

Saturday January 18, 2020
Omni King Edward Hotel
Toronto, ON



Men's Health Summit 2020



Overactive bladder



Sender Herschorn, MD, FRCSC
Division of Urology



University of Toronto

Disclosures

- Sender Herschorn
 - Grants/research support: CIHR, Astellas, Allergan, Ixaltis, Viveve
 - Honoraria: Astellas, Pfizer, Allergan, Boston Scientific

Learning objectives

- The participant will:
 - Become familiar with current OAB treatment guidelines
 - Understand the benefits of treating OAB in men
 - Be better prepared for selection of OAB drug therapy in older patients

Overactive Bladder: Definition

ICS Standardization Committee Definition:

“Urgency, with or without urge incontinence, usually with frequency and nocturia *can be described as the overactive bladder syndrome...*”

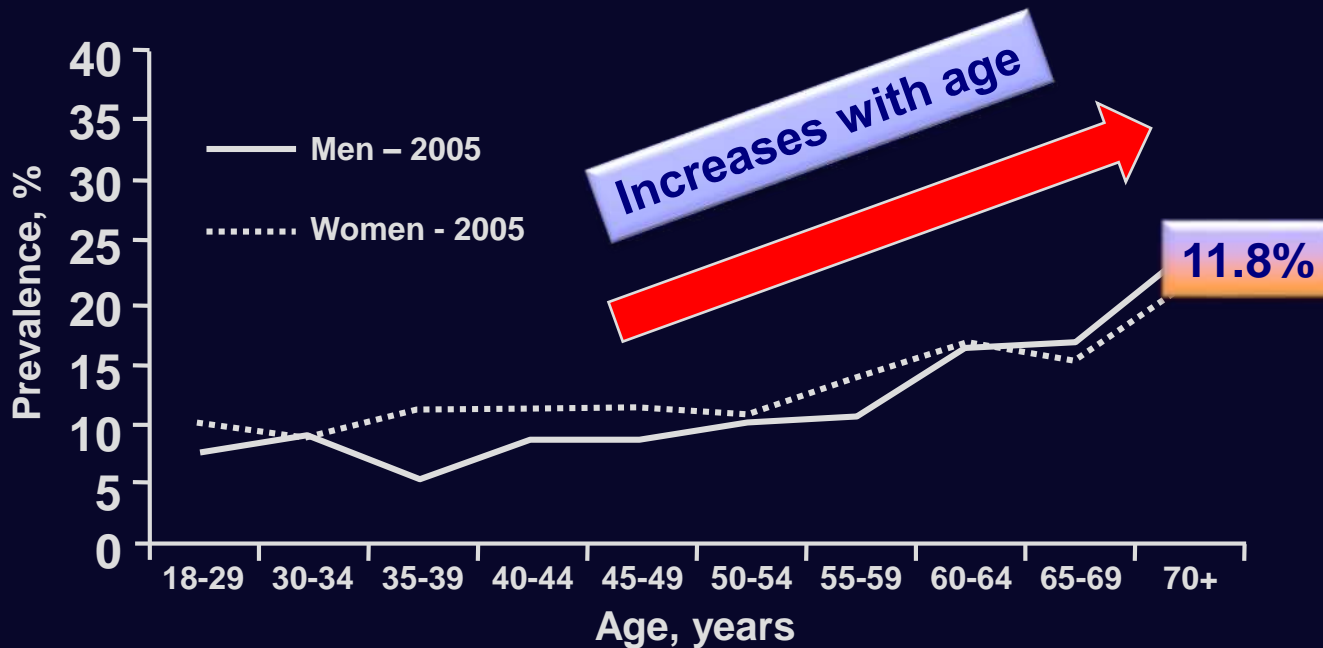
Overactive Bladder

- Symptom complex
 - **Urgency**
 - Frequency (>8/day)
 - Nocturia (>2)
 - +/- Urgency incontinence
- Associated with other conditions

Prevalence of OAB by Age

EPIC study 2005

19,165 participants in Canada, Germany, Italy, Sweden and UK



LUTS Are Similar for Men and Women

Storage	Voiding	Postvoiding
Urgency	Hesitancy	Dribbling
Frequency	Poor flow	Incomplete emptying
Urgency incontinence	Intermittency	
Nocturia	Straining	
Other incontinence		

LUTS Are Similar for Men and Women

Storage	Voiding	Postvoiding
Urgency	Hesitancy	Dribbling
Frequency	OAB symptoms	
Urgency incontinence	Intermittency	
Nocturia	Straining	
Other incontinence		

Possible co-existing conditions with OAB

- BPH, BPO, BOO, LUTS
- Prolapse
- Atrophic vaginitis
- Pelvic floor dysfunction
- Neuropathic process
- Painful bladder syndrome
- Diabetes
- GU malignancy
- Urinary tract infection
- Nocturnal polyuria

