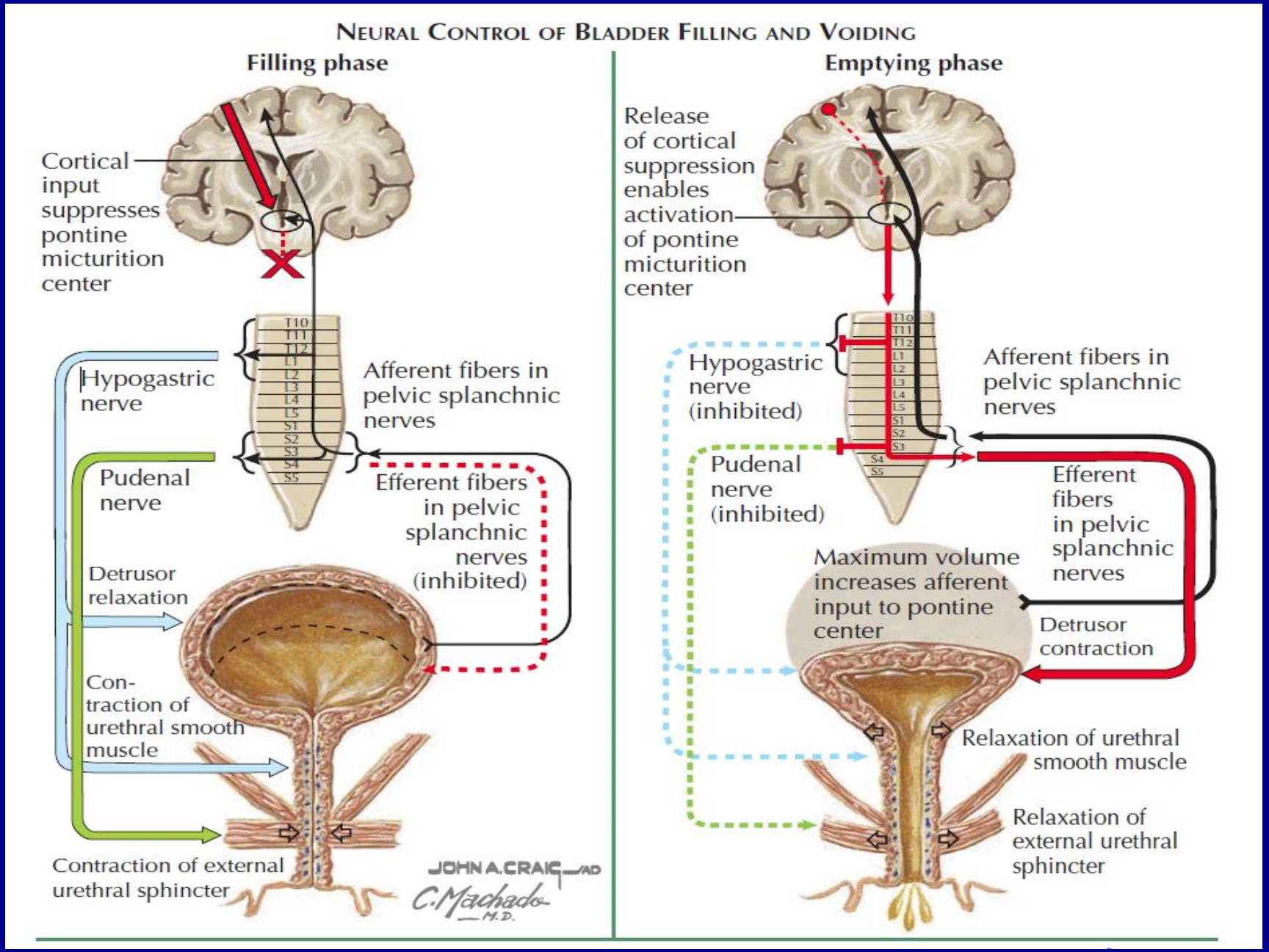
AŞIRI AKTİF MESANE FARMAKOTERAPİSİ

DOÇ.DR.M.MURAT DİNÇER,FECSM

Sağlık Bilimleri Ünv. Bağcılar SUAM , Üroloji B.D

27 Mart 2018


NEURAL CONTROL OF BLADDER FILLING AND VOIDING
Filling phase
Cortical input suppresses pontine micturition center
Hypogastric nerve
Pudenal nerve
Afferent fibers in pelvic splanchnic nerves
Efferent fibers in pelvic splanchnic nerves (inhibited)
Detrusor relaxation
Con-traction of urethral smooth muscle
Contraction of external urethral sphincter
T10 T11 T12 L1 L2 L3 L4 L5 S1 S2 S3 S4 S5
JOHN A. CRAIG MD
C. Machado M.D.
Emptying phase
Release of cortical suppression enables activation of pontine micturition center
Hypogastric nerve (inhibited)
Pudenal nerve (inhibited)
Afferent fibers in pelvic splanchnic nerves
Efferent fibers in pelvic splanchnic nerves
Maximum volume increases afferent input to pontine center
Detrusor contraction
Relaxation of urethral smooth muscle
Relaxation of external urethral sphincter
T10 T11 T12 L1 L2 L3 L4 L5 S1 S2 S3 S4 S5

OVERACTIVE BLADDER

Overactive Bladder
Editor- Sajjad Rahnama'i
Last Updated- June 1, 2018

Current definition

Overactive bladder syndrome (OAB) is defined as urinary urgency, usually with urinary frequency and nocturia, with or without urgency urinary incontinence [1,2].

History

In 2014 the International Consultation on Incontinence Research Society (ICI-RS) proposed 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 [3].
Previously, OAB symptoms were described as associated with the unstable bladder (A bladder contracting involuntarily during the filling phase of a cystometrogram) [4] also referred to as detrusor hyperreflexia [5] (if neurological disease was present) or detrusor overactivity [5] (if the cause was unknown or non-neurogenic).

Controversy

Other Pages in Terminology Discussions

Abdominal Leak Point Pressure / Valsalva Leak Point Pressure

Bladder diary / frequency

FORUMS

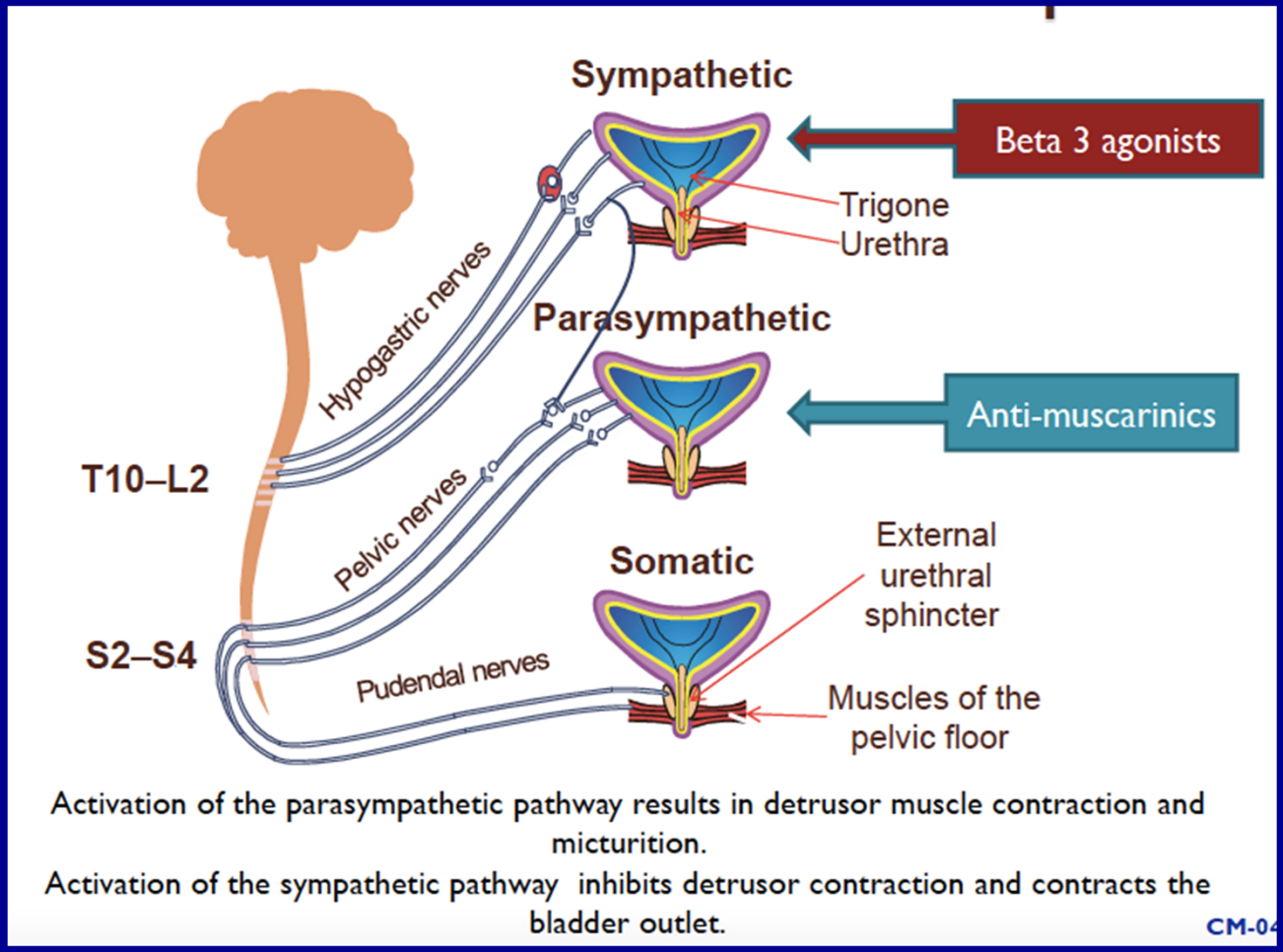
A Decade of Pharmacotherapy for Overactive Bladder: What Have We Learned?

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."

İşeme fizyolojisi ve terapötik hedefler



Activation of the parasympathetic pathway results in detrusor muscle contraction and micturition.

Activation of the sympathetic pathway inhibits detrusor contraction and contracts the bladder outlet.

