FACULTY AND DISCLOSURE

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ACTIVITY DESCRIPTION

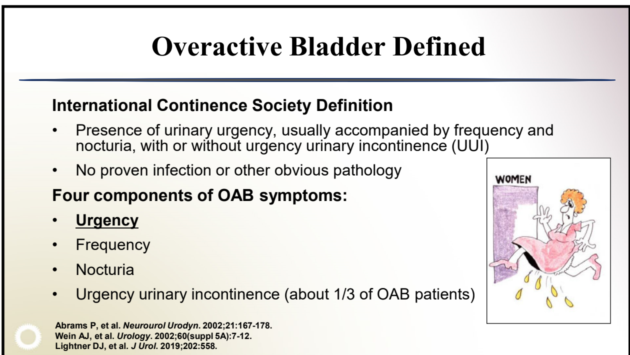
Target Audience

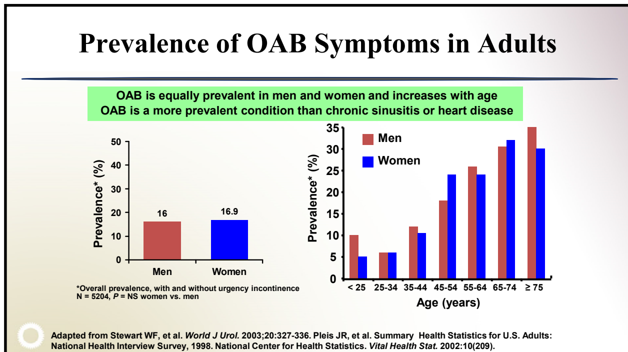
This educational initiative is designed as a comprehensive approach to address the practice needs of primary care providers, including primary care physicians, osteopathic physicians, physician assistants, nurse practitioners, and allied healthcare professionals, who are at the forefront of caring for adult patients who may be suffering from OAB.

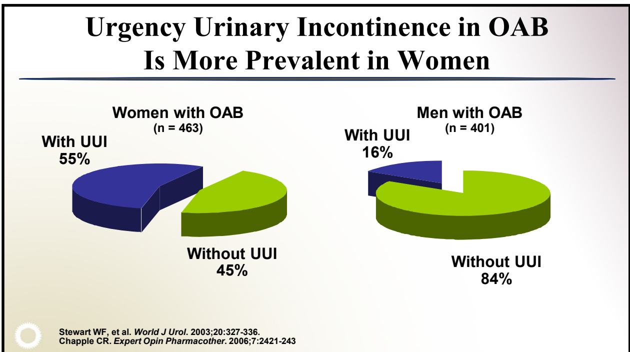
Learning Objectives

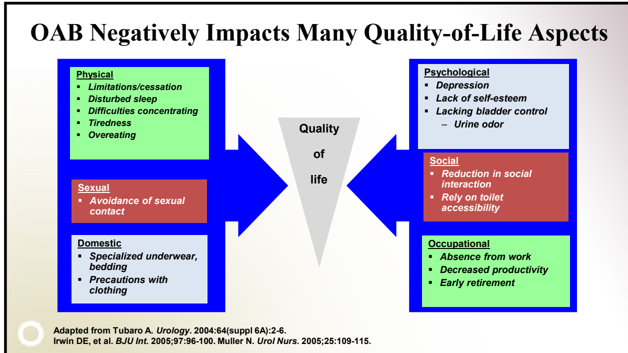
Upon completing this activity, participants will be able to:

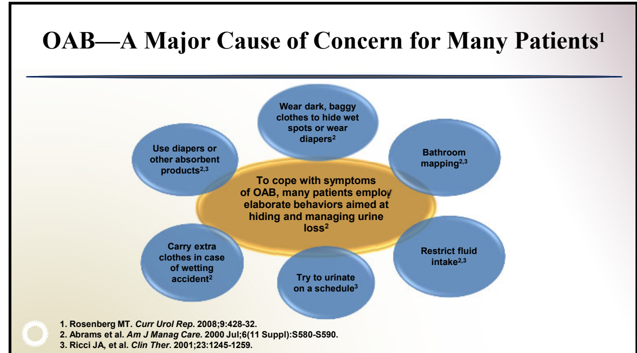
- Proactively screen and evaluate at-risk individuals for overactive bladder (OAB)
- Utilize communication strategies aimed to evaluate the impact of OAB on quality of life and educate patients on appropriate treatment options and expectations
- Identify patients with OAB who would benefit from combination therapy to maximize efficacy and tolerability











