelve week-old female SD rats were divided into three groups; control, diabetes and diabetes + EPA groups. The latter two groups were injected with streptozotocin (65 mg/kg) intraperitoneally to induce diabetes. Blood glucose levels were measured at 3 days, and only rats with blood glucose >350 mg/dl were used in the study. EPA (mg/kg/day) or sunflower oil (control and diabetes groups) were orally given. At 2 or 8 weeks, rats were evaluated for bladder microcirculation, ELISA for oxidative stress markers, cystometrogram, and organ bath study.

Results

The blood flow on the bladder surface was disturbed in the diabetes rats, and improved in the diabetes + EPA group. Oxidative stress markers in the bladder (malondialdehyde) increased in the diabetes rats, which was ameliorated in the silodosin group. Cystometrogram demonstrated increased non-voiding contraction in the diabetes group, which was ameliorated by EPA treatment (8.7 ± 1.7 in the control, 27.0 ± 4.1 in the diabetes group, and 13.4 ± 2.1 in the diabetes + EPA group). Organ bath study showed increased bladder contractility in diabetes rats compared to control, and EPA suppressed diabetes-induced hypercontractility.

Conclusions

EPA treatment suppressed the disturbed microcirculation and overactivity of the bladder seen in the diabetes rats.

Date & Time: May 9, 2016 10:30 AM-12:30 PM

Session Title: Urodynamics/Lower Urinary Tract Dysfunction/Female Pelvic Medicine: Basic Research & Pathophysiology II

Sources of Funding: None

MP 28-02

SUPRASPINAL AND SPINAL EFFECTS OF DOPAMINE UPTAKE INHIBITOR ON THE MICTURITION REFLEX IN URETHANE-ANESTHETIZED RATS

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INTRODUCTION

- Dopamine is an important neurotransmitter in the central nervous system, including neural pathways controlling the lower urinary tract (1, 2).
- It is unknown whether dopamine uptake inhibitor has a role in the regulation of neural mechanisms controlling the micturition reflex.

OBJECTIVES

To investigate the effects of GBR12935, a selective dopamine uptake inhibitor that increases endogenou dopamine concentration, on the micturition reflex in urethane anesthetized rats

METHODS

Adult female Sprague-Dawley rats (weighing 242-267 g) were used. Rats were maintained under standard laboratory conditions with a 12-h light/12-h dark cycle and free access to food pellets and tap water.

Drugs

GBR12935, a selective dopamine uptake inhibitor, was dissolved in saline.

Intrathecal administration of GBR12935

- Rats were anesthetized with isoflurane followed by urethane (1.2 g/kg subcutaneously).
- A midline abdominal incision was made, and a transvesical catheter (PE-60) with a fire-flared tip was inserted into the dome of the bladder and secured with silk thread for bladder filling and pressure recording. A 3-way stopcock was connected to the transvesical catheter to monitor the bladder pressure.
- Saline was continuously infused into the bladder

- In urethane-anesthetized rats, suppression of dopamine uptake by intracerebroventricularly administered GBR12935 has an inhibitory effect the micturition reflex, as shown by the observed increases in ICI and TP.
- The main function of GBR12935 seems to be mediated by modulation of afferent activity, rathe than efferent or smooth muscle activity, because GBR12935 induced increases in ICI and TP with affecting MP or BP.
- We postulate that the site of action may be the supraspinal site.

- Cystometric parameters were recorded and compared before and after drug administration.

Statistics

- All data values are expressed as the mean ± SD.
- A one-way ANOVA followed by Dunnett's multiple comparison test was used for the statistical analysis between the vehicle and drug-treated groups.
- Wilcoxon signed rank test was used to compare cystometric variables before and after treatment.
- For all statistical tests, p<0.05 was considered significant.

RESULTS

parameters after ation in normal rats

	GBR12935 (3 µg)	GBR12935 (10 µg)
	6	4
	10.1 (2.69)	9.7 (3.41)
	10.6 (1.67)	10.4 (4.34)

	99.2 (3.25)	127.1 (10.6)†	137.5 (9.7)†	152.1 (12.2)†	
BP, cmH$_2$0					
before	2.13 (0.51)	2.45 (0.78)	3.23 (1.56)	2.11 (0.23)	
after	2.46 (0.55)	3.21 (1.28)	2.91 (1.56)	2.71 (0.96)	
TP, cmH$_2$0					
before	4.32 (1.58)	4.28 (2.10)	4.67 (1.92)	5.01 (2.01)	
after	4.26 (1.26)	10.5 (1.02)*	14.1 (0.96)*	17.6 (1.95)*	
MP, cmH$_2$0					
before	25.1 (5.12)	23.8 (4.67)	27.1 (7.15)	25.1 (5.67)	
after	24.3 (5.21)	26.7 (5.41)	29.1 (9.25)	25.1 (5.43)	

* P<0.01 against t=0; † P<0.01 vs vehicle injection (Dunnett's multiple comparison test)

	98.1 (4.34)	98.4 (4.21)	104.5 (3.18)	107.2 (5.17)	
BP, cmH$_2$0					
before	3.21 (1.17)	2.16 (0.98)	2.09 (1.21)	3.93 (1.15)	
after	3.19 (0.81)	2.31 (1.51)	2.31 (1.05)	3.76 (0.89)	
TP, cmH$_2$0					
before	5.22 (1.16)	7.13 (2.78)	4.78 (2.22)	7.27 (2.28)	
after	5.55 (1.05)	6.99 (3.07)	5.21 (2.55)	7.16 (2.06)	
MP, cmH$_2$0					
before	27.1 (3.78)	30.1 (5.79)	24.8 (5.67)	28.1 (4.41)	
after	27.2 (3.15)	27.9 (2.89)	26.7 (2.11)	29.5 (2.35)	

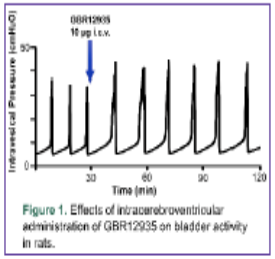

Figure 1. Effects of intracerebroventricular administration of GBR12935 on bladder activity in rats.

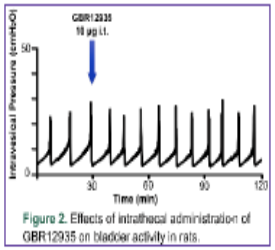

Figure 2. Effects of intrathecal administration of GBR12935 on bladder activity in rats.

CONCLUSIONS

- In urethane-anesthetized rats, suppression of dopamine uptake by intracerebroventricularly administered GBR12935 has an inhibitory effect on the micturition reflex, as shown by the observed increases in ICI and TP.
- The main function of GBR12935 seems to be mediated by modulation of afferent activity, rather than efferent or smooth muscle activity, because GBR12935 induced increases in ICI and TP without affecting MP or BP.
- We postulate that the site of action may be the supraspinal site.

REFERENCES

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Cevap aranıyor ?

- Etyopatogenez ?
- Yan etkiler ?
- Hangi mekanizma ?
- Santral etki mi ? , Periferal mi ?
- Etkinlik , tam ve kalıcı ?
- Çocuk , Yetişkin , Yaşlı ilaç seçimi ?