CM-04

AAM FARMAKOTERAPİSİ

- **ANTİKOLİNERJİK AJANLAR**
- **BETA 3 AGONİSTLER**
- **ÖSTROJENLER**
- **DESMOPRESSİN**
- **DULOKSETİN**

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

AAM tedavisinde

- 1. tercih

Beta 3 agonistler : ***Mirabegron***

ve / veya

Antimuskarinikler : ***solifenasin***

Darifenasin

propiverine

fesoterodine

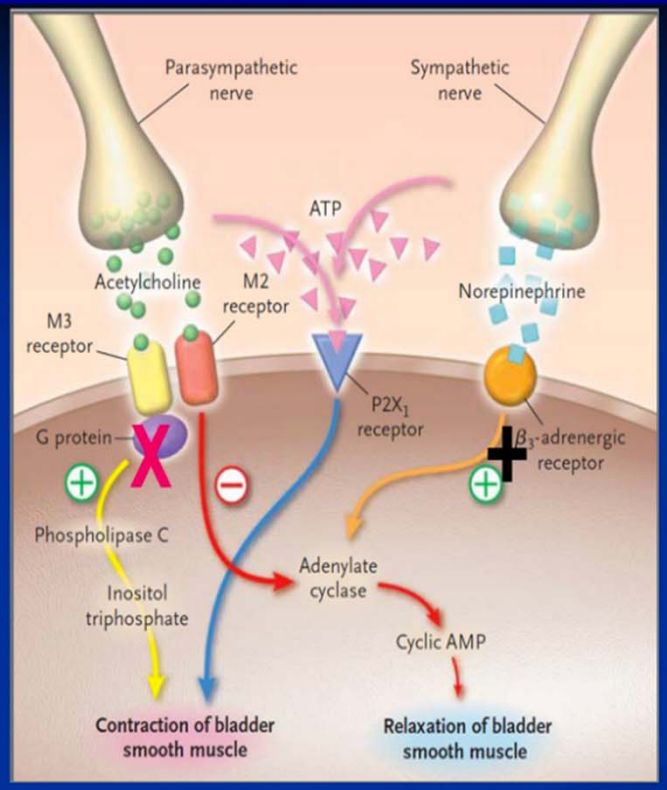
tolterodine

trospium

oksibutinin

Antimuscarinics

Decrease contraction contracción vesical



β3 Agonists

Produce bladder relaxation

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

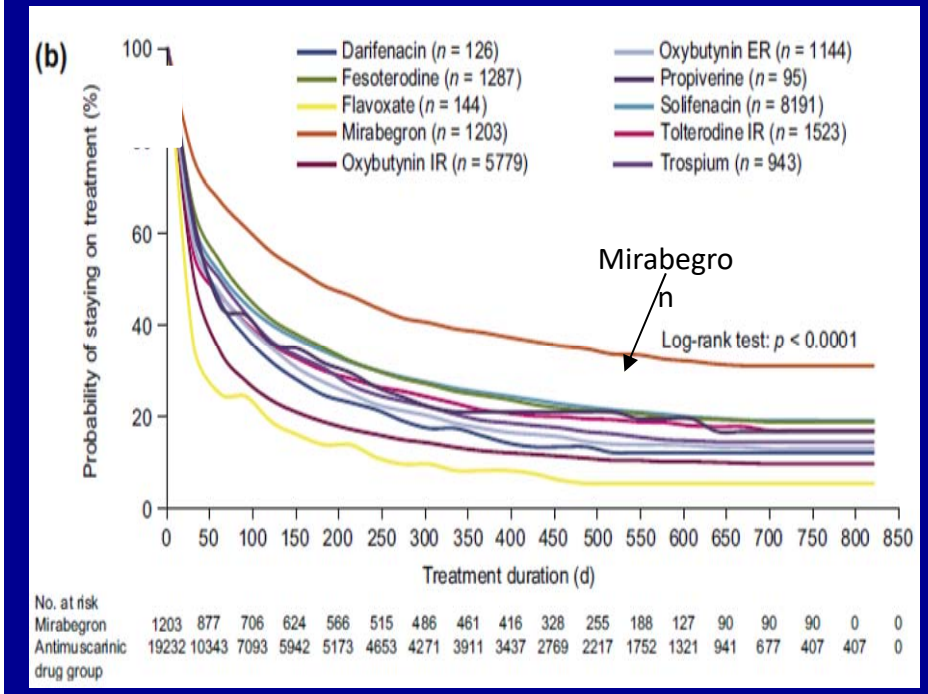
Ouslander NEJM 2004

Antimuskarinikler - Mirabegron

Guidelines	Mirabegron Recommendation		Last Updated
EAU[1]	In patients with UUI and an inadequate response to conservative treatments offer mirabegron, unless they have uncontrolled hypertension (Grade A)		**2019**
AUA[2]	Clinicians should offer oral anti-muscarinics or oral β[3]-adrenoceptor agonists as second-line therapy. Standard (Evidence Strength Grade B)		**2014**
CUA[3]	Second-line treatment of OAB should include the use of oral AMs, transdermal oxybutynin or oral beta-3 adrenoceptor agonist (Evidence strength Grade A)		**2017**
USANZ/ UGSA[4]	**AM Drugs**	Offer behavioural treatment as well as antimuscarinic drugs for adults with UUI	**2015**
	Mirabegron	Mirabegron is effective for the improvement of UUI	

1. Burkhard et al. EAU Guidelines on Urinary Incontinence in Adults. Retrieved from http://uroweb.org/guideline/urinary-incontinence/2019
2. Gormley EA et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. Retrieved from http://www.auanet.org/guidelines/ overactive-bladder-(oab)-(aua/sufu-guideline-2012-amended-2014) Updated 2014
3. Corcos J et al. CUA guideline on adult overactive bladder. Can Urol Assoc J 2017;11(5):E142-73.
4. http://dx.doi.org/10.5489/cuaj.4586
5. Tse V et al. Conjoin Urological Society of Australia and New Zealand (USANZ) and Urgynaecological Society of Australasia (UGSA) Guidelines on the management of adult non-neurogenic overactive bladder. BJU Int 2016; 117: 34–47

İlaç devamlılığı ?



	Mirabegron	Antimuskarinikler
Ort. Tedv süresi	221	75-108
12-ay devam	31.7%	13.8-22%
Tedavi uyumu	64.5%	18.6-49.2%

1. Chapple CR, et al. Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice. Eur Urol (2017), http://dx.doi.org/ 10.1016/j.eururo.2017.01.037
2. Wagg A et al. Persistence and adherence with the new beta-3 receptor agonist, mirabegron, versus antimuscarinics in overactive bladder: Early experience in Canada. Can Urol Assoc J 2015;9(9-10):343-50.

Original Investigation

Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults

Shannon L. Risacher, PhD; Brenna C. McDonald, PsyD, MBA; Eileen F. Tallman, BS; John D. West, MS; Martin R. Farlow, MD; Fredrick W. Unverzagt, PhD; Sujuan Gao, PhD; Malaz Boustani, MD, MPH; Paul K. Crane, MD, MPH; Ronald C. Petersen, MD, PhD; Clifford R. Jack Jr, MD; William J. Jagust, MD; Paul S. Aisen, MD; Michael W. Weiner, MD; Andrew J. Saykin, PsyD; for the Alzheimer's Disease Neuroimaging Initiative

CONCLUSIONS AND RELEVANCE The use of AC medication was associated with increased brain atrophy and dysfunction and clinical decline. Thus, use of AC medication among older adults should likely be discouraged if alternative therapies are available.

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Published online April 18, 2016.

HHS Public Access
Author manuscript
JAMA Intern Med. Author manuscript; available in PMC 2015 March 13.

Published in final edited form as:
JAMA Intern Med. 2015 March 1; 175(3): 401–407. doi:10.1001/jamainternmed.2014.7663.

Cumulative Use of Strong Anticholinergic Medications and Incident Dementia

kognitif yük ne kadar önemli?

- Yaşlı hastalarda, çoklu ilaç kullanımında, HT ve DM tablosu olan hastalarda KBB geçirgenliğinin artışı; artmış antikolinerjik kognitif yüke neden olmakta

- Daha önceki 10 yıllık dönemde hiçbir antikolinerjik maruziyeti olmayanlarla kıyaslandığında, antikolinerjik maruziyeti olan hastalarda
  - demans gelişme ihtimali: **%54**
  - Alzheimer hastalığına yakalanma ihtimali: **%63**

- yaşlı hasta grubunda antikolinerjik kognitif yük'ün birikici olduğu ve uzun süreli ilaç kullanan yaşlı hastaların
  - %23.2'de demans geliştiği
  - bu hastaların %79.9'unun Alzheimer hastalığına sahip olduğu

Mirabegron bir antikolinerjik olmadığından böyle bir risk içermemektedir.

Effect of mirabegron on cognitive function in elderly patients with overactive bladder: Results from a Phase IV placebo-controlled study (PILLAR)

Cristling TL[1], Campbell NL[2], Mangel J[3], Staskin D[4], Herschorn S[5], Elsouda D[6], Schermer CR[6]

[1]Department of Urology and The Landon Center on Aging, University of Kansas School of Medicine, Kansas City, KS, USA; [2]College of Pharmacy, Purdue University, Lafayette, IN, USA and Center for Aging Research, Indiana University, IN, USA; [3]Division of Urogynecology and Pelvic Reconstructive Surgery, MetroHealth Medical Center, Cleveland, OH, USA; [4]Division of Urology, St. Elizabeth's Medical Center, Boston, MA, USA; [5]Division of Urology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; [6]Medical Affairs, Astellas Pharma Global Development, Inc., Northbrook, IL, USA.

INTRODUCTION

- Antimuscarinics are often used for treatment of overactive bladder (OAB), but exposure to drugs with anticholinergic properties has been associated with adverse cognitive effects, particularly in patients aged ≥65 years
- Polypharmacy with drugs that have anticholinergic activity (e.g. tricyclic antidepressants, bronchodilators, ACE inhibitors and antipsychotics) may result in a problematic anticholinergic burden in the older patient population
- Mirabegron, a β3-adrenoreceptor agonist, with no adverse effects on cognition reported, represents an alternative to antimuscarinics for OAB treatment and has a potentially more favourable benefit-to-risk ratio than antimuscarinics in older patients
- PILLAR, a Phase IV, placebo-controlled study (NCT02258711) compared the efficacy and safety of flexibly dosed mirabegron vs placebo for the treatment of OAB with incontinence ("wet" OAB) in patients aged ≥65 years[1]
  - Previously presented primary efficacy and safety results showed that treatment with mirabegron was statistically superior to placebo in alleviating major OAB symptoms and associated bother, and was well tolerated
- The planned analysis presented here examined the effect of mirabegron on cognitive function, measured by the 30-item Montreal Cognitive Assessment (MoCA), a rapid, sensitive, general screening instrument for mild cognitive impairment in patients
  - Through repeated administration, the MoCA can capture decline in cognitive function over time, although it has also been used to track improvements

METHODS

- PILLAR was a Phase IV, double-blind, randomized, placebo-controlled, parallel group, multicentre, 12-week study conducted at 103 sites in the US and Canada between October 2014 and December 2017[1]
- Community-dwelling patients aged ≥65 years with wet OAB (≥1 incontinence episode and ≥8 urgency episodes over a 3-day diary, and an average of ≥8 micturitions/24 h) were randomised 1:1 to receive mirabegron or placebo, stratified by age <75/≥75 years
- The study was designed and powered to detect a difference between the placebo and mirabegron groups
- There were no exclusion criteria regarding cognitive status on entry to the study
- Patients randomized to mirabegron initially received 25 mg/day but this could be increased to 50 mg/day after Week 4 or 8 based on patient/investigator discretion
- The MoCA was conducted at Baseline and end-of-treatment (EoT; Week 12), administered by trained clinic staff, in either English or Canadian French
  - On a scale of 1 to 30, higher MoCA scores indicate better cognitive function; a MoCA score <26 indicates impaired cognitive function.
- All analyses on MoCA outcomes were undertaken on the Safety Analysis Set (SAF; all randomized patients who received ≥1 dose of double-blind study medication)
- The study protocol was Institutional Review Board/Independent Ethics Committee-approved.