Key Populations: Patients With Diabetes and Obesity

- Survey of 1359 patients with T2DM who were screened at a dedicated diabetes center[1]
  - 22.5% had OAB
  - 48.0% of those with OAB had incontinence
- Overweight and obese women with T2DM: high prevalence of UI
  - Higher than other complications commonly associated with diabetes (retinopathy, 7.5%; microalbuminuria, 2.2%; neuropathy, 1.5%)[2]
- Important implications for screening for bladder dysfunction

T2DM, type 2 diabetes mellitus.

1. Liu RT, et al. *Urology.* 2011;78:1040-1045.
2. Phelan S, et al; Action for Health in Diabetes Research Group. *Diabetes Care.* 2009;32:1391-1397.

Effective Questioning to Detect OAB

The first complaint may not be the chief complaint

- What brings you here today? What are your concerns?
- What is your most distressing symptom?
- How are you handling your urinary symptoms?
  - What do you mean you urinate frequently?
  - How long have you experienced these symptoms?
- What have you tried to solve your problems?
- When asking these questions:
  - **Respect the patient's situation**
  - **Consider a treatment plan**
  - **Aim for patient-centered medicine**

Marschall-Kehrel D, et al. *Urology.* 2006;68(suppl 2A):29-37.

Useful Questions to Direct the Diagnosis of OAB

Question	
Do you have to rush to go to the toilet? Do you do this because of a sudden intense feeling so you have to urinate IMMEDIATELY?	Urgency
Do you feel that you urinate too often during the day?	Frequency
Do you have to get up during the night to urinate? Does the urge to urinate wake you?	Nocturia
When you feel the urge to go to the bathroom, do you have leaks or wetting accidents?	Urgency urinary incontinence

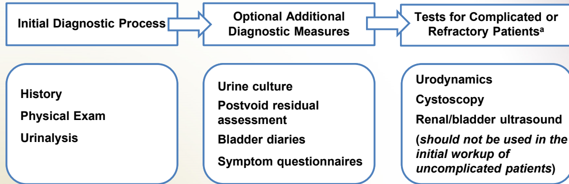
Rosenberg MT, et al. *Cleve Clin J Med.* 2005;72:149-156.
Irwin DE, et al. *Eur Urol.* 2006;50:1306-1315.

Preparing for a "Doorknob Moment"

- Turn the moment into a platform for next steps. Schedule a follow-up appointment for further discussion before your patient leaves the office.
  - "A topic this important needs a separate visit to explore this in detail"
- Give "homework."
  - OAB Self-assessment
  - Bladder diary
  - Ask your patient to fill out an OAB self-assessment tool.

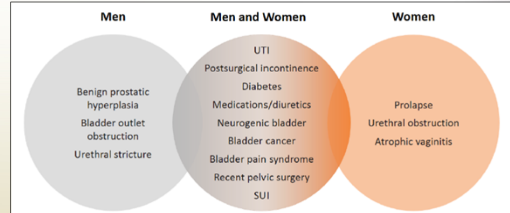
Urology Care Foundation. https://www.urologyhealth.org/educational-resources/overactive-bladder-assessment-tool.

AUA/SUFU OAB Guidelines: Diagnostic Workup



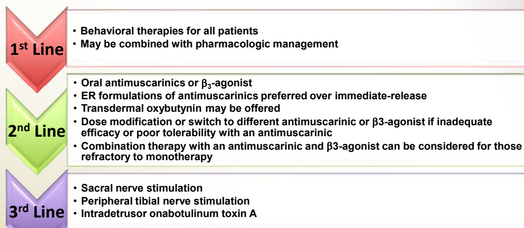
[a]Patients who failed multiple treatments
Lightner DJ, et al. *J Urol.* 2019;202:558.