Diagnosis of OAB

Importance of history

- **Clinical principle (AUA):** The clinician should engage in a diagnostic process to document symptoms and signs that characterize OAB and exclude other disorders that could be the cause of the patient's symptoms; the minimum requirements for this process are a careful history, physical exam, and urinalysis.
- There is a universal agreement that taking a history should be the first step in the assessment of OAB patients (**Level of evidence 2b, Grade B) (CUA)**)

Initial assessment

■ Urinalysis

- To R/O UTI and hematuria
 - Dipstick
 - Microscopy
 - Culture

■ Asymptomatic bacteriuria (>10⁵ CFU/ml)

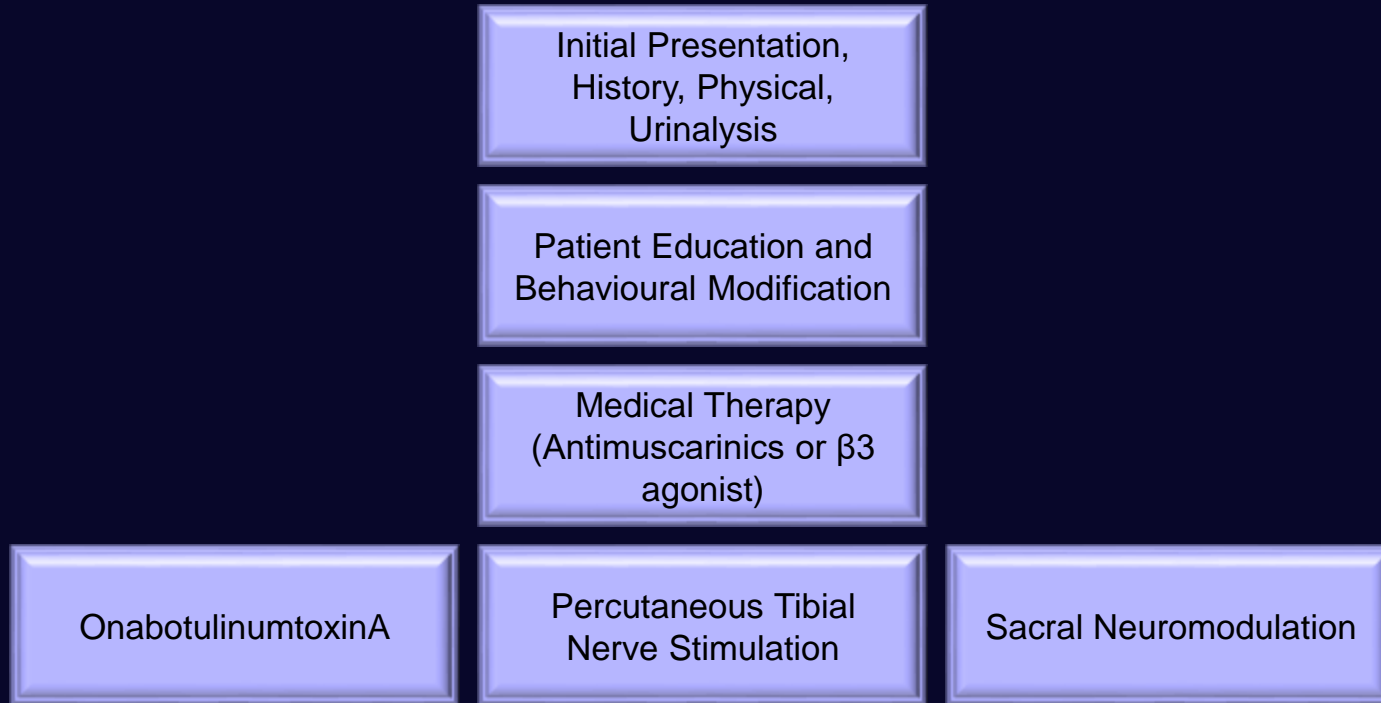
- Frequent in elderly, diabetic and catheterized patients, or in those with neurogenic lower urinary tract dysfunction
- Not to be routinely treated
 - Except in pregnant women (**Level of evidence 1a, Grade B**)
 - Before urological procedures (**Level of evidence 3b, Grade B**)

Additional tests

- **Postvoid residual (PVR) (CUA)**
 - Voiding symptoms
 - Incontinence or prostatic surgery
 - Neurologic diagnoses
 - To minimize risks
 - >250-300mL may be of concern
 - Bladder scan preferable to catheterization