RESULTS

- Of 2380 patients screened, 948 were randomized to mirabegron and 943 to placebo; one patient in the placebo group did not receive treatment
- Of 887 randomized patients who received ≥1 dose of study drug, 72.3% were female, 79.8% were white, and 29.1% were aged ≥75 years (Table 1)
  - There were no notable differences in Baseline demographics between groups
  - 226 patients received mirabegron 25 mg; 214 patients uptitrated to 50 mg
- All patients had ≥1 comorbidity and 94.3% were receiving ≥1 concomitant medication
- One third of patients in the SAF had a history of psychiatric disorders, the most common being depression (17.2%), insomnia (13.7%) and anxiety (11.4%)
- The Baseline mean (standard error [SE]) MoCA total scores were 28.9 (0.1) and 28.8 (0.1) in the mirabegron and placebo groups, respectively (Table 2)

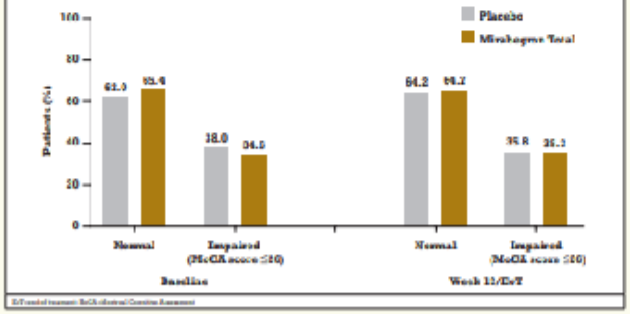
Table 1. Baseline characteristics, by age group

	Placebo (N=447)	Mirabegron Total (N=440)
Female sex, n (%)	324 (72.5)	317 (72.0)
Age, mean ± SD	71.1 ± 5.0	71.7 ± 5.6
Age ≥75 years, n (%)	134 (30.0)	125 (28.4)
BMI (kg/m²), mean ± SD	30.2 ± 6.4	31.7 ± 7.3
Category, n (%)		
<25	91 (20.4)	108 (24.5)
≥25–<30	180 (39.6)	167 (38.0)
≥30	201 (45.0)	160 (40.6)
Ethnicity, n (%)		
Not Hispanic or Latino	398 (89.0)	401 (91.1)
Hispanic or Latino	43 (9.6)	41 (9.3)
Unknown	4 (0.9)	3 (0.7)
Race, n (%)		
White	351 (80.8)	348 (79.2)
Asian	54 (12.4)	59 (13.4)
Black or African American	25 (5.7)	33 (7.5)
Other	6 (1.4)	4 (0.9)
Country, n (%)		
United States	385 (86.0)	385 (87.5)
Canada	63 (14.0)	55 (12.5)
MoCA total score* Category, n (%)		
Normal (≥26)	265 (59.3)	276 (62.7)
Mild (18–25)	182 (40.7)	164 (37.3)
Moderate (10–17)	0	0
Severe (<10)	0	0
Missing	0	0

*MoCA = Montreal Cognitive Assessment; SD = standard deviation.

- Among patients with MoCA data available at Baseline/EoT, 34.5% (147/425) and 38.0% (156/411) of mirabegron and placebo group patients, respectively, had impaired cognitive function at Baseline (MoCA total score ≤26)
  - At Week 12/EoT, 38.2% (160/419) of mirabegron patients and 31.8% (127/411) of placebo patients had impaired cognitive function (Figure 1)

Figure 1. MoCA score at Baseline and Week 12/EoT



EoT=end of treatment; MoCA=Montreal Cognitive Assessment

- There was no statistically significant change in adjusted mean (SE) MoCA total score from Baseline to EoT in the mirabegron group (0.0 [0.1]) or the placebo group (0.1 [0.1]; Table 2)
  - Changes in MoCA subscale scores were minimal and similar between groups

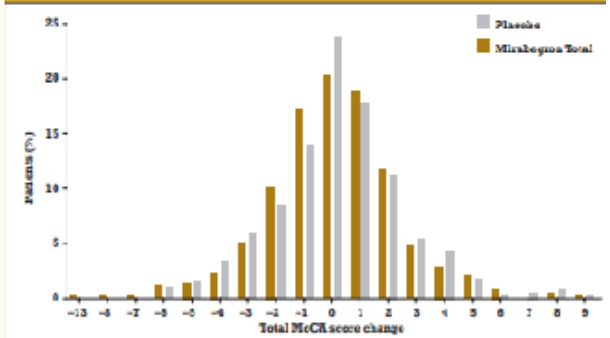
Table 2. Change from Baseline to EoT in MoCA total and subscale scores

	Placebo	Mirabegron Total
MoCA total score		
Baseline, mean (SE)*	28.8 (0.1)	28.9 (0.1)
EoT, mean (SE)†	28.1 (0.1)	28.0 (0.1)
Adjusted change from Baseline, mean (SE)	0.1 (0.1)	0.0 (0.1)
95% two-sided CI	[-0.1, 0.3)	(-0.2, 0.2)
p-value	-	0.540
MoCA subscale scores Change from Baseline, mean (SD)‡		
Attention Points	-0.0 (0.9)	-0.1 (0.9)
Language Points	0.0 (0.7)	0.0 (0.7)
Naming Points	-0.0 (0.4)	0.0 (0.4)
Visuospatial/Executive Points	0.0 (1.0)	-0.1 (1.0)
Abstraction Points	0.0 (0.5)	-0.0 (0.5)
Delayed Recall Points	0.2 (1.4)	0.2 (1.3)
Orientation Points	0.0 (0.4)	0.0 (0.4)

*n=440 for Baseline and 443 for Mirabegron Total.
†n=419 for EoT and 411 for Mirabegron Total.
‡n=411 for Baseline and 406 for Mirabegron Total.
SD=standard deviation; SE=standard error

- Of 425 patients receiving mirabegron and 411 patients receiving placebo, 49 patients (24 patients in each of the mirabegron and placebo groups) had declines in MoCA score of ≥4 points at Week 12
  - Distribution of score changes is shown below (Figure 2)

Figure 2. Percentage of patients with indicated MoCA score change at Week 12/EoT



EoT=end of treatment; MoCA=Montreal Cognitive Assessment

CONCLUSIONS

- Using the MoCA, treatment with mirabegron for 12 weeks had no adverse impact on cognitive function in patients aged ≥65 years
- As those aged ≥65 years are often under-represented in clinical trials, the results for this study population, including a significant proportion aged ≥75 years, are clinically relevant
  - This is of particular importance given that the potential for cognitive adverse events are of concern to older patients receiving OAB medication
- Together with the efficacy demonstrated during the PILLAR study,[1] these data suggest that mirabegron represents a viable alternative for treatment of older patients with OAB

REFERENCE

1. Wagg A, et al. Presented at the International Continence Society 48th Annual Meeting, 28–31 August 2018, Philadelphia, PA, USA. Abstract #288.

ACKNOWLEDGEMENTS

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Presented at the 34th Annual Congress of the European Association of Urology, 15–19 March 2019, Barcelona, Spain

PT237

Chance of OAB patients to become symptom-free upon anti-muscarinic treatment depends on age and gender

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Background

- Bothersome symptoms and symptom severity exhibit a wide-range in OAB patients.
- Treatment expectations on improvement and rapid onset of effects are high.
- Muscarinic receptor antagonists are a first-line drug treatment of OAB or urgency incontinence.
- Long-term adherence to muscarinic receptor antagonists in the treatment of OAB is poor, partly due to unmet expectations on treatment outcomes.
- Patient counseling on realistic expectations is important, but outcomes are reported as improvements (absolute or percentage) based on mean outcomes.

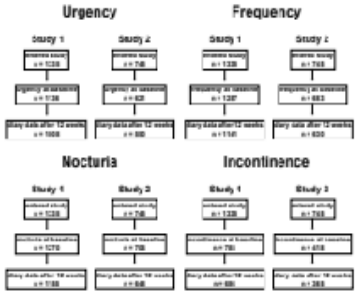
Objective

- To explore the probability of becoming free of a given symptom upon treatment
- Explore role of baseline severity, gender and age

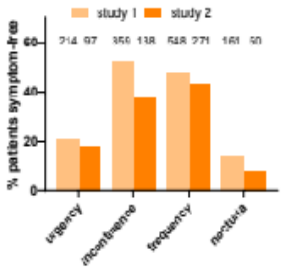
Patients and Methods

- Two non-interventional studies performed under ethical committee approval in patients receiving propiverine ER (30-45 mg/day; dose adjustment during study permitted) were analyzed.
- For each symptom exhibited at baseline, % of patients not exhibiting that symptom after 12 weeks was calculated (0 episodes for urgency, nocturia or incontinence; ≤7 voids/24 h for frequency).
- Subgroups based on baseline symptom severity (based on median values of a symptom), gender and age (≤68 vs. ≥69 years as based on median age) were also analyzed.
- Based on the post-hoc nature of the subgroup analyses, no P-values were calculated; rather we looked for consistency of findings across the two studies.