Differential Diagnosis of OAB



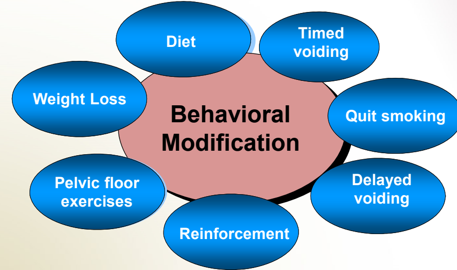
OAB, overactive bladder; SUI, stress urinary incontinence; UTI, urinary tract infection
Gormley EA, et al. *J Urol.* 2015;193:1572-80.

AUA/SUFU OAB Treatment Guidelines

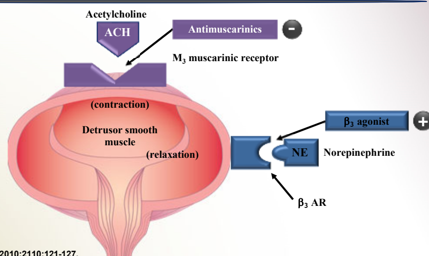


Lightner DJ, et al. *J Urol.* 2019;202:558.

Behavioral Modification



OAB Pharmacotherapy: Different Receptor Pathways



Takeda M, et al. *J Pharmacol Sci.* 2010;2110:121-127.
Fowler CJ, et al. Nat Rev Neurosci. 2008;8:453-466.

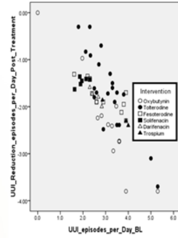
Antimuscarinics Used in OAB Treatment

Immediate Release		
Drug	**Dose**	**Dosing**
Oxybutynin IR	5 mg	2–4 times per day
Tolterodine IR	1–2 mg	Twice per day
Trospium chloride	20 mg	Twice per day
Extended Release		
Darifenacin	7.5 mg, 15 mg	Daily
Fesoterodine	4 mg, 8 mg	Daily
Oxybutynin ER	5–30 mg	Daily
Oxybutynin TDS	3.9 mg	Twice per week
Oxybutynin 10% gel	100 mg	Daily
Solifenacin	5 mg, 10 mg	Daily
Tolterodine ER	2, 4 mg	Daily
Trospium chloride XR	60 mg	Daily

Physicians' Desk Reference. www.pdr.net.

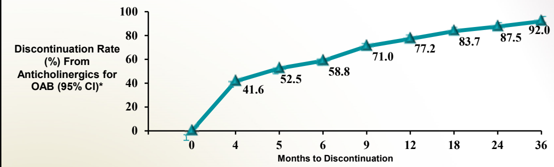
Antimuscarinics – Leader of the Pack?

- Review of randomized trials revealed no compelling evidence for differential efficacy across medications
- The choice of medication for a particular patient depends on the patient's history of:
  – Prior antimuscarinic use
  – Adverse events impact on the patient
  – Patient preferences
  – Comorbidities
  – Use of other medications
  – Availability of and resources to acquire specific medications



Lightner DJ, et al. *J Urol.* 2019;202:558.

High Discontinuation Rate with Antimuscarinics



- 3 out of 4 episodes of OAB drug treatment were discontinued by first year of treatment
- ~60% of OAB treatment episodes were discontinued at 6 months, 77% by 1 year, and 92% by 3 years
- **Study Design:** UK study. Overall drug discontinuation for all women prescribed anticholinergic medications (N=29,369). Unadjusted cumulative incidence of discontinuation (95% CI).

*Cumulative incidence of discontinuation was determined using the Kaplan-Meier method.
Gopal M, et al. *Obstet Gynecol.* 2008;112:1311-1318.

