Faculty and Disclosure

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Diane K. Newman, DNP reported the following relevant financial relationships with ineligible companies:
Advisory Board: Urovant Sciences
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All relevant financial relationships have been mitigated.
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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:

- Utilize communication and diagnostic techniques for early detection and diagnosis of overactive bladder (OAB) among at-risk patients
- Review patient factors to consider when selecting between anticholinergics and beta-3 adrenoceptor agonists for OAB treatment
- Select appropriate OAB pharmacologic therapy based on efficacy data, safety profile, and patient factors and preferences

Overactive Bladder Defined

International Continence Society Definition

- Presence of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI)
- No proven infection or other obvious pathology

Four components of OAB symptoms:

- Urgency
- Frequency
- Nocturia
- Urgency urinary incontinence

Abrams P, et al. *Neurourol Urodyn.* 2002;21:167-178.
Wein AJ, et al. *Urology.* 2002;60(suppl 5A):7-12.
Lightner DJ, et al. *J Urol.* 2019;202:558.

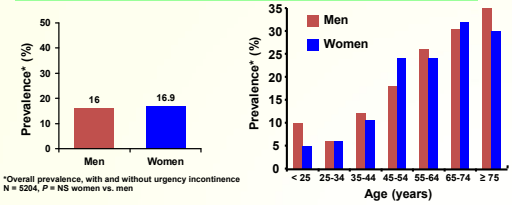
Current ICS Terminology for OAB

- **Urgency**
  - Sudden, difficult-to-defer, compelling desire to pass urine
  - Must differentiate from normal "urge" or desire to urinate that can be deferred with certain strategies
- **Urgency Urinary Incontinence**
  - Involuntary leakage accompanied, or immediately preceded, by urgency
- **Frequency/nocturia**
  - Subjective complaint he/she voids too often during the day (>8/day) or at night (≥1/night)

ICS, International Continence Society.
Abrams P. *Urology.* 2003;61:37-49.
Lightner DJ, et al. *J Urol.* 2019;202:558.

Prevalence of OAB Symptoms in Adults

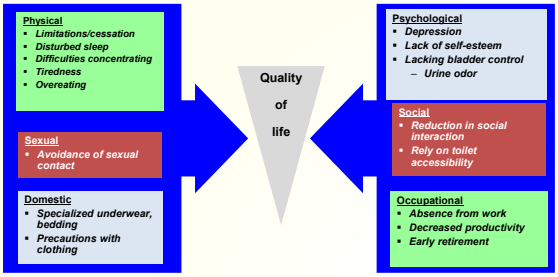
OAB is equally prevalent in men and women and increases with age
OAB is a more prevalent condition than chronic sinusitis or heart disease



*Overall prevalence, with and without urgency incontinence
N = 5204, *P* = NS women vs. men

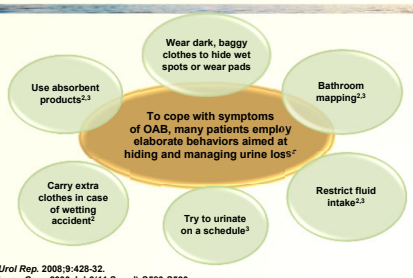
Adapted from Stewart WF, et al. *World J Urol.* 2003;20:327-336. Pleis JR, et al. Summary Health Statistics for U.S. Adults: National Health Interview Survey, 1998. National Center for Health Statistics. *Vital Health Stat.* 2002:10(209).

OAB Negatively Impacts Many Quality-of-Life Aspects



Adapted from Tubaro A. *Urology*. 2004:64(suppl 6A):2-6.
Irwin DE, et al. *BJU Int*. 2005;97:96-100. Muller N. *Urol Nurs*. 2005;25:109-115.

OAB—A Major Cause of Concern for Many Patients[1]



1. Rosenberg MT. *Curr Urol Rep*. 2008;9:428-32.
2. Abrams et al. *Am J Manag Care*. 2000 Jul;6(11 Suppl):S580-S590.
3. Ricci JA, et al. *Clin Ther*. 2001;23:1245-1259.

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 do you handle your urinary symptoms?
  - What do you mean you urinate frequently? How often are you urinating?
  - 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

Do you have to rush to go to the toilet? Do you do this because of an sudden intense need 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

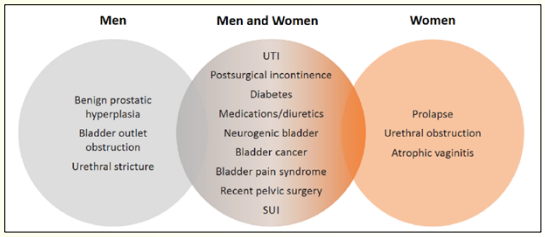
Rosenberg MT, et al. *Cleve Clin J Med*. 2005;72:149-156.
Irwin DE, et al. *Eur Urol*. 2006;50:1306-1315.