Patient Flow

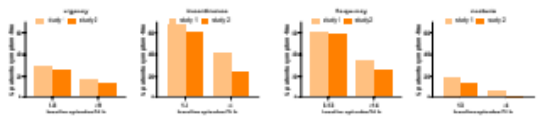


Overall chance to become symptom free

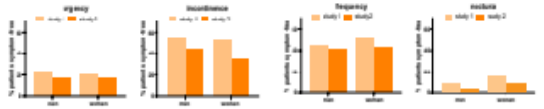


	Study 1		Study 2	
	%	n	%	n
Urgency				
All	**21.2**	**214**	**17.6**	**97**
1-8 episodes	28.3	129	24.9	58
≥9 episodes	15.9	91	12.3	39
Men	21.6	76	17.5	36
Women	20.6	129	17.1	55
≤68 years	25.1	125	22.6	61
≥69 years	17.5	88	13.1	36
Frequency				
All	**48.0**	**548**	**43.0**	**271**
8-13 voids	60.3	365	57.9	201
≥14 voids	34.1	183	24.7	70
Men	44.4	173	41.3	92
Women	50.8	370	43.0	160
≤68 years	52.3	306	46.7	148
≥69 years	43.9	242	39.6	122
Nocturia				
All	**13.9**	**161**	**7.7**	**50**
1-3 episodes	19.5	130	11.8	45
≥4 episodes	6.4	31	1.9	5
Men	9.7	38	5.2	12
Women	16.2	110	9.1	35
≤68 years	16.8	97	12.3	39
≥69 years	11.2	64	3.3	11
Incontinence				
All	**52.3**	**350**	**37.8**	**138**
1-3 episodes	68.0	200	59.9	88
≥4 episodes	40.6	159	22.9	50
Men	52.7	108	43.7	45
Women	51.5	239	34.8	85
≤68 years	61.1	190	40.7	70
≥69 years	45.0	161	33.0	62

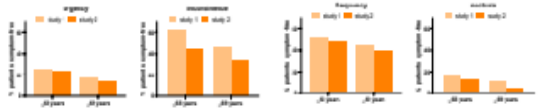
Subgroups by baseline symptoms



Subgroups by gender



Subgroups by age



Conclusions

The chance to become free of a given symptom was greatest for frequency and incontinence, intermediate for urgency and smallest for nocturia.
Less baseline symptoms, younger age and female gender (frequency and nocturia only) are associated with a greater chance of success.
Such data, perhaps applicable to muscarinic antagonists as a class, can be used in the evidence-based counseling of OAB patients regarding realistic treatment expectations.

Ethics statements
The underlying studies had been approved by the ethical committee of the Landesärztekammer Sachsen and were funded by Apogepha.

DAR AÇILI GLOKOM

- Glokom insidansı yaşla birlikte artar ve AAM ve glokomun yaşlı bireylerde sıklıkla birlikte bulunduğu bilinmektedir[1,2].
- Açık açılı glokomdan daha az yaygın olan ancak hastalığın daha ciddi bir formu olan kontrol edilemeyen dar açılı glokomu olan hastalarda antimuskarinik önerilmez[3].
- Yaşlı kişilerde veri bulunmasa da normal göz içi basıncı olan >18 yaş erişkinlerde yapılan 8 haftalık, randomize, çift kör, plasebo kontrollü bir çalışmada mirabegron 100mg QD, göz içi basıncını plaseboya kıyasla arttırmamıştır; herhangi bir glokom AO'su bildirilmemiştir[4].

1- Eskandar OS, Eckford SD, Whittaker KW. Treatment of overactive bladder (OAB) with anti-cholinergic drugs and the risk of glaucoma. J Obstet Gynaecol 2005;25:419-21 2- Kato K, Furuhashi K, Suzuki K, et al. Overactive bladder and glaucoma: a survey at outpatient clinics in Japan. Int J Urol 2007;14:595-7 3- Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA 2014;311:1901-11 4- Novack GD, Lewis RA, Vogel R, et al. Randomized, doublemasked, placebo-controlled study to assess the ocular safety of mirabegron in healthy volunteers. J Ocul Pharmacol Ther 2013;29:674-80

MIRABEGRON & İDRAR RETANSİYONU

- AÜSS olan ve antimuskarinik tedavisi alan erkek hastalarda akut üriner retansiyon riski klinik çalışmalarda düşük olsa (<%3) da[1] toplum tabanlı bir popülasyonda antimuskarinik kullanımı ve akut üriner retansiyon arasında bir ilişki görülmüştür[2].
- Mirabegron, (50mg ve 100mg QD dozlarında) miksiyon basıncında, PVR hacminde ya da işeme kontraksiyonunda değişiklik yapmadan mesane kapasitesini arttırır[3-5].
- AÜSS olan ve mesane çıkış obstrüksiyonu olan erkeklerde yapılan 12 haftalık bir faz II çalışmasında mirabegron plaseboya kıyasla ürodinamik işeme parametrelerini (maksimum üriner akım ve maksimum üriner akımdaki detrüsör basıncı) olumsuz etkilememiştir[6].

1- Kaplan SA, Roehrborn CG, Abrams P, et al. Antimuscarinics for treatment of storage lower urinary tract symptoms in men: a systematic review. Int J Clin Pract 2011;65:487-507 2- Martin-Merino E, Garcia-Rodriguez LA, Masso-Gonzalez EL, et al. Do oral antimuscarinic drugs carry an increased risk of acute urinary retention? J Urol 2009;182:1442-8 3- Andersson KE. Prospective pharmacologic therapies for the overactive bladder. Ther Adv Urol 2009;1:71-83
4- Leon LA, Hoffman BE, Gardner SD, et al. Effects of the beta 3-adrenergic receptor agonist disodium 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl] amino]propyl]-1,3-benzodioxole-2,2- dicarboxylate (CL-316243) on bladder micturition reflex in spontaneously hypertensive rats. J Pharmacol Exp Ther 2008;326:178-85 5- Tyagi P, Tyagi V. Mirabegron, a b3-adrenoceptor agonist for the potential treatment of urinary frequency, urinary incontinence or urgency associated with overactive bladder. IDrugs 2010;13:713-22 6- Nitti VW, Rosenberg S, Mitcheson DH, et al. Urodynamics and safety of the b3-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. J Urol 2013;190:1320-7

Kardiyovasküler Etkiler

- M2 reseptörler kalp hızının düzenlenmesinde rol oynar. Blokajı kalp hızını arttırır.

- M3'e M2'den daha selektif antimuskariniklerin kalp hızını arttırma etkileri düşüktür
(Andersson KE 2007)

Darifenasin (53x)
Solifenasin (15x)
Oksibutinin (6x)

•Tolterodin, Fesoterodin, Trospiyum M3-M2 etkileri nonselektif

•Tolterodin 4, 8mg, Fesoterodin 4mg kalp hızını plaseboya göre sırasıyla 8, 12, 3.3 atım/dak arttırır
(Chapple C 2007, Schiffers 2010)

Kalp atım hızında 5 atımlık bir artış uzun dönemde mortalite riskini %17 arttırır
(Jouven X 2009, Hozawa A 2004)

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.

- Hipertansiyon (%9.9), nasofarenjit (%4.1), İYE (%3.1%), başağrısı, ağız kuruluğu, ekstremite ağrısı

Wagg et al. Age Ageing, 2014

Mirabegron & Hipertansiyon?

DOĞRU BİLİNEN YANLIŞ!

Kontrolsüz Hipertansiyon:

- **Üç antihipertansif ilaç içeren,**
  - **Bir tanesi etkili diüretik olan,**
  - **Her bir ilacın etkin dozda kullanıldığı**

⇒ tedavi rejimine rağmen, kan basıncının hedefin üstünde kalması

- **Bütün hipertansifler <140/90 mmHg**
- **Yüksek risk (DM., inme, M.İ., KBY, proteinüri) ⇒ 130/80 mmHg**

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Diagnosis and Management of Resistant Hypertension

Jul 10, 2017 | **Debabrata Mukherjee, MD, FACC**

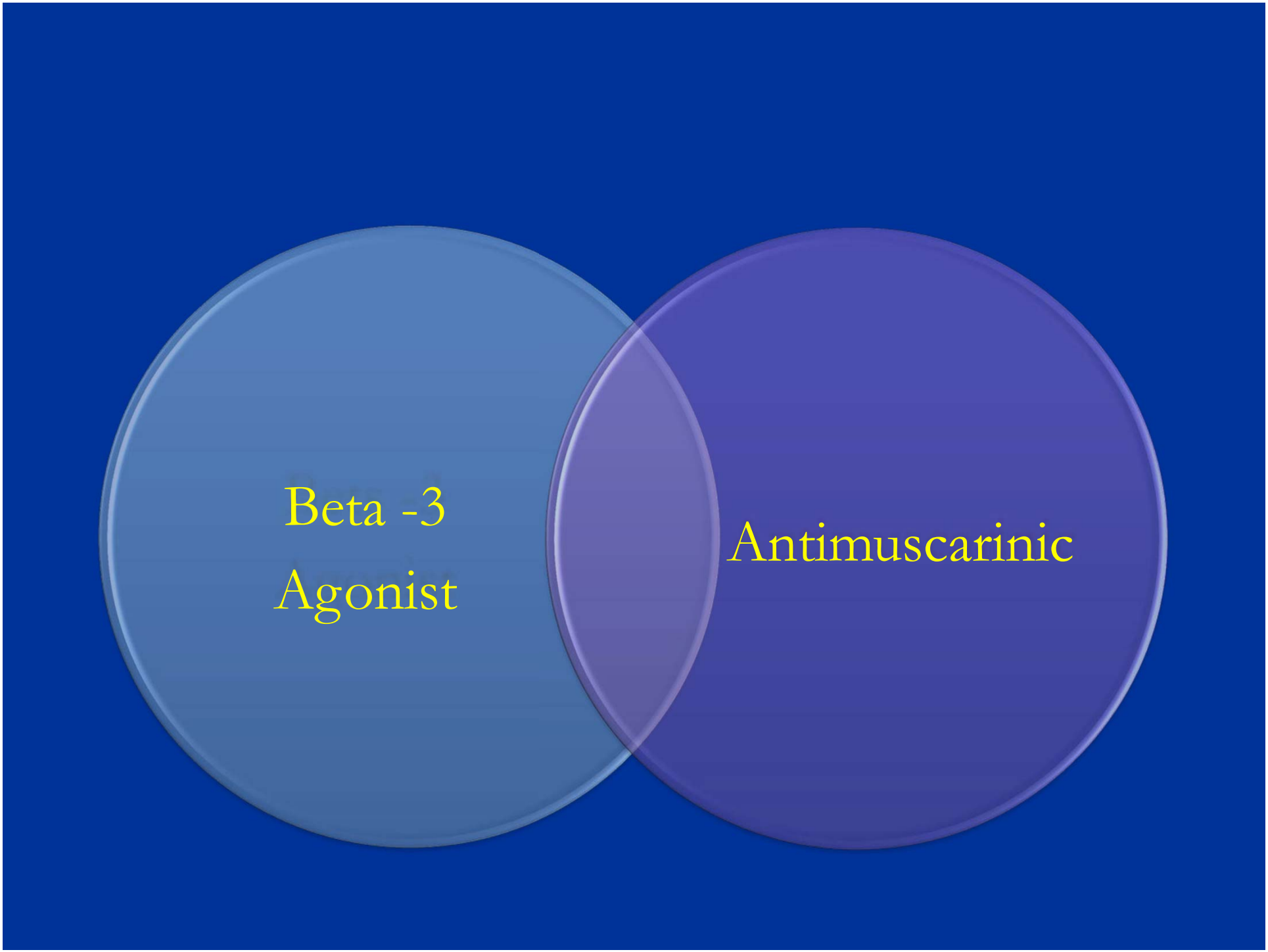
Share via: Print **Font Size** A A A

Authors: Sheppard JP, Martin U, McManus RJ.