Gormley EA, et al. J Urol. 2015;193:1572-80
Corcos et al. CUAJ, 2017; 11(5):E142-73
[https://www.auanet.org/guidelines/overactive-bladder-\(oab\)-guideline#x2938](https://www.auanet.org/guidelines/overactive-bladder-(oab)-guideline#x2938) - 2019

Management of OAB



OAB therapy

- **Expert Opinion**

OAB is not a disease; it is a symptom complex that generally is not a life-threatening condition. After assessment has been performed to exclude conditions requiring treatment and counseling, **no treatment is an acceptable choice made by some patients and caregivers.**

- **Clinical Principle**

Clinicians should provide education to patients regarding normal lower urinary tract function, what is known about OAB, the benefits vs. risks/burdens of the available treatment alternatives and the fact that acceptable symptom control may require trials of multiple therapeutic options before it is achieved.

First-line therapy

- **Standard (AUA):** Behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) should be offered as first line therapy to all patients with OAB.
- **CUA Guidelines similar**
 - BT and PFMT effective methods of treatment in certain cases (**Evidence strength Grade B**)(CUA).
 - Lifestyle changes - fluids/caffeine intake, weight control, dietary modifications, management of bowel regularity, and optimization of other comorbidities (i.e., diabetes, CHF, OSA) can be effective (**Evidence strength Grade B/C**).(CUA)

Gormley EA, et al. J Urol. 2015;193:1572-80
Corcos et al. CUAJ, 2017; 11(5):E142-73
[https://www.auanet.org/guidelines/overactive-bladder-\(oab\)-guideline#x2938](https://www.auanet.org/guidelines/overactive-bladder-(oab)-guideline#x2938) - 2019

Behavioural + pharmacologic

- **Recommendation (AUA):** Behavioral therapies may be combined with pharmacologic management. (Grade C)

Second-line treatments (CUA)

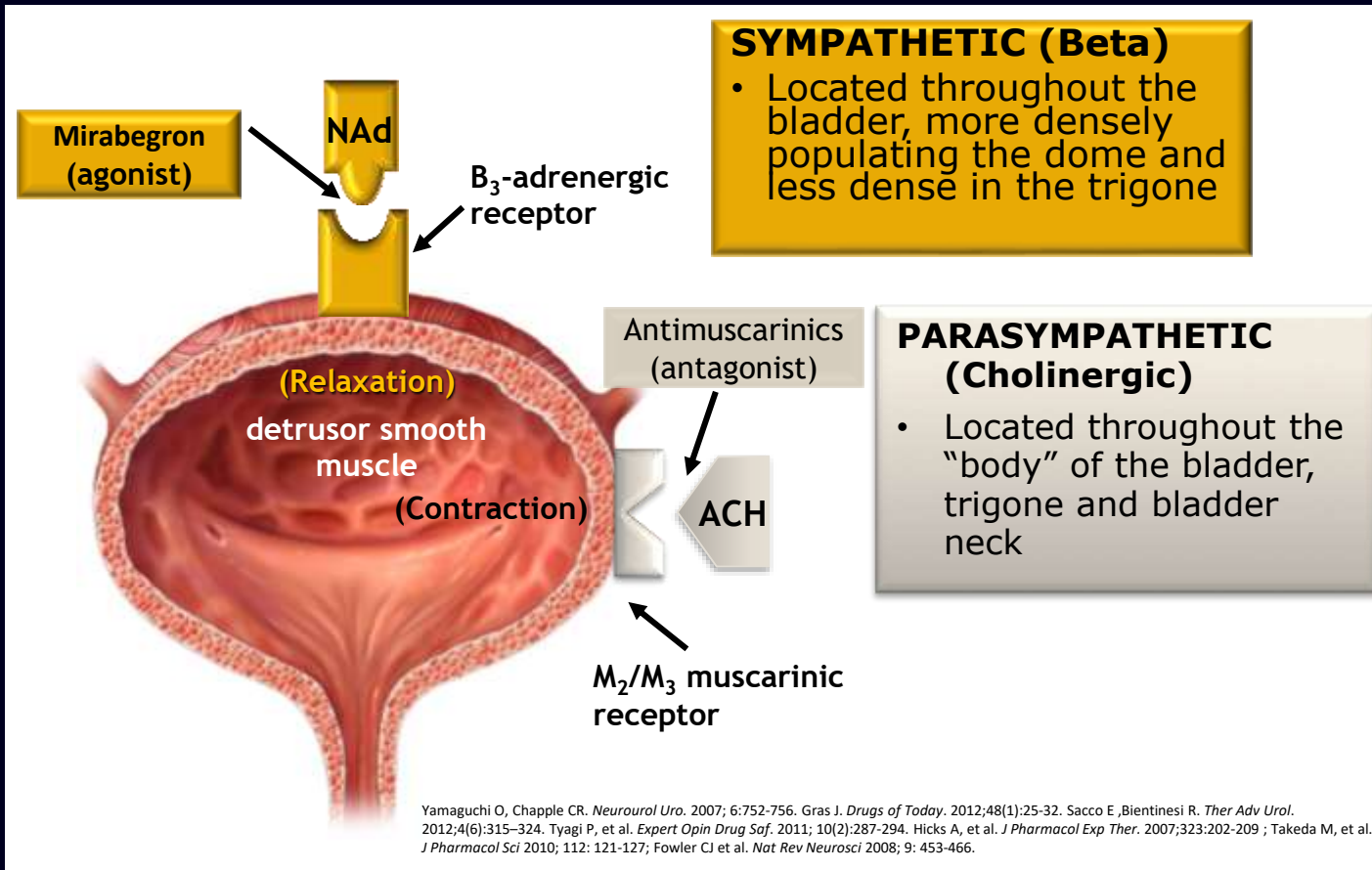
- Oral AMs, transdermal oxybutynin or oral beta-3 agonist (*Evidence strength Grade A*).
- Start with lowest dose (*Evidence strength Grade B*).
- If the initial drug is not tolerated or inadequate, give an alternative drug with different mechanism (*Expert opinion*).
- Watch for adverse events and contraindications (*Expert opinion*).
- Avoid Immediate release formulations of AMs if other formulations are available (*Evidence strength Grade A*).
- Persistent incontinence after initial treatment with an AM could be treated with combination of solifenacin and mirabegron (*Evidence strength Grade C*).