AUA/SUFU OAB Guidelines: Diagnostic Workup

Initial Diagnostic Process	Optional Additional Diagnostic Measures	Tests for Complicated or Refractory Patients[a]
History Physical Exam Urinalysis	Urine culture Postvoid residual assessment Bladder diaries Symptom questionnaires	Urodynamics Cystoscopy Renal/bladder ultrasound (*should not be used in the initial workup of uncomplicated patients*)

[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.

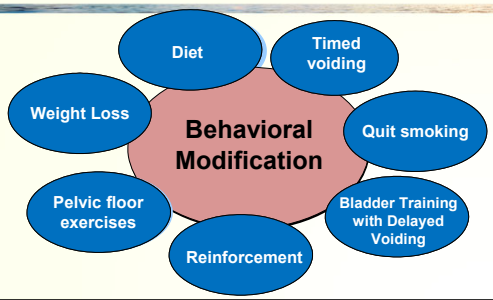
AUA/SUFU OAB Treatment Guidelines

1st Line

- Behavioral therapies for all patients
- May be combined with pharmacologic management

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

Behavioral Modification



Lifestyle Changes Affect OAB Symptoms

- **Alter fluid intake**
  - Reduce in patients with high fluid intake (>2400 mL/day)
    - May lessen episodes of incontinence and voiding frequency
  - Increase in patients with a low fluid intake (<1500 mL/day)
    - May improve urine concentration, lessening irritation of the bladder lining
- **Quit smoking**
  - Nicotine irritates detrusor muscle causing bladder contraction and urgency
  - Repeated coughing may cause urinary leakage
- **Modify diet**
  - Reduce caffeine
- **Reduce weight**
  - Lessen pressure on the bladder
- **Regulate bowel function**
  - Constipation and straining increase pressure on the bladder

Newman DK, et al. *Curr Opin Obstet Gynecol.* 2013;25:388-394.
Newman DK, Wein AJ. *Urol Clin North Am.* 2013;40:613-635.

Bladder Training

Established treatment for urgency incontinence since 1960s

- Goal is to improve bladder function
  - Improve urgency control
  - Prolong intervals between voiding
  - Increase bladder capacity
  - Reduce incontinent episodes
  - Eliminate bladder overactivity

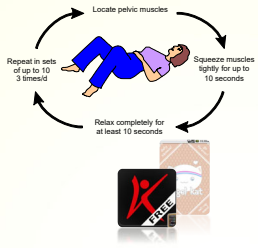
Bladder Training: Mechanism of Action

Effective for stress, urge, and mixed incontinence

- Hypotheses:
  - Improves brain's ability to inhibit bladder contractions through urgency suppression
  - Improves brain's facilitation over urethral closure during bladder filling
  - Improves central modulation of afferent sensory impulses
  - Increases individual awareness and changes behavior related to the circumstances that lead to bladder symptoms

Pelvic Floor Rehabilitation: Pelvic (Kegel) Muscle Exercises

- Exercises increase muscle tone/strength
- Supports urinary sphincter, preventing leakage
- Rapid, active pelvic muscle contractions ("quick flicks") inhibit unstable bladder contraction once it starts
- Recommended by ACP as first-line treatment for women with SUI and in combination with bladder training in women with mixed UI



ACP, American College of Physicians.
Newman DK, Sung VW, Borello-France D. *Neurourol Urodyn.* 2018; Jan 37(1);14-20.
Qaseem A, et al. *Ann Intern Med.* 2014;161:429-440.

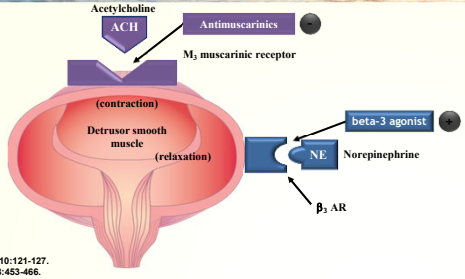
AUA/SUFU OAB Treatment Guidelines

1st Line
- Behavioral therapies for all patients
- May be combined with pharmacologic management

2nd Line
- Oral antimuscarinics or beta-3 agonist
- ER formulations of antimuscarinics preferred over immediate-release
- Transdermal oxybutynin may be offered
- Dose modification or switch to different antimuscarinic or beta-3 agonist if inadequate efficacy or poor tolerability with an antimuscarinic
- Combination therapy with an antimuscarinic and beta-3 agonist can be considered for those refractory to monotherapy

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

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.