Citation: Diagnosis and Management of Resistant Hypertension. *Heart* 2017;Jun 29:[Epub ahead of print].

The following are key points to remember about this review on the diagnosis and management of resistant hypertension:

1. High blood pressure (hypertension) is one of the most important risk factors for cardiovascular diseases and is a significant cause of morbidity and mortality worldwide.
2. Resistant hypertension is generally defined as uncontrolled clinic blood pressure (>140/90 mm Hg) after treatment with three or more antihypertensives.
3. The National Institute for Health and Care Excellence (NICE) guidelines specify that these three antihypertensives should include optimal doses of an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin receptor blocker), a calcium channel blocker, and a diuretic


Beta -3
Agonist
Antimuscarinic

LEUVEN

03:56

Combination treatment for OAB

- Is somewhat better then monotherapy
- Has no synergistic side effects

- Is not (yet) the holy grail

- Instead of dose escalation or progression to invasive treatments (Botox/Neuromodulation), combination treatment might have benefit

EAU19 BARCELO
15-19 March

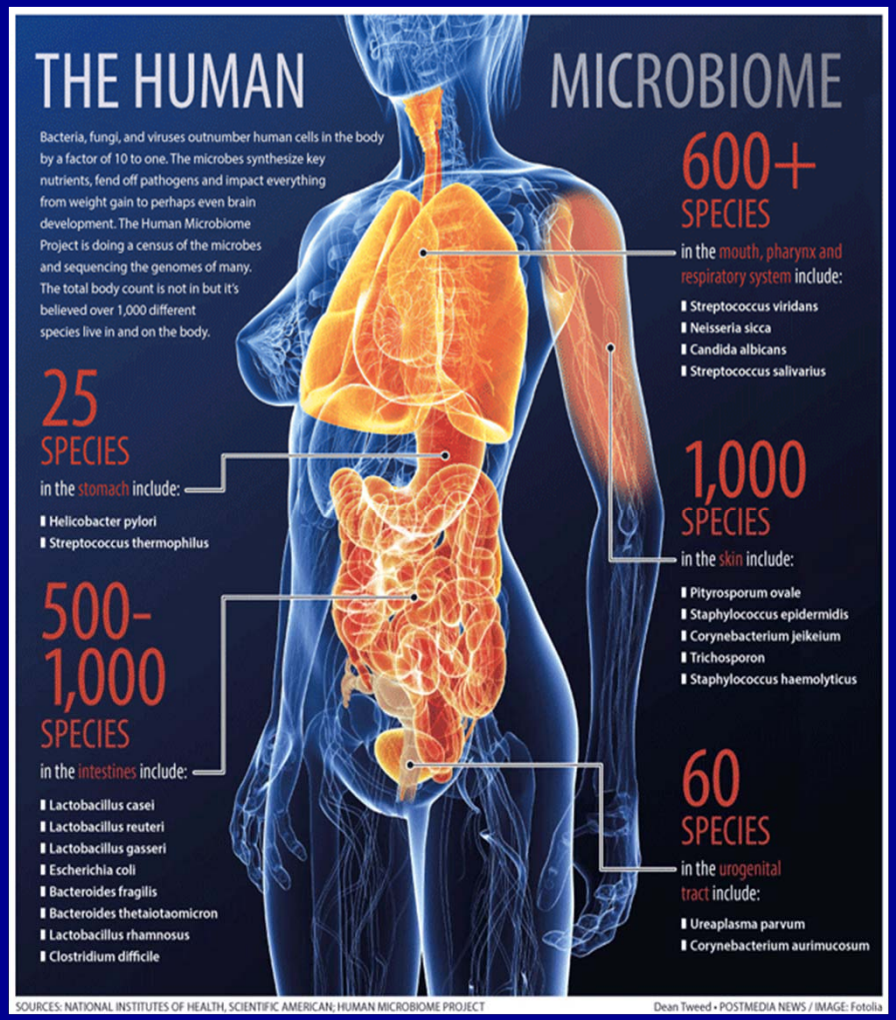
Treatment failure: overlooked cause?

- 110 women with refractory OAB had cystoscopy and biopsy
- The patients had undergone conservative management (lifestyle change, bladder retraining, and physiotherapy) and previous treatment with two or more antimuscarinics
- Histopathology showed chronic cystitis in 94, follicular cystitis in 3, acute and chronic cystitis in 2, transitional cell carcinoma in 6, and no abnormality in 1, suggesting that OAB refractory to antimuscarinics may be caused by chronic inflammation

Digesu GA Eur Jobstet Gynecol Reprod Biol 2013;169

İnsan Mikrobiyom Projesi - I (HMP)

- Sağlıklı insan vücudunda bulunan mikrobiyomlarının belirlenmesi için başlatılan bir çalışmadır.
- İnsan genetik ve metabolik tabiatının mikrobiyal bileşenlerinin belirlenmesi ve bu bileşenlerin normal fizyolojiye ve hastalık oluşumuna nasıl katkıda bulunduğunu araştırmayı amaçlamaktadır.

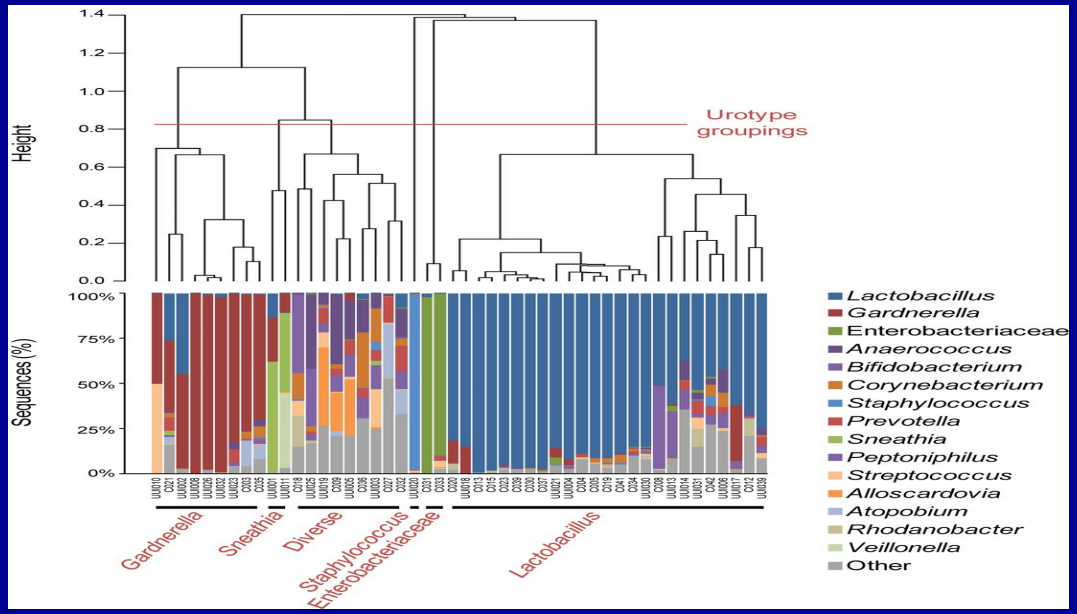


Peterson J, Garges S, Giovanni M, McInnes P, Wang L, Schloss JA, Bonazzi V, McEwen JE, Wetterstrand KA, Deal C, Baker CC, Di Francesco V, Howcroft TK, Karp RW, Lunsford RD, Wellington CR, Belachew T, Wright M, Giblin C, David H, Mills M, Salomon R, Mullins C, Akolkar B, Begg L, Davis C, Grandison L, Humble M, Khalsa J, Little AR, Peavy H, Pontzer C, Portnoy M, Sayre MH, Starke-Reed P, Zakhari S, Read J, Watson B, Guyer M (2009) The NIH human microbiome project. Genome Res 19:2317–2323

Üriner Mikrobiom

Üriner mikrobiyota potansiyel nörotransmitterlerin üretimi yoluyla, uriner sistem sinyal iletimi ve sistemin düzgün gelişimi için gerekli olabileceği ve bu fonksiyonların kaybının "aşırı aktif mesane" ve "interstisyel sistit" gibi hastalıkların nedeni olabileceği düşünülmüştür.

Lewis DA, Brown R, Williams J, White P, Jacobson SK, Marchesi JR, Drake MJ (2013) The human urinary microbiome; bacterial DNA in voided urine of asymptomatic adults. Front Cell Infect Microbiol 3:41.



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Role of corticotropin-releasing factor on bladder function in rats with psychological stress

Seki M., Zha X-M., Ito H., Aoki Y., Matsuta Y., Taga M., Inamura S., Yokoyama O.
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Objective

- Corticotropin-releasing factor (CRF) is a main factor of the hypothalamic-pituitary-adrenocortical axis and stress-related peptide.
- CRF and CRF-related peptides are distributed in the peripheral viscera such as the bladder.
- We investigated the contribution of psychological stress and CRF on bladder function.
- We hypothesized that psychological stress affects bladder function not only via spinal CRF, but also via bladder CRF.

Materials and Methods

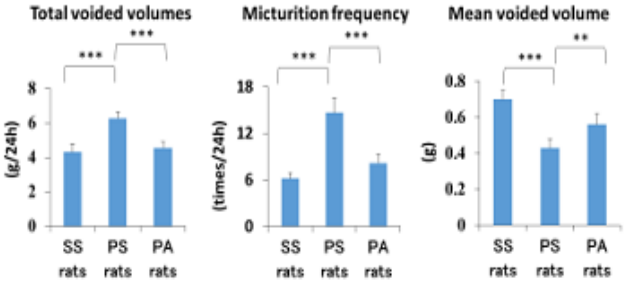
- **Male Wister Kyoto (12 weeks old) rats in the 3 treatment groups;**
  1. Rats exposed to sham stress (SS rats; n= 8)
  2. Rats exposed to psychological stress (PS rats; n= 8)
  3. Rats exposed to psychological stress treated with intraperitoneal CRF-R1 antagonist antalarmin (200 μg/kg/day) for 7 days during the stress exposure (PA rats; n= 8).
- **Psychological stress exposure**
  - We adopted a communication box method to induce purely psychological stress without physical stress interference (see below).
- **Measurement of micturition characteristics**
  - We kept rats in metabolic cages and calculated 24-hour micturition frequency, mean voided volume per micturition, and 24-hour urine output.
- **Measurement of CRF in the plasma and bladder wall**
  - CRF in the bladder and plasma were measured by enzyme-linked immunoassay using a YK131 Mouse/RAT CRF-HS ELISA KIT.
- **Measurement of mRNA (Real-Time PCR)**
  - The level of target mRNAs expression in the bladder was analyzed using the SYBR green fluorescence relative quantification method with an ABI 7300 Real-Time PCR System.
- ***In vitro* organ bath studies**
  - 2 × 5 mm bladder strips containing the urothelium of rats were cut longitudinally from the dome to the neck of the bladder.
  - We measured the contraction induced by K^+ (100 mM) and carbachol (cumulative doses; 10^{-7}, 3×10^{-7}, 10^{-6}, 3×10^{-6}, 10^{-5}, 3×10^{-5} M) in organ baths.