Pharmacologic Management of Overactive Bladder

Antimuscarinic Medication – Level of evidence

Drug	Level of Evidence	Grade of Recommendation
Darifenacin	1	A
Fesoterodine	1	A
Solifenacin	1	A
Toterodine	1	A
Trospium	1	A
Oxybutynin	1	A
Propiverine	1	A

OAB drug treatment



Efficacy and safety of daily mirabegron 50 mg in male patients with overactive bladder: a critical analysis of five phase III studies

Andrea Tubaro, José E. Batista, Victor W. Nitti, Sender Herschorn, Christopher R. Chapple, Mary Beth Blauwet, Emad Siddiqui, Moses Huang and Matthias Oelke

Ther Adv Urol

2017, Vol. 9(6) 137–154

DOI: 10.1177/

1756287217702797

© The Author(s), 2017.

Reprints and permissions:

<http://www.sagepub.co.uk/journalsPermissions.nav>

- 5 phase 3 studies – 808 men
 - Superiority vs. placebo for reducing frequency; in ‘Beyond’ study comparable to solifenacin for reducing frequency, urgency, UUI
 - AEs similar to placebo
- ***Alternative to antimuscarinics***

also have a history of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH)/benign prostatic enlargement (BPE) or concomitant use of α_1 -blockers.

Results: In the pooled studies, mirabegron 50 mg demonstrated superiority *versus* placebo (treatment difference: -0.37 [95% confidence interval (CI): -0.74, -0.01]) for reducing

Correspondence to:

Andrea Tubaro

Department of Urology,
Sant'Andrea Hospital,
'Sapienza' University, Via
di Grottarossa 1035–1039,
00189 Rome, Italy
andrea.tubaro@mac.com

José E. Batista

Urodynamics Unit, URD/
Hospital Quiron Teknon,
Barcelona, Spain

Victor W. Nitti

Department of Urology,
NYU Langone Medical
Center, New York, NY, USA

Sender Herschorn

Department of Surgery/
Urology, University of
Toronto, Toronto, ON.

OAB and BOO

- Men with LUTS also have OAB symptoms
- Benefit of adding an anticholinergic to an alpha blocker in the treatment of patients with symptomatic BOO from BPH

Antimuscarinics add-on in males

- Tolterodine
- Oxybutynin ER
- Propiverine
- Solifenacin
- Fesoterodine

- **Mainly 12-week trials with alpha-blockers**
- **Significant improvement in storage symptoms**
- **Non-significant improvement in many outcome measures**
- **Low risk of retention**