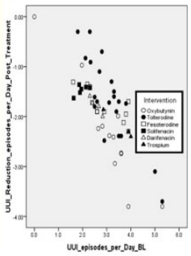
Antimuscarinics Used in OAB Treatment

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.**

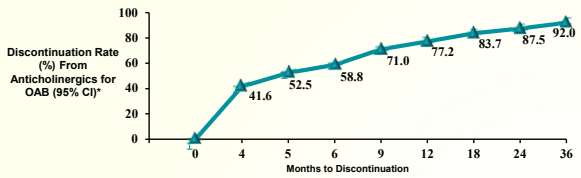
Antimuscarinics – Leader of the Pack?

- 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



AUA/SUFU. Available at: https://www.auanet.org/education/guidelines/overactive-bladder.cfm. Amended 2014.

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.

Minimizing Impact of Adverse Effects

- Majority of patients discontinue after a few weeks or months
- Side effects commonly cited as reason for discontinuation

Constipation
- Education
- Dietary fiber
- Fluid
- Psyllium-based fiber supplements

Dry mouth
- Oral lubricants
- Avoid EtOH-based mouthwash
- Small sips of water
- Sugar-free candies/gum

- Alternate antimuscarinics or dose reduction

Kelleher CJ, et al. *Br J Obstet Gynaecol*. 1997;104:988-93.
Benner JS, et al. *BJU Int*. 2010;105:1276-82.
D'Souza AO, et al. *J Manag Care Pharm*. 2008;14:291-301.

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.

Beta-3 Agonists for OAB Treatment

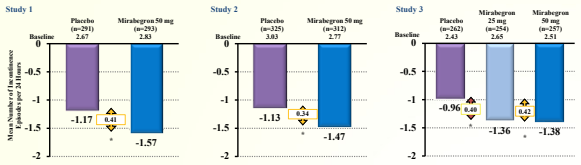
Mirabegron
- Indication: Overactive bladder in adult patients with symptoms of urge urinary incontinence, urgency, and urinary frequency, either alone or in combination with the muscarinic antagonist solifenacin succinate
- Available in 2 extended-release doses (25 mg and 50 mg)
  - If needed, titrate to higher dose after 4 to 8 weeks
- Not recommended with severe uncontrolled hypertension

Vibegron
- Indication: Overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults
- Available in one 75-mg dose (no titration required)
- Tablets are crushable (can be mixed with applesauce and taken with water)
- No clinically meaningful effects on blood pressure or heart rate*

Myrbetriq™ (mirabegron) prescribing information, Astellas Pharma US, Inc. April 2021.
Gemtesa® (vibegron) prescribing information, Urovant Sciences, Inc., Irvine, CA. December 2020.
*Weber MA, et al. *Blood Press Monit*. 2022;27:128-34.

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.

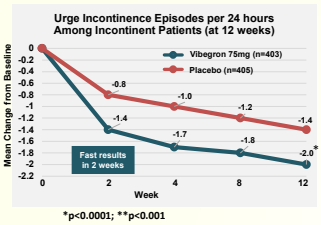
Mirabegron Long-term Safety Data: 52-week Active-Controlled Trial

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

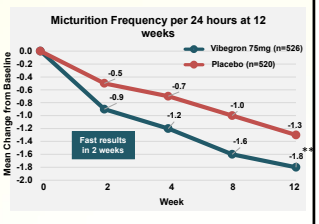
	Mirabegron 50 mg (%)	Tolterodine ER 4 mg (%)
No. of patients	812	812
Hypertension	9.2	9.6
Urinary tract infection	5.9	6.4
Headache	4.1	2.5
Nasopharyngitis	3.9	3.1
Back pain	2.8	1.6
Dry Mouth	**2.8**	**8.6**
Dizziness	2.7	2.6
Sinusitis	2.7	1.5
Influenza	2.6	3.4
Arthralgia	2.1	2.0
Cystitis	2.1	2.3

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



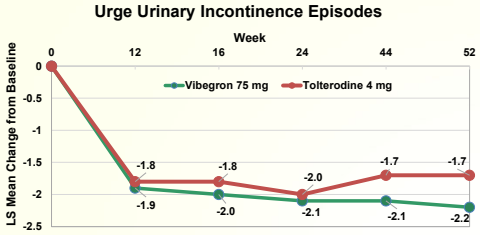
*p<0.0001; **p<0.001



Staskin D, et al. *J Urol.* 2020;204:316-324.
*Frankel J, et al. *Adv Ther.* 2022;39:959-70.

Significantly more patients taking vibegron reported **patient-perceived improvements** vs. placebo*

Vibegron Long-Term Efficacy: UUI Episodes Over 52 Weeks



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

Vibegron Long-Term Safety Data: 52-Week Active-Controlled

	Vibegron 75 mg n (%)	Tolterodine 4 mg 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.