A communication box method

A (1, 3, 5, 7, 9): Electrified chamber
- Rats received electric shock (0.2 mA) for 10 s at intervals of 50 s through the floor. The rats revealed nociceptive responses such as jumping up, defecation, and crying.

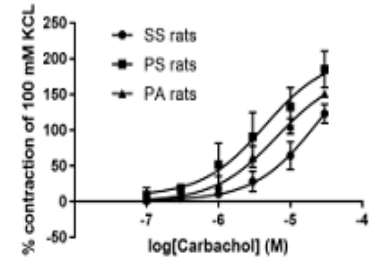
B (2, 4, 6, 8): Psychological stress(PS) / sham stress(SS)-received chamber
- A plastic plate was placed on each of the grid floors to prevent electric shock.
- The PS Rats received psychological stress from the rats in compartment A. The SS rats received sham stress because rats in compartment A did not receive electric shocks (120 min every day for 7 days).

Micturition parameters



Sham stress (SS), psychological stress (PS), and psychological stress treated with antalarmin (PA) rats (n=8: each). Values represent means ± standard error of the mean (SEM). **: p <0.01, *** : p <0.001. ANOVA

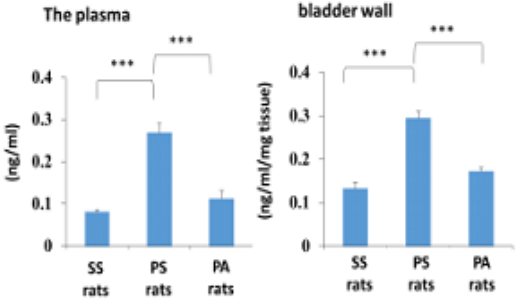
Contractile responses of bladder strips to cumulative doses of carbachol



	SS rats	PS rats	PA rats
$LogEC_{50}$	-4.63±0.13	-5.36±0.13**	-5.19±0.064**
E_{max}	123.2±12.3	185.2±25. 7***	151.2±3.8†

n=8: each. Values represent means ± SEM **: p <0.01 vs. SS rats, ***: p <0.001 vs. SS rats, and †: p <0.05 vs. PS rats. ANOVA

Protein amounts of CRF



n=8: each. Values represent means ± SEM. ***: p <0.001. ANOVA

Relative expressions of mRNA in the bladder

	SS rats	PS rats	PA rats
CRF	1	4.73±1.00**	2.54±1.42†
CRF receptor 1	1	3.91±1.36**	2.10±0.85
M_2	1	5.31±1.39**	3.53±1.04†
M_3	1	3.30±0.77**	2.08±0.53†
Alpha $_{1a}$	1	1.03±0.13	0.94±0.16
Alpha $_{1b}$	1	1.07±0.22	0.84±0.26
Alpha $_{1d}$	1	1.10±0.32	0.94±0.30

n=8: each. Values represent means ± SEM.
**p <0.01 vs. SS rats, †p <0.05 vs. PS rats ANOVA

Results

- Mean voided volume per micturition was significantly lower in PS rats compared to SS rats, which was antagonized by antalarmin treatment.
- Increases in plasma and bladder CRF, and mRNA expressions of bladder CRF, CRF-R1, and M2/3 muscarinic receptors, were found in PS rats.
- CRF did not influence bladder contraction in itself; however, stress increased the response of muscarinic contraction of bladder strips.
- These changes were antagonized by antalarmin treatment.

Conclusion

- Psychological stress induces bladder dysfunction with increases in serum and bladder CRF protein and mRNA overexpression of CRF-R1, M_2, and M_3 muscarinic receptors of the bladder in rats.
- Endogenous CRF increased muscarinic contractions of the bladder strips, which were partially prevented by a CRF-R1 antagonist.
- These results support the hypothesis that psychological stress influences bladder function via a local CRF-muscarinic receptor signaling pathway.

Conflict of Interest Disclosure; I have no potential conflict of interest to report.

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Dysregulation of phospholamban and beta 3-adrenergic receptor expression might lead to bladder detrusor overactivity via SERCA inhibition

Katia Monastyrskaya [1,2], Mustafa Besic [2], Ali Hashemi Gheinani [2], and Fiona C. Burkhard [1,2]

UNIVERSITÄT BERN

Introduction

Bladder outlet obstruction (BOO) induces organ remodeling accompanied by urodynamic changes in bladder function. Previously, using mRNA and miRNA sequencing, we determined mRNA and miRNA expression profiles in biopsies of BPO patients. We identified biomarkers of urodynamic BOO phenotypes (Gheinani AH et al., 2017). Men with benign prostatic hyperplasia (BPH) and benign prostatic obstruction often present with lower urinary tract symptoms including overactive bladder (OAB). OAB is often associated with detrusor overactivity (DO). Although the symptomatic diagnosis of OAB does not always correlate with DO, DO is an objective, measurable characteristic of bladder dysfunction. Our NGS data revealed specific mRNAs and miRNAs dysregulated in patients with DO. Here we sought to investigate the regulation of beta 3-adrenergic receptor and other components of detrusor contractile apparatus, including phospholamban in a larger patients' cohort and in bladder cell-based models.

Experimental setup

The representative urodynamic evaluation is shown in Fig.1. Based on questionnaires and urodynamic examination, the patients were divided into following groups: group 1 designated "Control" or "C" - normal bladder function; group 2 designated "DO" - BPO with detrusor overactivity (DO); group 3 designated "BO" - BPO without DO, group 4 designated "UA" - BOO with detrusor underactivity or acontractile bladders.

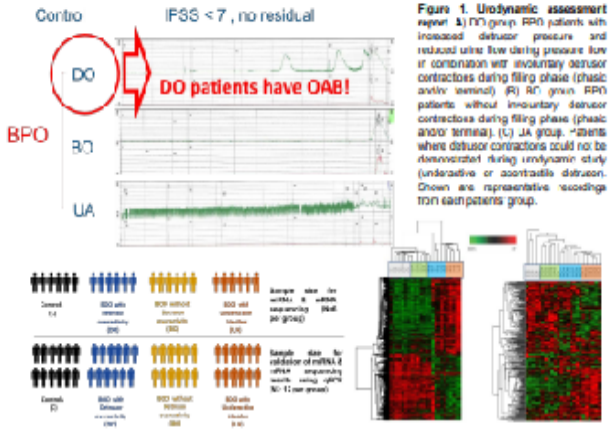


Figure 1. Urodynamic assessment report. **(A)** DO group: BPO patients with increased detrusor pressure and reduced urine flow during pressure flow in combination with involuntary detrusor contractions during filling phase (phasic and/or terminal). **(B)** BO group: BPO patients without involuntary detrusor contractions during filling phase (phasic and/or terminal). **(C)** UA group: patients where detrusor contractions could not be demonstrated during urodynamic study (underactive or acontractile detrusor). Shown are representative recordings from each patients group.

Figure 2. Patients grouping for NGS and data validation by qPCR.

Figure 3. NGS results - clustering of high variance mRNAs and miRNAs in accordance with functional phenotype. Log2 fold change of significantly regulated mRNA and miRNAs (Y-axis) and 24 samples (X-axis) are presented.

Gene enrichment analysis and pathway elements in DO group

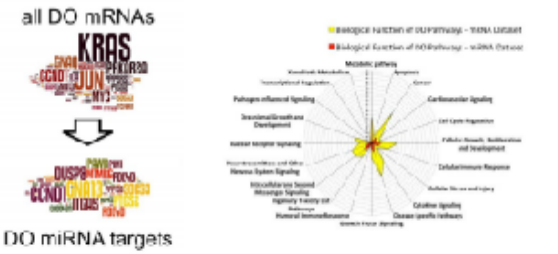
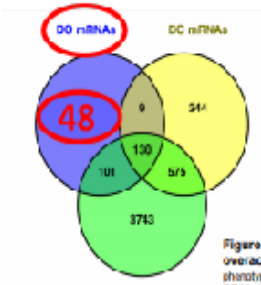


Figure 4. Main pathway elements and biological functions in DO group. The word clouds show pathway elements in mRNA dataset (top), and in miRNA target dataset (bottom). The radar graphs for biological functions of 10 mRNA dataset pathways (yellow) and 20 expressed miRNA targets pathways (red) in DO patients.

Differentially expressed mRNAs, specific for bladder overactivity, participate in contractility pathways

We compared mRNAs, differentially expressed in bladder phenotypes. While the overall number of regulated genes was increasing from DO to BO and UA group, 48 mRNAs were only regulated in DO patients (mRNAs with ±1.5 fold change, p-value <0.05 and < 0.15) (Fig.5). We performed pathway analysis using only these 48 regulated mRNAs. Four out of 10 significant pathways are connected to muscle contractility (Fig. 6)



- 48 mRNAs are regulated in DO only
- Some might be contributing to the urodynamic phenotype

Pathway analysis with DO-only mRNAs

Figure 5. DO-specific mRNAs, which might contribute to the overactive bladder phenotype. We compared the NGS data of BPO phenotypes and determined 48 transcripts, regulated only in patients with DO/bladder overactivity.

Figure 6. Pathway analysis of DO-specific genes. Ten significant pathways were built by MetaCore pathway analysis using 48 DO-specific transcripts as an input. Four are involved in regulation of muscle contractility (arrows).

Smooth muscle contraction pathway in DO: up-regulation of contractile and regulatory elements

Functional phenotype of DO, characterized by bladder overactivity, is in agreement with molecular changes observed in the bladders of these patients. Some important contractility and Ca^{2+} signaling regulators are altered only in this group.