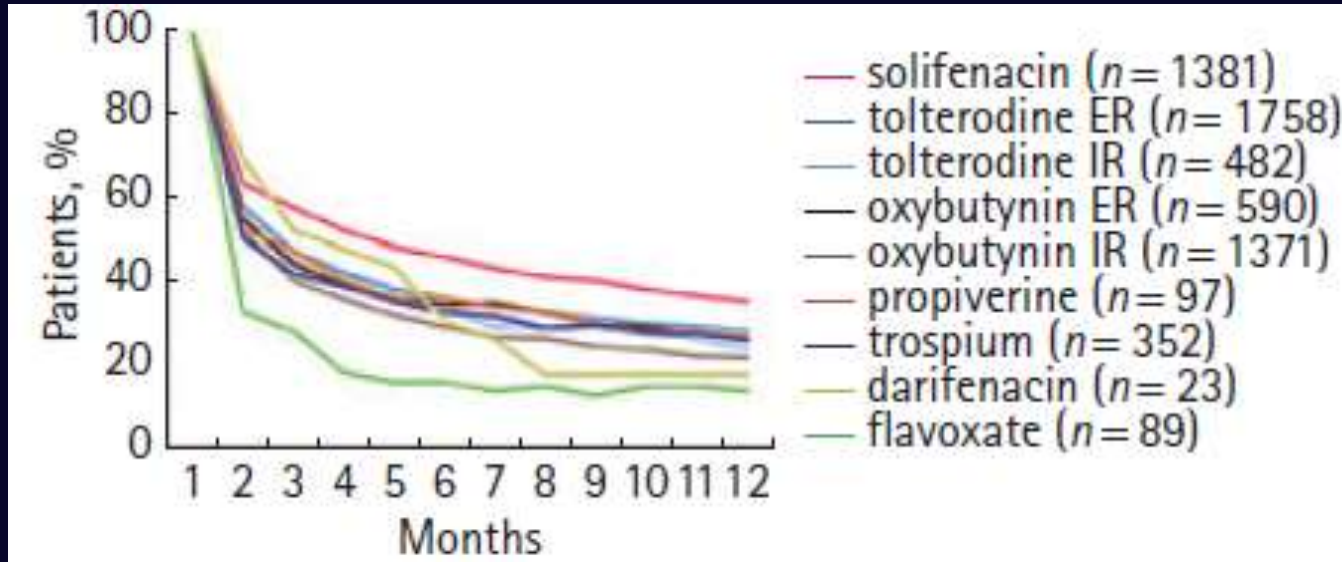
Add-on mirabegron to alpha blocker – PLUS study

- 676 men with persistent OAB symptoms despite treatment with tamsulosin
- RCT: 380 randomized to add-on mirabegron vs. placebo
- At 12 weeks, treatment group had:
 - Improvement in frequency, urgency episodes per day, mean voided volume per micturition, and total urgency frequency score ($p < 0.05$)
 - AEs: patients requiring catheterization: 2 vs. 0, both continued in study

OAB treatment rates

- 7,244,501 patients ≥ 45 y with OAB in IMS Health data set
 - 24.4% treated; 75.6% untreated
 - Only 25.6% of those treated were men
 - Increasing diagnosis and treatment with increasing age
 - Consistently fewer men treated than women ($p < 0.001$)

Levels of Treatment Persistence Over 12 Month With Antimuscarinic Treatment



- Data were extracted from the medical records of >1,200,000 registered patients via general practice software, and anonymized prescription data were collated for all eligible patients with documented OAB ($n = 4833$).
- **After 12 months <35% of patients were still on antimuscarinic treatment**

Persistence and adherence of mirabegron vs. antimuscarinics in Canada

- 19,485 pts. (74% female, 92% naïve, 20% ≥65y)

Median number of days on drug	Experienced	Naïve
Mirabegron	299	196
AMs	96-242	70-100
Persistence at 12 months		
Mirabegron	39%	30%
AMs	14-35%	14-21%

- Patients remained on mirabegron longer and had greater persistence and adherence rates