Treating OAB: Consider Patient Factors

- 55-year-old woman with history of type 2 diabetes mellitus, hypertension
- 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 incontinence pads when going out
    - Restricts travel and fluid intake
    - Experiences anxiety in unfamiliar settings (must be aware of nearest bathroom)

Treating OAB: Consider Patient Factors (cont'd)

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

- Antimuscarinic
- Beta-3 agonist
- Combination therapy
- None of the above

Treating OAB: Consider Patient Factors (cont'd)

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

Aging population + **Polypharmacy Concerns** + **Multiple Comorbidities**

= **Optimal OAB Treatment in the Geriatric Population?**

- 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.

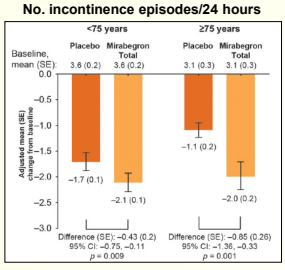
Drug-Drug Interactions with OAB Medications

- Primary drug-drug interactions are related to cytochrome P450 (CYP) 2D6
  - CYP2D6 is involved in metabolism of many commonly-used medications, including those for hypertension, depression, diabetes
  - Antimuscarinics: Primarily metabolized by CYP2D6
  - Mirabegron: Inhibitor of CYP2D6
  - Vibegron: No CYP2D6 interaction
- Digoxin: Monitor levels when used concomitantly with a beta-3 agonist

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

Mirabegron Significantly Reduces Incontinence Episodes in the Elderly

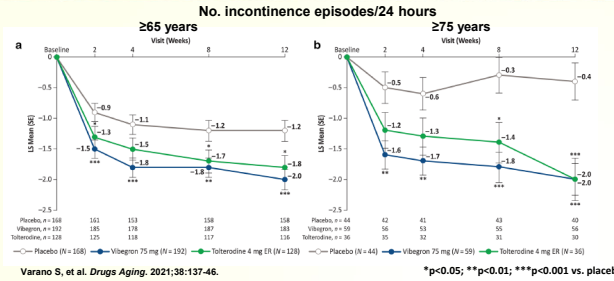
No. incontinence episodes/24 hours



- 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
  - Micturitions per 24 hr
  - Improved mean volume per micturition

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

Vibegron in the Elderly: Significant Reduction in Incontinence Episodes



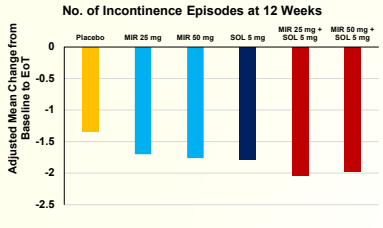
Varano S, et al. *Drugs Aging*. 2021;38:137-46.

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

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

Combination Therapy Improves Outcomes Over Monotherapy



- A 12-week, 6-arm, randomized, double-blind trial comparing monotherapy (mirabegron or solifenacin) vs. mirabegron + solifenacin 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.

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

Translating Knowledge into Practice
What would you choose for…

A 59-year-old woman who is generally healthy and experiencing UUI with 1-2 incontinence episodes each day, occasional nocturia?

A. Behavioral therapy
B. Antimuscarinic
C. Beta-3 agonist
D. Referral to a specialist

Translating Knowledge into Practice
What would you choose for…

A 76-year-old man with UUI, uses several incontinence pads when going out, has mild cognitive impairment, had inadequate results with behavioral therapy, and lives alone in an apartment?

A. Antimuscarinic
B. Beta-3 agonist
C. Combination therapy
D. Referral to a specialist

Translating Knowledge into Practice
What would you choose for…

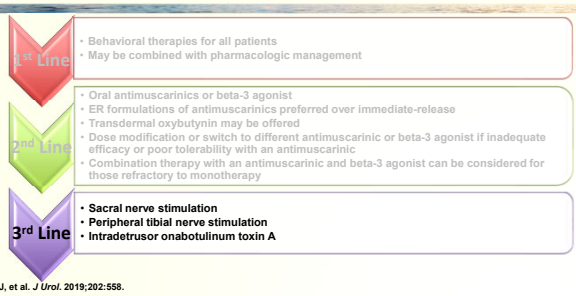
A 67-year-old woman with a 35 pack-year smoking history, a 2-month history of urgency and pelvic pain, and hematuria identified on urinalysis?

A. Antimuscarinic
B. Beta-3 agonist
C. Combination therapy
D. Referral to a specialist

When to Consider Referral

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

AUA/SUFU OAB Treatment Guidelines



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

Conclusions

- OAB is highly prevalent in men and women and substantially impacts quality of life
- Communicate with patients to set goals and manage expectations
- Utilize a treat-to-target approach that involves regular assessment and treatment adjustments