Figure 7. Smooth muscle contraction pathway with DO-regulated elements (circles)

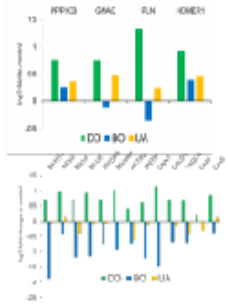
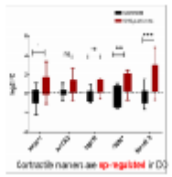


Figure 8. DO group-specific up-regulation of contractile proteins and regulatory pathway elements, including phospholamban (PLN)
Graphs are based on NGS data (n= 3 per group)

Validation of NGS data: significant down-regulation of ADRB3 and up-regulation of PLN in DO group

Beta 3 adrenergic receptor is implicated in regulation of bladder relaxation, and its agonist Mirabegron is an approved anti-overactivity drug. We investigated the regulation of phospholamban (PLN), β3-AR (ADRB3), contractile and regulatory proteins in a larger patients' cohort using qPCR (Fig. 9).



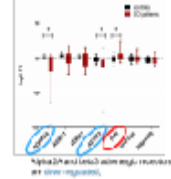
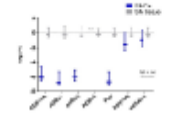
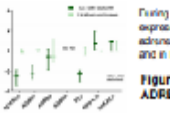


Figure 9. qPCR for validation of NGS data. Biopsies of 10 controls and 22 obstructive patients with DO, showing symptomatic bladder overactivity, were examined by qPCR. We could confirm the increase of contractile and smooth muscle markers and SERCA-regulator protein Phospholamban (PLN) and down-regulation of ADRB3 and ADRA2A in DO group.

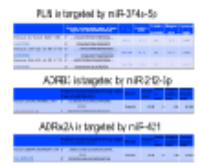


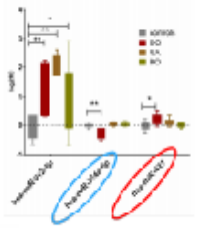


During maturing, bladder SMC and urothelium cells undergo gene expression changes. We compared the expression of β3-adrenergic receptor and phospholamban in SMC and UC cells and in bladder tissues (Fig. 10).

Figure 10. Culturing down-regulates PLN. ADRB3 is detected only in SM tissue

MicroRNAs might affect contractility in DO bladders





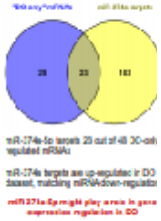


Figure 11. Target prediction

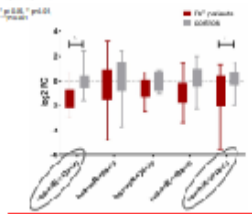


Figure 12. Expression of regulatory miRNAs in patient groups and the significance of miR-374a-5p for DO phenotype. Based on NGS data (n=6 per group). miR-374a-5p is down-regulated, and miR-210 up-regulated specifically in DO group. Ca^{2+} induced miR-210-5p is elevated in all functional strips of DO.

Down-regulation of miR-374a-5p might have consequences for gene expression in DO

Figure 13. NGS data validation in a larger DO patients cohort. miR-100a-3p and miR-374a-5p are significantly down-regulated

Conclusions

- *PLN* is up-regulated and *ADRB3* down-regulated in DO patients.
- De-phosphorylated PLN (gene expression up-regulation and diminished PKA-β3-AR–mediated phosphorylation) inhibits SERCA.
- Inhibition of SERCA leads to Ca^{2+} increase, induces miR-210-5p and down-regulates its target *ADRB3*.
- Ensuing feed-forward loop might contribute to myogenic bladder overactivity in DO.

Affiliations and Funding

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Randomised, open-label, tolterodine-controlled, comparative study of the novel antimuscarinic agent imidafenacin in patients with overactive bladder

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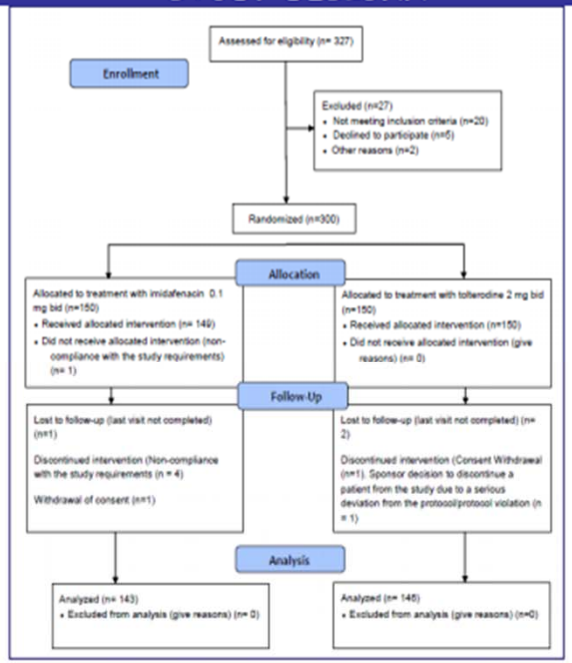
OBJECTIVES

The role of the selective antimuscarinic imidafenacin in Caucasian patients with overactive bladder (OAB) has not been previously assessed. To evaluate the safety and efficacy of imidafenacin 0.2 mg versus tolterodine 4 mg per day in patients with OAB.

METHODS

This study was a randomized, open-label, tolterodine-controlled, comparative multicenter trial of 300 randomized Caucasian patients with OAB symptoms for 12 weeks. The full analysis set comprised 289 patients. The primary efficacy endpoint was the change in the mean number of micturitions per day. The secondary endpoints were the change in incontinence episodes, voiding frequency, the OAB Awareness Tool score and the European Quality of Life Questionnaire (EQ-5D) score. Superiority of tolterodine over imidafenacinin the mean number of micturitions/24 hours was the null hypothesis

STUDY DESIGHN



RESULTS

	IMIDAFENACIN	TOLTERODINE
Number patient (randomized)	143	146
Number of voidings /24 hours		
Baseline	12.5 (3.49)	11.9 (2.65)
Change from baseline (P = 0.6437)	-3.6 (3.01)	-3.4 (2.63)
Urgency incontinence episodes/24 hours		
Baseline	2.5 (2.40)	2.4 (2.25)
Change from baseline (P < 0,001)	-2.1 (2.18) *	-1.9 (1.77)
Urgency incontinence episodes/daytime		
Baseline	2.0 (1.89)	1.9 (1.79)
Change from baseline (P = 0,01)	-1.7 (1.65) *	-1.5 (1.41)
Urgency incontinence episodes/nighttime		
Baseline	0.5 (0.75)	0.5 (0.80)
Change from baseline (p=0.18)	-0.4 (0.76)	-0.4 (0.64)
OAB Awareness Tool at week 2, 4, 8 and 12 visit		
Baseline	24.3 (7.52)	23.8 (7.12)
Change from baseline (P = 0.5321).	-14.2 (8.45)	-14.5 (8.02)
EQ-5D-based at week 12 visit		
Baseline	0.8 (0.17)	0.8 (0.17)
Change from baseline (P = 0.3743).	0.1 (0.14)	0.1 (0.15)

The clinical efficacy and safety of imidafenacin are not inferior to those of tolterodine for the treatment of Caucasian patients with OAB.

PT 233

Efficacy of the novel β_3 adrenergic receptor agonist vibegron for the treatment of nocturia in patients with overactive bladder: A post hoc analysis of phase 3 study

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Introduction & Objectives

The prevalence of nocturia increases with age and nocturia markedly impair patient quality of life. Various causes, including overactive bladder (OAB) and nocturnal polyuria(NP) contribute to nocturia. However, current OAB medications have insufficient efficacy for nocturia in patients with OAB.

Vibegron, a novel β_3 adrenergic receptor agonist, demonstrated prominent efficacy and safety in the treatment of OAB at phase 3 study in Japan.

We conducted a post hoc analysis of a randomized, double-blind, placebo-controlled, 12-week, phase 3 study to examine the efficacy of vibegron on nocturia in patients with OAB.

Materials & Methods

This analysis was conducted on patients with nocturia ≥1 per night at baseline, extracted from the phase 3 study, to assess the efficacy of vibegron comparing vibegron 50mg(V 50), 100mg(V 100), and placebo (PBO) groups, and to evaluate parameters related to nocturia.

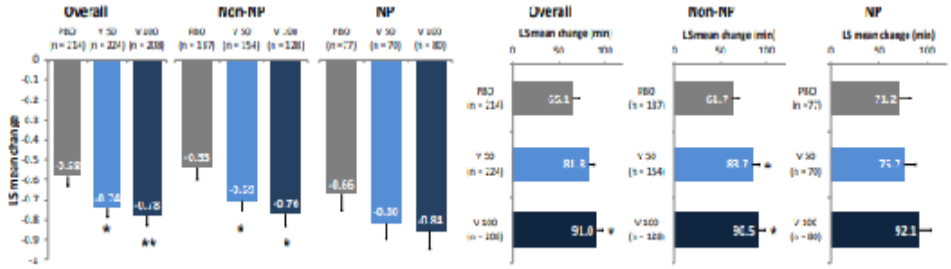
Furthermore, nocturnal voiding parameters were analyzed by stratifying patients into NP and non-NP groups. Correlation was examined between nocturia parameters and hours of undisturbed sleep (HUS).

Patient characteristics

Treatment group	PBO (n=224)	V 50 (n= 227)	V 100 (n=216)	*P*-value
Women, n (%)	201 (89.7)	203 (89.4)	194 (89.0)	0.968
Age (years)	61.2 ± 11.4	59.9 ± 11.5	60.7 ± 11.0	0.477
BMI (kg/m²)	23.37 ± 4.15	23.15 ± 4.33	23.23 ± 3.98	0.847
Duration of OAB symptoms (months)	62.0 ± 63.6	56.8 ± 61.5	70.0 ± 79.1	0.122
No Previous anticholinergic therapy for 1 year, n (%)	194 (86.6)	190 (83.7)	195 (89.4)	0.206
Hypertension, n (%)	69 (30.8)	68 (30.0)	66 (30.3)	0.981
Nocturnal polyuria (NPI ≥ 0.33), n (%)	81 (36.2)	71 (31.3)	85 (39.0)	0.226
Voided volume/24 h (mL)	1746.7 ± 434.5	1720.7 ± 439.3	1714.7 ± 412.8	0.705
NPI	0.316 ± 0.098	0.308 ± 0.090	0.315 ± 0.095	0.577
Number of voids/24 h	11.74 ± 2.44	11.74 ± 2.40	11.54 ± 2.42	0.508
Number of nocturnal voiding/24 h	1.75 ± 0.80	1.69 ± 0.77	1.69 ± 0.78	0.566
Volume per nocturnal void (mL)	204.3 ± 69.5	202.4 ± 72.1	206.8 ± 75.8	0.813
Volume of the first nocturnal voiding (mL)	208.0 ± 95.5	210.5 ± 102.7	201.1 ± 93.1	0.570
HUS (min)	182.6 ± 74.6	185.8 ± 75.4	172.0 ± 69.7	0.117

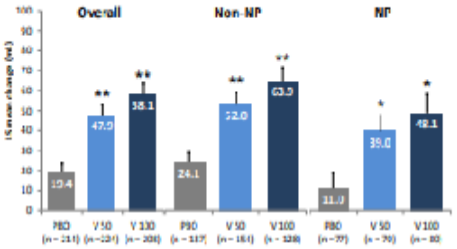
Data represent the mean ± standard deviation. †SBP ≥140 mmHg or DBP ≥ 90 mmHg.