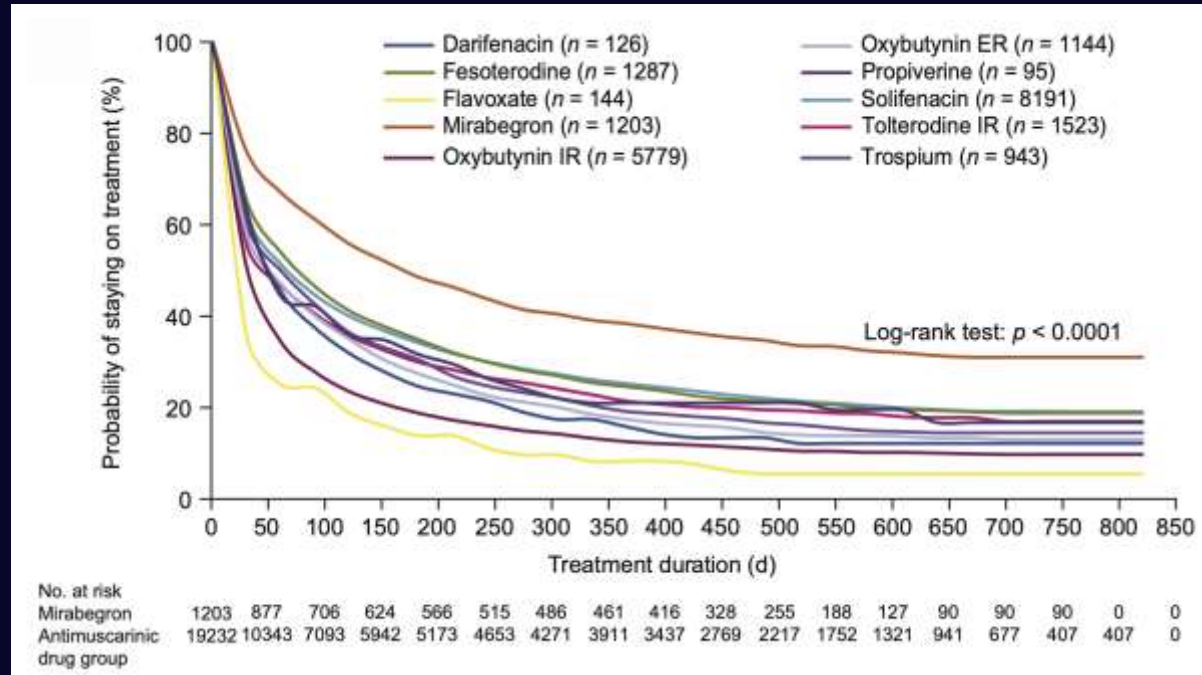
Systematic review adherence and persistence: AMs vs. mirabegron

- 30 studies with electronic claims databases
- Overall persistence 5% to 47% and 1-year adherence 15% to 44%

	AMs	Mirabegron
1-year persistence	12-25%	32-38%
Median time to discontinuation	<5 months (1 study 6.5 months)	5.6-7.4 months
Medication possession ratio mean (median)	0.41-0.53 (0.19-0.49)	0.59 (0.65)
Mean proportion of days covered	0.55	0.66

- Mirabegron had better characteristics

Mirabegron vs. AMs 12-mo persistence

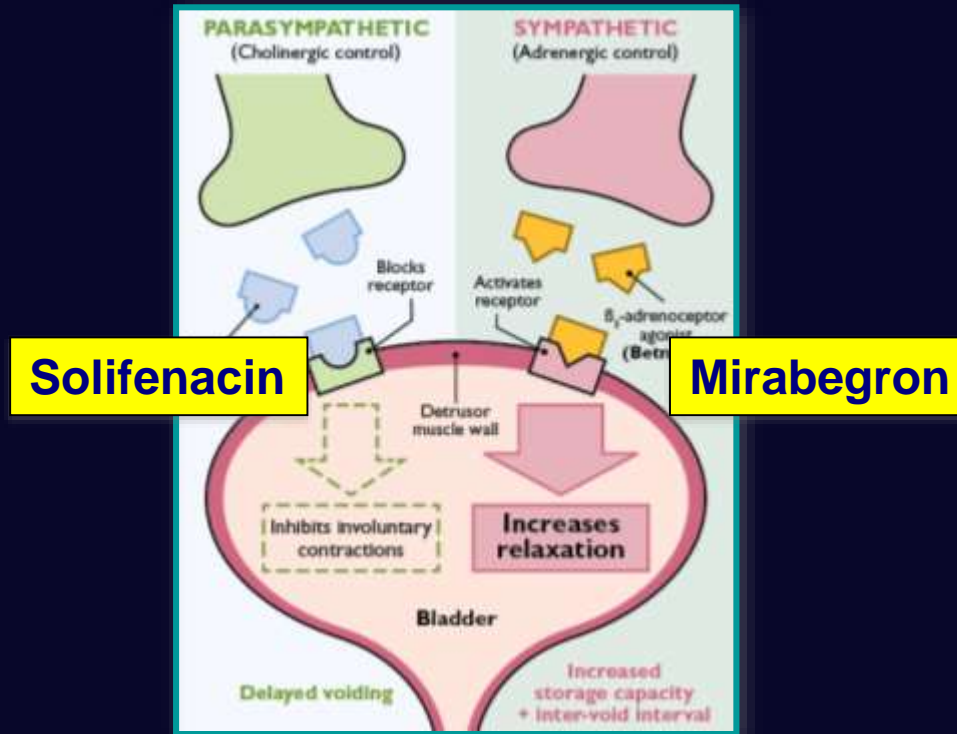


- 21,966 patients in UK prescription database
- Persistence and adherence statistically better than other AMs

Antimuscarinics and beta-3 agonists in OAB

- Mode of Action

Mode of action of OAB treatments



Combination

EUROPEAN UROLOGY 70 (2016) 136–145

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



European Association of Urology



Platinum Priority – Voiding Dysfunction

Editorial by Barbara Padilla-Fernández and David Castro-Díaz on pp. 146–147 of this issue