Antimuscarinic Side Effects

- Mad as a hatter: CNS, delirium
- Red as a beet: Direct vasodilation
- Blind as a bat: Cycloplegia
- Hot as a hare: Thermoregulation
- Dry as a bone: ↓ Sweat & secretions

Cognitive Impairment and Antimuscarinic Use

Bladder ACHs in Study	Journal	Authors	Conclusions	N
Oxybutynin, Fesoterodine, Tolterodine, Trospium, Solifenacin, Darifenacin	*BJU International*	Welk McArthur	ACH medications significantly increased risk of dementia	47,324
Oxybutynin, Fesoterodine, Tolterodine, Trospium, Solifenacin, Darifenacin, Favoxate	*JAMA Internal*	Coupland	Strong ACHs associated with increased risk of dementia	284,343
Oxybutynin, Trospium, Tolterodine, Favoxate, Solifenacin, Propiverine	*BMC Geriatrics*	Wang	Higher cumulative ACH exposure is associated with increase in risk of dementia	16,412
Oxybutynin, Tolterodine	*BMJ*	Richardson	ACH drugs are linked to future dementia persisting up to 20 years after exposure	40,770
Darifenacin, Tolterodine, Oxybutynin, Trospium, Solifenacin	*JAMA Neurology*	Risacher	ACH medication associated with increased brain atrophy and clinical decline; should be discouraged among older adults	402
Oxybutynin, Fesoterodine, Tolterodine, Trospium, Solifenacin, Darifenacin, Favoxate	*JAMA Internal*	Gray	Dementia and Alzheimer's were associated with 10-year cumulative dose of ACHs	3,434

Welk B, McArthur E. *BJU Int.* 2020;126:183-190.
Wang Y-C, et al. *BMC Geriatr.* 2019;19:380.
Risacher SL, et al. *JAMA Neurol.* 2016;73:721-32.
Coupland CAC, et al. *JAMA Intern Med.* 2019;179:1084-93.
Richardson K, et al. *BMJ.* 2018;361:k1315.
Gray SL, et al. *JAMA Intern Med.* 2015;175:401-7.

Adjusting OAB Therapy: Excess Adverse Effects

- AUA Guidelines - manage constipation and dry mouth before abandoning effective therapy
- May include
  − Bowel management
  − Fluid management
  − Decrease dose
  − Change medication
    - Within class
    - Other class
- Refer to specialist

Gormley EA, et al. *J Urol.* 2012;188(6 Suppl):2455-2463.
Lightner DJ, et al. *J Urol.* 2019;202:558.

β3-Adrenergic Agonists for OAB Treatment

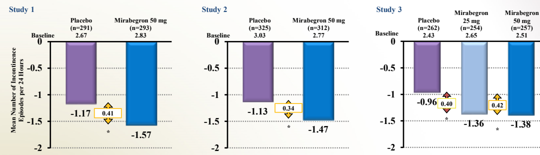
Mirabegron
- First FDA-approved β3-adrenergic agonists to treat:
  – Overactive bladder in adult patients with symptoms of urge urinary incontinence, urgency, and urinary frequency, either alone or in combination with the muscarinic antagonist solifenacin succinate
- Selective β3-agonist relaxes detrusor muscle and increases bladder capacity
  – Avoids activation of β1 and β2-adrenergic agonist receptor (no adverse effects such as increased heart rate and muscle tremors)
  – Also approved to treat neurogenic detrusor overactivity in pediatric patients (≥3 years)
- Available in 2 extended-release doses (25 and 50 mg)

Vibegron
- Newly FDA-approved β3-agonist approved for:
  – The treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults
- Available in one dose (75 mg)

Myrbetriq™ (mirabegron) prescribing information, Astellas Pharma US, Inc. April 2021.
Gemtesa® (vibegron) prescribing information, Urovant Sciences, Inc., Irvine, CA. December 2020.

Mirabegron Reduces the Mean Number of Incontinence Episodes per 24 Hours

Adjusted Mean Change From Baseline to Final Visit (12 weeks)



For incontinence episodes per 24 hours, the analysis population is restricted to patients with at least 1 episode of incontinence at baseline.
*Statistically significant improvement vs placebo at the 0.05 level with multiplicity adjustments.

