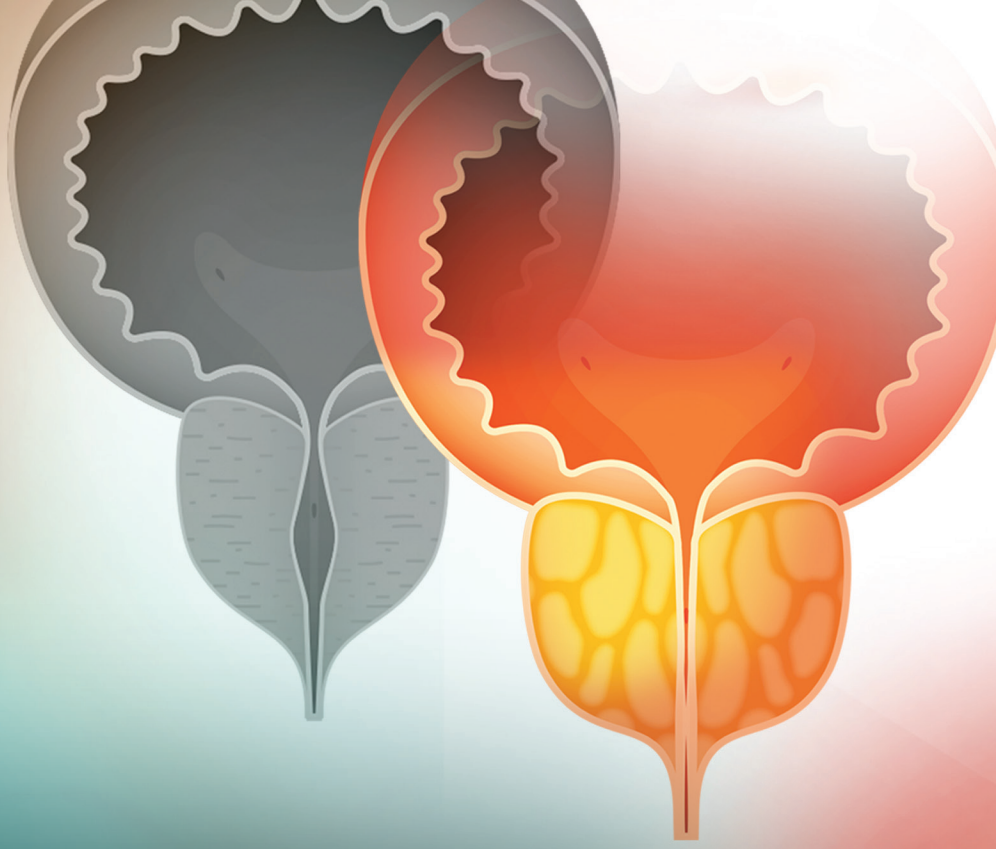


Enhancing Diagnostic Pathways and Personalized Care for BPH and OAB in the Primary Care Setting

TUESDAY, OCTOBER 7, 2025

This event is not a part of the official program of FMX.

MED LEARNING GROUP
This activity is provided by Med Learning Group.
This activity is supported by an independent medical educational grant from Sumitomo Pharma America.



I. **Introduction**

II. **Advanced Diagnostic Techniques for BPH and OAB**

A. Comprehensive Evaluation of BPH

a. Use of advanced diagnostic tools: (TRUS) and urodynamic studies
b. Role of PSA testing and MRI
c. Differentiating BPH from other causes of LUTS

B. Diagnostic Criteria in OAB

a. Advanced diagnostic modalities: urodynamic studies, cystoscopy, and bladder diaries
b. Importance of excluding other urological conditions
c. Understanding patient-specific factors that influence symptom presentation

III. **Case Study Discussion**

IV. **Treatment Landscape for BPH and OAB**

A. Pharmacologic Treatments for BPH

a. Alpha-blockers and 5-alpha reductase inhibitors (5ARIs)
b. Exploring combination therapies
c. Investigating the role of PDE5 inhibitors in dual treatment of BPH and ED

B. Pharmacologic Treatments for OAB

a. Anti-ACh agents, β3-AR agonists, and their mechanisms of action
b. Evaluation of the benefits and risks of combining anti-ACh agents with β3-AR agonists

V. **Whiteboard Animation & Analysis**

The pharmacodynamics and pharmacokinetics of current BPH and OAB treatments, with a focus on combination therapy mechanisms

VI. **Disease Management: SDM, MDT, and AE Monitoring**

A. Individualizing Treatment Plans

a. Utilize SDM for selecting the most appropriate pharmacologic treatment based on patient-specific factors, including preferences and values, comorbidities, and symptom severity.

b. Patient education and Decision Aids

B. Multidisciplinary Care and Addressing AEs

a. Monitoring treatment effectiveness and managing AEs

b. Criteria for referrals and making effective referrals: Who, When, and Why?

VII. Case Study Discussion

VIII. Conclusions and Q&A

Enhancing Diagnostic Pathways and Personalized Care for BPH and OAB in the Primary Care Setting

FACULTY

Matt T. Rosenberg, MD
Mid-Michigan Health Centers
Jackson, Michigan

PROGRAM DESCRIPTION

This program describes the diagnostic criteria for prostatic hyperplasia (BPH) and overactive bladder syndrome (OAB), including key features, differential diagnoses, screening tools, testing methods, and when urology referral is warranted; evaluate clinical data and guideline recommendations for current and emerging treatments for BPH and OAB; and utilize SDM and MDT approaches to individualize treatment, improve adherence, and appropriately manage comorbidities and AEs.