Efficacy and Safety of Mirabegron Add-on Therapy to Solifenacin in Incontinent Overactive Bladder Patients with an Inadequate Response to Initial 4-Week Solifenacin Monotherapy: A Randomised Double-blind Multicentre Phase 3B Study (BESIDE)

Marcus J. Drake^{a,}, Christopher Chapple^b, Ahmet A. Esen^c, Stavros Athanasiou^d, Javier Cambroneró^e, David Mitcheson^f, Sender Herschorn^g, Tahir Saleem^h, Moses Huang^h, Emad Siddiqui^h, Matthias Stölzelⁱ, Claire Herholdt^h, Scott MacDiarmid^j, on behalf of the BESIDE study investigators*

Combination

BJUI
BJU International



BJUI
BJU International

Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study)

Sender Herschorn*, Christopher R. Chapple[†], Paul Abrams[‡], Salvador Arlandis[§], David Mitcheson[¶], Kyu-Sung Lee^{**}, Arwin Ridder^{††}, Matthias Stoelzel^{††}, Asha Paireddy^{††}, Rob van Maanen^{††} and Dudley Robinson^{††}

Department of Surgery/Urology, University of Toronto, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [†]Department of Urology, Royal Hallamshire Hospital, Sheffield, UK, [‡]Bristol Urological Institute, Southmead Hospital, Bristol, UK, [§]Hospital Universitario La Fé, Valencia, Spain, [¶]St. Elizabeth's Medical Center, Brighton, MA, USA, ^{}Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, ^{††}Astellas Pharma Global Development, Leiden, The Netherlands, and ^{††}Kings College Hospital, London, UK*

Long-term combination treatment with solifenacin and mirabegron in patients with overactive bladder (SYNERGY II)



- All treatments were generally well tolerated over the 12-month study period
 - Slightly increased frequency of overall TEAEs in the combination group
 - Most common TEAEs were dry mouth (combination and solifenacin) and nasopharyngitis (mirabegron)
- Clear and clinically relevant improvements in efficacy with combination compared with each monotherapy, both in terms of
 - Primary variables: mean number of incontinence episodes/24 h and micturitions/24 h
 - Secondary variables: MVV per micturition, OAB-q Symptom Bother scores, TS-VAS score

Combination drugs for OAB

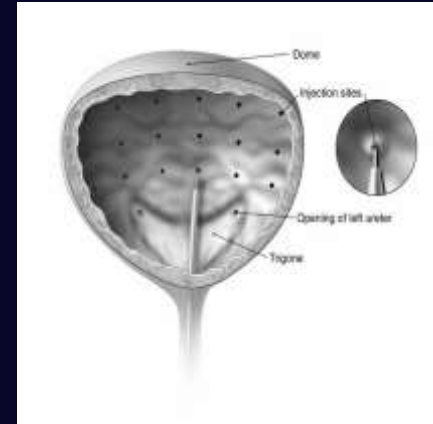
- **Second-Line Treatments: Pharmacologic Management**
- New Statement 12.
 - Clinicians may consider combination therapy with an anti-muscarinic and β 3 adrenoceptor agonist for patients refractory to monotherapy with either anti-muscarinics or β 3-adrenoceptor agonists. Option (*Evidence Strength Grade B*)

Refractory OAB

- Patients who are refractory to behavioral and pharmacologic therapy should be evaluated by an appropriate specialist if they desire additional therapy. ***Expert Opinion***

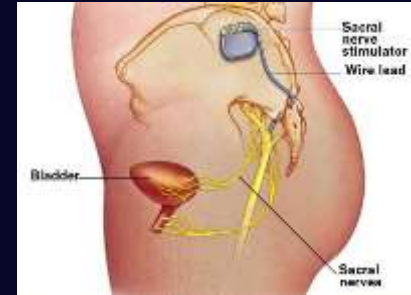
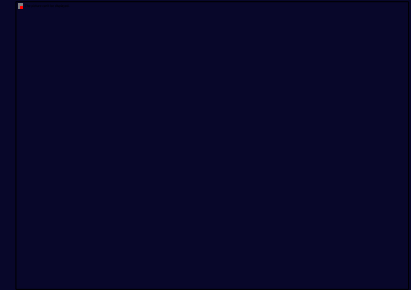
Third-line treatments (AUA)

- Intradetrusor onabotulinumtoxinA (100U) in the carefully-selected and thoroughly-counseled patient who has been refractory to first- and second-line OAB treatments.
- The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. **Standard Option (Evidence Strength Grade B C)**



Other third-line treatments

- Peripheral tibial nerve stimulation **(C)**
- Sacral neuromodulation **(C)**
- CUA assigned **level B** evidence.