Myrbetriq™ (mirabegron) prescribing information, Astellas Pharma US, Inc. April 2021.

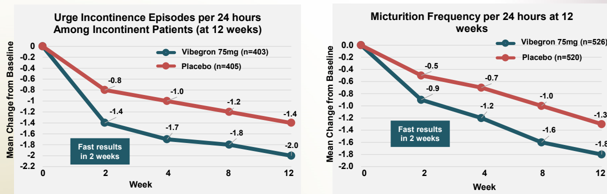
Mirabegron Long-term Safety Data: 52-week Active-Controlled Trial

Percent of Patients With Adverse Reactions, Derived From All Adverse Events, Reported by >2% of Patients Treated With Mirabegron 50 mg Once Daily

	Mirabegron 50 mg (%)	Tolterodine ER 4 mg (%)
No. of patients	812	812
Hypertension	9.2	9.6
Urinary tract infection	5.9	6.4
Headache	4.1	2.5
Nasopharyngitis	3.9	3.1
Back pain	2.8	1.6
Constipation	2.8	2.7
Dry mouth	2.8	8.6
Dizziness	2.7	2.6
Sinusitis	2.7	1.5
Influenza	2.6	3.4
Arthralgia	2.1	2.0
Cystitis	2.1	2.3

Myrbetriq® (mirabegron extended-release tablets) prescribing information, Astellas Pharma US, Inc., April 2021.
Chapple CR, et al. *Eur Urol.* 2013;63:296-305.

Vibegron Reduces Urge Incontinence Episodes and Micturition Frequency Over 12 Weeks



Staskin D, et al. *J Urol.* 2020;204:316-324.

Vibegron Safety Profile: 12-Week Data

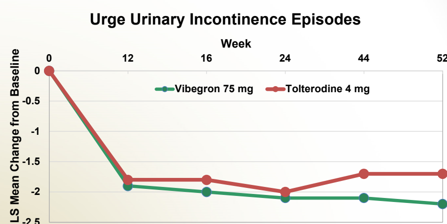
Adverse events reported ≥2.0% of patients taking vibegron 75 mg for up to 12 weeks

	Vibegron 75 mg n (%)	Tolterodine 4 mg n (%)
Number of patients	545	540
Headache	22 (4.0)	13 (2.4)
Nasopharyngitis	15 (2.8)	9 (1.7)
Diarrhea	12 (2.2)	6 (1.1)
Nausea	12 (2.2)	6 (1.1)
Upper respiratory tract infection	11 (2.0)	4 (0.7)

Gemtesa® (vibegron) prescribing information, Urovant Sciences, Inc., Irvine, CA. December 2020.

Vibegron Efficacy is Durable Over 52 Weeks (EMPOWUR)

Urge Urinary Incontinence Episodes



Staskin D, et al. *J Urol.* 2021;205:1421-29.

Vibegron Safety Profile: 52-Week Data from EMPOWUR Trial

	Vibegron 75 mg n (%)	Placebo n (%)
Number of patients	273	232
Hypertension	24 (8.8)	20 (8.6)
UTI	18 (6.6)	17 (7.3)
Headache	15 (5.5)	9 (3.9)
Diarrhea	13 (4.8)	4 (1.7)
Nasopharyngitis	13 (4.8)	12 (5.2)
Constipation	10 (3.7)	6 (2.6)
Nausea	10 (3.7)	7 (3.0)
Upper RTI	10 (3.7)	1 (0.4)
Dry mouth	5 (1.8)	12 (5.2)

AEs with frequency >3% in either treatment group

Staskin D, et al. *J Urol.* 2021;205:1421-29.