Change in the frequency of nocturnal voiding

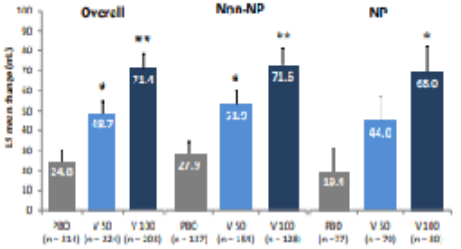


LSmean: Least squares mean by constrained longitudinal data analysis, * P <0.05, ** P <0.001 vs. PBO
Changes from baseline to week 12

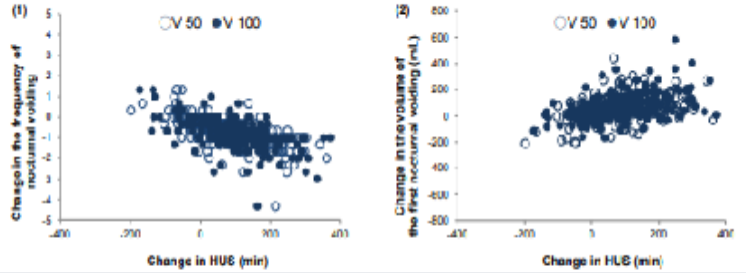
Change in the volume per nocturnal void



Change in the volume of the first nocturnal voiding



Correlations of change in HUS with change in the frequency of nocturnal voiding and in the volume of the first nocturnal voiding



Variable	V 50			V 100		
	n	ρ†	*P* value	n	ρ†	*P* value
(1) HUS vs. Frequency of nocturnal voiding	224	-0.570	<0.001	208	-0.622	<0.001
(2) HUS vs. Volume of the first nocturnal voiding	224	0.419	<0.001	208	0.423	<0.001

†: Spearman rank correlation coefficient

Results

- In all patients, both vibegron 50mg and 100mg significantly decreased the frequency of nocturnal voiding compared with placebo.
- Regardless of the presence or absence of NP, vibegron increased the volume per nocturnal void and the volume of the first nocturnal voiding, compared with placebo respectively.
- HUS was prolonged with vibegron 50mg, and significantly prolonged with vibegron 100mg compared with placebo.
- In the patients treated with vibegron, a negative correlation was found between the change in the frequency of nocturnal voiding and HUS. There was a positive correlation between the change in the volume of the first nocturnal voiding and HUS.

Conclusions

The present study demonstrated that vibegron decreases nocturnal voids, and increases voided volume, regardless of the presence or absence of NP. The HUS was significantly prolonged after treatment with vibegron. Vibegron can be an effective treatment option for nocturia in patients with OAB.

PT235
#AM19-0426

Exploration of Litoxetine (LTX)
A Potential Novel Treatment for Mixed Urinary Incontinence (MUI)

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On behalf of participating investigators in Canada, France, Georgia, Poland, UK and Ukraine

Introduction and Scientific Rationale

Serotonin plays an important role in modulating continence/micturition, potentiating the guarding reflex and inhibiting the micturition reflex. Animal studies showed that LTX, an oral selective serotonin reuptake inhibitor and multifunctional serotonin agonist and antagonist, increases urethral pressure and sphincter muscle tone and bladder capacity[1,2]. The serotonin selectivity of litoxetine, and the weaker affinity for epinephrine, norepinephrine and dopamine transporters, have the potential to provide a good cardiovascular safety profile and reduce the risk of nausea which is the most frequent side effect following treatment with serotonin reuptake inhibitors.

Taken together, this suggests a useful therapeutic potential for LTX in patients who suffer from stress and urge incontinence events

Material and Method

An RCT phase 2 study was conducted to evaluate efficacy, safety and tolerability of 3 doses of LTX (LTX40, LTX20, LTX10) versus placebo (PBO) BID in women with Mixed Urinary Incontinence (MUI), which occurs in about around 35% of women with UI.

MUI was defined as at least 7 incontinence episodes (IE) per week, at least 3 of which were stress IEs.

The design comprised a 2-week screening period, a 2-week single (subject)-blind PBO run-in period, and a 12-week double-blind Treatment Period when subjects were randomized to receive litoxetine 40, 20 or 10 mg BID (LTX40, LTX20, LTX 10) or placebo BID (PBO). The treatment period was followed by a 1-week dose-tapering period and a 4 week safety follow up period.

Results

198 subjects (57±12 years of age with 44±21 IEs/week at baseline) were randomized.

Effect on incontinence

LTX40 reduced incontinence events by 62% after 12 weeks of treatment, while PBO reduced incontinence events by 51% over the same time period. Based on adjusted means, LTX40 numerically reduced IE 23% more effectively than PBO in the overall patient population, but did not reach statistical significance. It is hypothesized that this could be due to the high placebo effect and variability in the overall population.

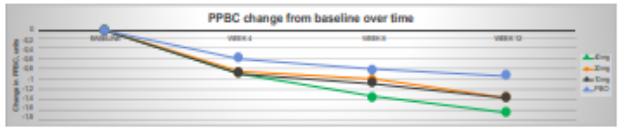
Subsequently, a post hoc analysis was performed to explore the treatment effect in the more severe patient population (split at the median,38.3 events/week).

In this severe patient population, LTX40 reduced IE by 75% over 12 weeks of treatment, while PBO remained similar (54%) to the effect seen in the overall population.
The treatment difference (ratio LTX40:PBO) was 0.55, showing (p=0.045) that LTX40 was 45% more effective than PBO to reduce IEs in this population. LTX20 showed a numeric (statistically ns) improvement of 33% over PBO while the effect of LTX10 was similar to PBO.
The treatment effect in the severe patient population was also evaluated separately on stress and urge events, as detailed in the table below:

Treatment group (BID)	Treatment difference in the severe UI population (ratio LTX to PBO)		
	Effect on incontinence events (all)	Effect on stress incontinence events	Effect on urge incontinence events
LTX40	0.55[a] (=LTX is 45% more effective than PBO)	0.46	0.44[c]
LTX20	0.67	0.28[b]	0.68
LTX10	0.92	0.52	0.92

a) p=0.045 b) p=0.004 c) p=0.043

Effect on patient reported outcomes:
Patients' perception of outcomes was evaluated by Patient's Perception of Bladder Condition (PPBC), Patient Global Improvement Index (PGI-I) and King's Health Questionnaire (KHQ).
PPBC, which was evaluated at week 4, week 8 and week 12, showed a gradual improvement over time:



Following 12 weeks of treatment, a net 56% of patients receiving LTX40 and 32% of patients receiving PBO reported "no /very minor/some minor problems" in the PPBC.
A responder analysis was conducted to determine clinically meaningful improvement:

Treatment group BID	Proportion of subjects who improve		
	PPBC by 2 units	PGI-I by 2 units	KHQ by total score of 15%
LTX40	65%	47%	71%
LTX20	54%	44%	64%
LTX10	41%	46%	64%
PBP	30%	33%	50%

Up to 71% of subjects treated with LTX40 experienced a clinically significant improvement of at least 15% in KHQ overall. KHQ was further analysed by domain in parts 1 and 3. The proportion of subjects with an improvement of 10 units (Minimally Important difference; MID) in each domain is summarised below.

Treatment group (BID)	MID; proportion of subjects with improvement by 10 units								
	Part 1					Part 3			
	General Health	Incontinence Impact	Role limitations	Physical limitations	Social limitations	Personal relationships	Emotions	Sleep/ energy	Severity measures
LTX40	76%	65%	76%	82%	76%	38%	79%	74%	56%
LTX20	64%	36%	76%	78%	62%	16%	76%	69%	71%
LTX10	72%	49%	69%	64%	64%	31%	72%	59%	46%
PBO	54%	46%	72%	63%	59%	39%	63%	59%	52%

Safety:
41.9% of randomized subjects reported treatment emergent adverse events (TEAE); 56.3% of subjects in the LTX40 group, 42.3 %, 35.4%, 34.0% in LTX20, LTX10 and PBO groups respectively.

11% of subjects terminated the study prior to completing the 12week study period; 8 % terminated due to adverse events. One adverse events - a case of somnolence - in the LTX40 group was reported as an SAE.

The most frequently reported AE in LTX treated subjects was nausea, which was reported in 12%, 10%, 6% and 2% of subjects in the LTX40, 20, 10 and PBO groups respectively.
Nausea, together with headache, asthenia/fatigue, hypertension, vomiting, diarrhoea and rash were determined as expected adverse drug reactions (ADRs). TEAEs were generally mild to moderate in severity, and resolved spontaneously.

Interpretation and Conclusions

A pronounced PBO effect of 51% following 12 weeks treatment was observed despite a blinded 2week PBO run in period designed to minimise the placebo effect. It is possible that the use of the handheld electronic diary provided an enhanced training effect, elicited behavioral response and enforces life style modifications during the study – effects which would not be attainable in general medical practice but impairs the statistical evaluation of a clinical study. Despite not statistically significant due to the unexpected magnitude of the placebo response in the overall population, this RCT has demonstrated a meaningful treatment effect of litoxetine. The effect was more pronounced (up to 45% beyond PBO, p<0.05) in patients with more severe UI, where effects also seem to be dose related. The improvement in incontinence frequency is also accompanied by improvement in patient perception of their bladder condition. LTX appears to be well tolerated.

Based on this data it is suggested that LTX may become a useful treatment for subjects with urinary incontinence of both stress and urge character, addressing a significant unmet medical need.

Bibliography

1. F. Pérez-Martínez, P. Lluel, R. Vela-Navarrete: Effects of litoxetine on acetic acid-induced detrusor overactivity and striated anal sphincter functions in rabbits: Comparison with duloxetine. European Urology Supplements 16(3):e 354, 2017
2. M. Méen, M. Guérard, X. Gamé, P. Lluel: Effects of litoxetine on urethral pressure and detrusor overactivity in anesthesized female rats. European Urology Supplements 16(3):e 185, 2017

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