Gormley EA, et al. J Urol. 2015;193:1572-80
Corcos et al. CUAJ, 2017; 11(5):E142-73
[https://www.auanet.org/guidelines/overactive-bladder-\(oab\)-guideline#x2938](https://www.auanet.org/guidelines/overactive-bladder-(oab)-guideline#x2938) - 2019

Additional treatments

- Indwelling catheterization, augmentation cystoplasty, or other urinary diversions are rare long-term management strategies for OAB and should only be considered after all other medical and surgical options have been exhausted and only after careful consideration of the likely benefits and risks.
(Evidence strength Grade D)

OAB treatment in the elderly

Elderly concerns

- Anticholinergic burden - polypharmacy
 - Xerostomia (dry mouth)
 - Constipation
 - Cognition

Drugs with strong ACh properties

- Antihistamines
- Antidepressants
- Antimuscarinics
- Antiparkinsonian
- Antipsychotics
- Skeletal muscle relaxants
- Antiarrhythmics
- Antiemetics

>50 drugs

ACh drugs and dementia – Case-control study

- 40,770 patients with a new diagnosis of dementia (2006-2015) and 283,933 controls without dementia
- Daily ACh drugs 4-20 years before diagnosis
- 14,553 (35%) cases and 86,403 (30%) controls given ≥ 1 drug with ACB of 3 (definite ACh activity)
 - Dementia was associated with increasing ACB score.
 - GI drugs with ACB 3 and Cardiovascular drugs with ACB of 1 NOT linked to dementia.
 - Risk increased with greater exposure to anti-depressant, urological (oxybutynin/tolterodine), and anti-Parkinsonian drugs with ACB of 3

OAB treatment in elderly

- **Trospium¹**
 - Hydrophilicity and quaternary amine structure may limit BBB penetration
- **Transdermal oxybutynin¹**
 - Avoids first pass metabolism through liver and decrease AM AEs
- **Fesoterodine**
 - RCTs in aged and vulnerable elderly²; pooled analysis³
- **Darifenacin¹**
 - M3 specific and weak affinity for brain M1 receptors
- **Solifenacin**
 - Observational study⁴
- **Mirabegron⁵**

1. McFerren and Gomelsky, Drugs Aging 2015; 32:809-19

2. Dubeau et al. J Urol 2014; 191:395-404

3. Wagg, Arumi, Herschorn et al. Age Ageing, 2017; 46:620-6

4. Hampel et al. Urol Int; 2017; 98:350-7

5. Wagg, et al. European Urology, 2019 <https://doi.org/10.1016/j.eururo.2019.10.002>

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



- 888 patients ≥ 65 , 12-week RCT mirabegron vs. placebo
- Sig. improvement in frequency, incontinence, voided volume, urgency, UUI episodes vs. placebo
- No impact on MoCA

Efficacy, safety, and tolerability of mirabegron in patients aged ≥ 65 yr with overactive bladder wet: a phase IV, double-blind, randomised, placebo-controlled study (PILLAR)

Adrian Wagg^{a,}, David Staskin^b, Eli Engel^c, Sender Herschorn^d, Rita M. Kristy^e, Carol R. Schermer^e*

^a Geriatric Medicine, University of Alberta, Edmonton, Alberta, Canada; ^b Division of Urology, St Elizabeth's Medical Center, Boston, MA, USA; ^c Bayview Research Group, LLC, Valley Village, CA, USA; ^d Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; ^e Astellas Pharma Global Development, Inc., Northbrook, IL, USA

Adherence and its impact on costs and absenteeism

- 2001-2011 claims database of 27 large US employers
- 1.5 million employees; 2960 prescribed OAB drugs
- 380 (12.8%) $\geq 80\%$ adherent; 2580 (87.2%) $< 80\%$ adherent
- Lower adherence – increased copay and copay as a percentage of salary
- High adherence – lower medical, sick leave, and short-term disability costs, and higher drug costs

Drug persistence affects PROs

- 952 OAB pts. who started antimuscarinics in prospective observational study
- All pts. paid drug and prescription costs
- Drug persistence and compliance at 4, 12, 24 weeks
- At 24 weeks 56.8% on drug
- Persistent pts. had sig. higher OABSS and OABq short form than non-persistent.
 - Older age and OAB dry

Follow-up

- The clinician should offer follow up with the patient to assess compliance, efficacy, side effects and possible alternative treatments.

Expert Opinion

Conclusions

- Bothering OAB is common in men and women and increases with age.
- Diagnosis is straightforward
- Treatment approach involves patient education, behavioural therapy and medications.
- More than one therapeutic trial may be necessary and may involve different medications.
- Third-line therapy available for refractory patients
- Long-term follow-up required.
- Successful treatment is beneficial