β3-Agonists and Hypertension

Results from 52-week phase III placebo-controlled study[1]

	Vibegron (n=273) n (%)	Placebo (n=232) n (%)
Hypertension	24 (8.8)	20 (8.6)

Results from 52-week double-blind, active-controlled study[2]

	Mirabegron 50 mg (n=812)	Tolterodine ER 4 mg (n=812)
Hypertension	9.2%	9.6%

1. Staskin D, et al. *J Urol.* 2021;205:1421-29.
2. Myrbetriq® (mirabegron extended-release tablets) Prescribing Information. Astellas Pharma US, Inc., Northbrook, IL. April 2021.

Patient Case

- 55-year-old woman with long history of type 2 diabetes mellitus
- BMI = 32 kg/m^2
- At today's visit, she complains of urgency urinary incontinence
  - Has experienced incontinence episodes for over 2 years but has been reluctant to talk about it
  - Cannot sit through a two-hour movie
  - Experiences 2–3 daily incontinence episodes
    - Uses diapers when going out
    - Restricts travel and fluid intake
    - Experiences anxiety in unfamiliar settings (must be aware of nearest bathroom)

Patient Case: Discussion Points

In addition to behavioral therapy, which of the following would you recommend?

- Antimuscarinic
- β3-agonist
- Combination therapy
- None of the above

Patient Case: Discussion Points

How would your treatment selection change if the patient:

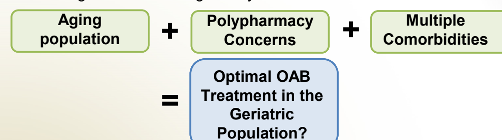
- Was a 77-year-old female with OAB?
- Was a 59-year-old man with BPH?
- Partially benefited from previous antimuscarinic monotherapy?

Tailoring OAB Therapy: Utilizing a Treat-to-Target Approach

- Communicate with patients to set and manage treatment expectations
- Monitor regularly for efficacy and tolerability
- Adjust therapy when needed
  - Dosage, add-on, combination
- Manage adverse effects
- Consider patient factors (age, comorbidities, etc.)

Considerations When Treating OAB in the Elderly

- OAB prevalence of ~30% among those 65 years and older (compared to ~16% in general adult population)
  - As high as 50% among elderly in LTCF

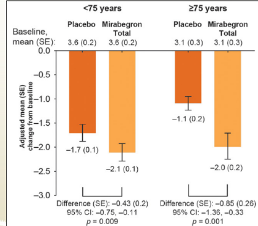


- Because of the potential risk for dementia with prolonged use of anticholinergics, caution should be used in patients over 65 years.

Rutman MP, et al. *Clin Drug Invest.* 2021;41:293-302.
MacDiarmid SA. *Rev Urol.* 2008;10:6-13.

Mirabegron Significantly Reduces the Number of Incontinence Episodes in the Elderly (PILLAR)

No. incontinence episodes/24 hours



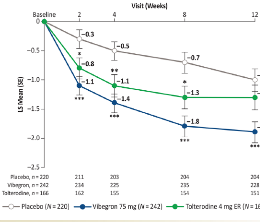
- Compared mirabegron vs. placebo among elderly OAB patients (≥65 years of age)
- Patients treated with mirabegron had a statistically significant:
  - Reduction in mean incontinence episodes per 24 hr
  - Reduction in micturitions per 24 hr
  - Improved mean volume per micturition

There were no changes in mental status over 12 weeks with mirabegron

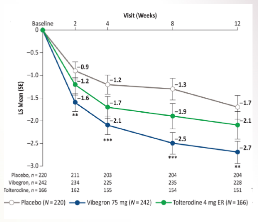
Wagg A, et al. *Eur Urol.* 2020;77:211-220.

Vibegron Improves OAB Symptoms Compared to Tolterodine in Adults ≥65 Years (EMPOWUR)

Avg. Daily Number of Micturitions



Avg. Daily Urgency Episodes

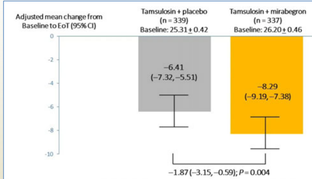


Varano S, et al. *Drugs Aging.* 2021;38;137-146.

*P<0.05; **P<0.01; ***P<0.001 vs. placebo

Mirabegron Add-On Therapy Improves OAB Symptoms in Men Receiving Tamsulosin for BPH (PLUS)

Mean Change in TUFS
(Total Urgency and Frequency Score)



- Compared mirabegron vs placebo in men taking tamsulosin for underlying BPH
- Mirabegron add-on resulted in significant improvement in:
  - Mean number of micturitions per day
  - Mean volume voided per micturition
  - Urgency episodes per day
  - Total urgency and frequency score (TUFS)

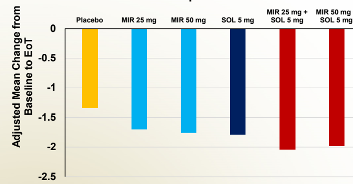
Kaplan SA, et al. *J Urol.* 2020;203:1163-71.

Adjusting Pharmacologic Therapy for OAB: Balancing Efficacy and Tolerability

- Consider the goals of the individual
- Balance efficacy and tolerability
  - Start with the lowest dose
  - Monitor medication adherence, lifestyle and behavioral therapy
  - Titrate the dose if response to treatment not meeting patient's goals and adverse effects are safe and tolerable
  - Consider add-on/combination therapy if adequate response is not achieved with monotherapy
  - If possible, manage adverse effects before stopping an effective therapy

Mirabegron + Solifenacin Combination Improves Outcomes Over Monotherapy (SYNERGY)

No. of Incontinence Episodes at 12 Weeks

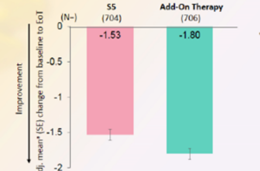


- A 12-week, 6-arm, randomized, double-blind trial comparing monotherapy with combination therapy in adults with wet OAB
- Combination therapy provided consistent improvement in efficacy compared to respective monotherapies across most outcome parameters including:
  - Urgency
  - Urinary incontinence episodes/24 h
- Combination therapy was well tolerated without any new safety concerns

Herschorn S, et al. *BJU Int.* 2017;120:562-75.

Mirabegron Add-on to Solifenacin Reduces Incontinence Episodes Compared to Solifenacin Monotherapy (BESIDE)

Change from baseline to EoT (week 12) in mean number of incontinence episodes/24 hour



- Assessed safety and efficacy of adding mirabegron 50 mg to low-dose solifenacin 5 mg in patients with inadequate response to solifenacin monotherapy
- Patients on maximum-dose solifenacin (10 mg) had higher rates of treatment-emergent adverse events vs. combination therapy
- Subgroup analysis in older adults found no difference in incontinence episodes with combination therapy vs. maximum-dosed solifenacin

Combination therapy reduces overall anticholinergic burden without losing effectiveness

Drake MJ, et al. *Eur Urol.* 2016;70:136-45.

Mirabegron Combination with Muscarinic Antagonist

- Indicated in combination with the muscarinic antagonist solifenacin succinate for treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency
- Combination regimen: Mirabegron 25 mg PO QD plus solifenacin succinate 5 mg PO QD
- May increase mirabegron dose to 50 mg PO QD after 4-8 weeks based on individual efficacy and tolerability

The Importance of the Primary Care Provider

- Vital member in the OAB management pathway
- Screen and identify, especially high-risk patients
- Efficiently diagnose OAB vs. other lower urinary tract disorders
- Effectively manage a number of OAB patients
- Knowing when to refer to a specialist
- Encourage, cheerlead, manage expectations

When to Consider Referral

- Hematuria
- Recurrent urinary tract infections
- Pelvic pain
- Pelvic organ prolapse
- Neurogenic bladder
- Partial and non-responders

Conclusions

- OAB is highly prevalent in men and women and substantially impacts quality of life
- Communicate with patients to set goals and manage expectations
- Focus on meeting reasonable expectations (e.g., <100% dryness may be reasonable)
- Utilize a treat-to-target approach that involves regular assessment and treatment adjustments