TARGET AUDIENCE

This activity is intended for primary care physicians involved in the management of patients with benign prostatic hyperplasia (BPH) and overactive bladder syndrome (OAB).

LEARNING OBJECTIVES:

After completing the CME activity, learners should be better able to:

- Describe the diagnostic criteria for BPH and OAB, including key features, differential diagnoses, screening tools, testing methods, and clinical scenarios warranting urology referral.
- Evaluate clinical data and guideline recommendations for current and emerging treatments for BPH and OAB and best practices for routine treatment monitoring.
- Utilize SDM and MDT approaches to individualize treatment, improve adherence, and appropriately manage comorbidities and AEs.

JOINT ACCREDIDATION STATEMENT

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AAFP ACCREDITATION
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Enhancing Diagnostic Pathways and Personalized Care for BPH and OAB in the Primary Care Setting

Matt T. Rosenberg, MD
Mid-Michigan Health Centers
Jackson, Michigan

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Learning Objectives

- Describe the diagnostic criteria for benign prostate hyperplasia (BPH) and overactive bladder (OAB), including key features, differential diagnoses, screening tools, testing methods, and clinical scenarios warranting urology referral
- Evaluate clinical data and guideline recommendations for current and emerging treatment for BPH and OAB and best practices for treatment monitoring
- Utilize shared decision making (SDM) and multidisciplinary care team (MDT) approaches to individualize treatment, improve adherence, and appropriately manage comorbidities and AEs

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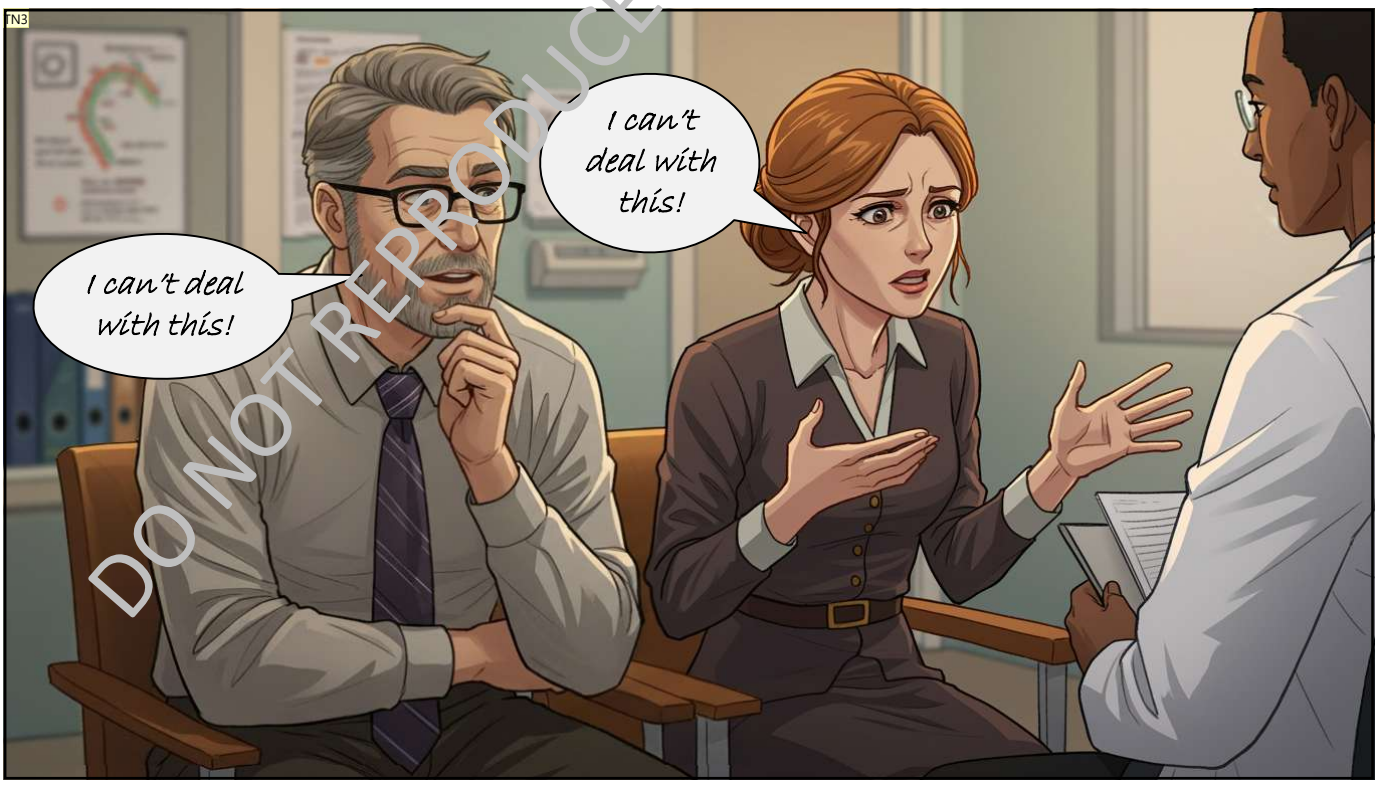
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Patient 1 (female)

- 48 years old
- Symptom onset: : 3.5 years
- Surgical history: hysterectomy for uterine fibroids, 2 years ago
- Medication: none, plenty of multivitamins
- Allergies: none
- Career: Corporate exec
- Social history: Doesn't smoke
- Physical exam: non-contributory
- Labs: non-contributory



7

Patient 2 (male)

- 51 years old
- Symptom onset: 3.5 years
- Past medical history: hypertension
- Surgical history: inguinal hernia repair
- Medication: Lisinopril 10mg qd
- Allergies: none
- Career: school psychologist
- Physical examination: non-contributory
- Labs: non-contributory



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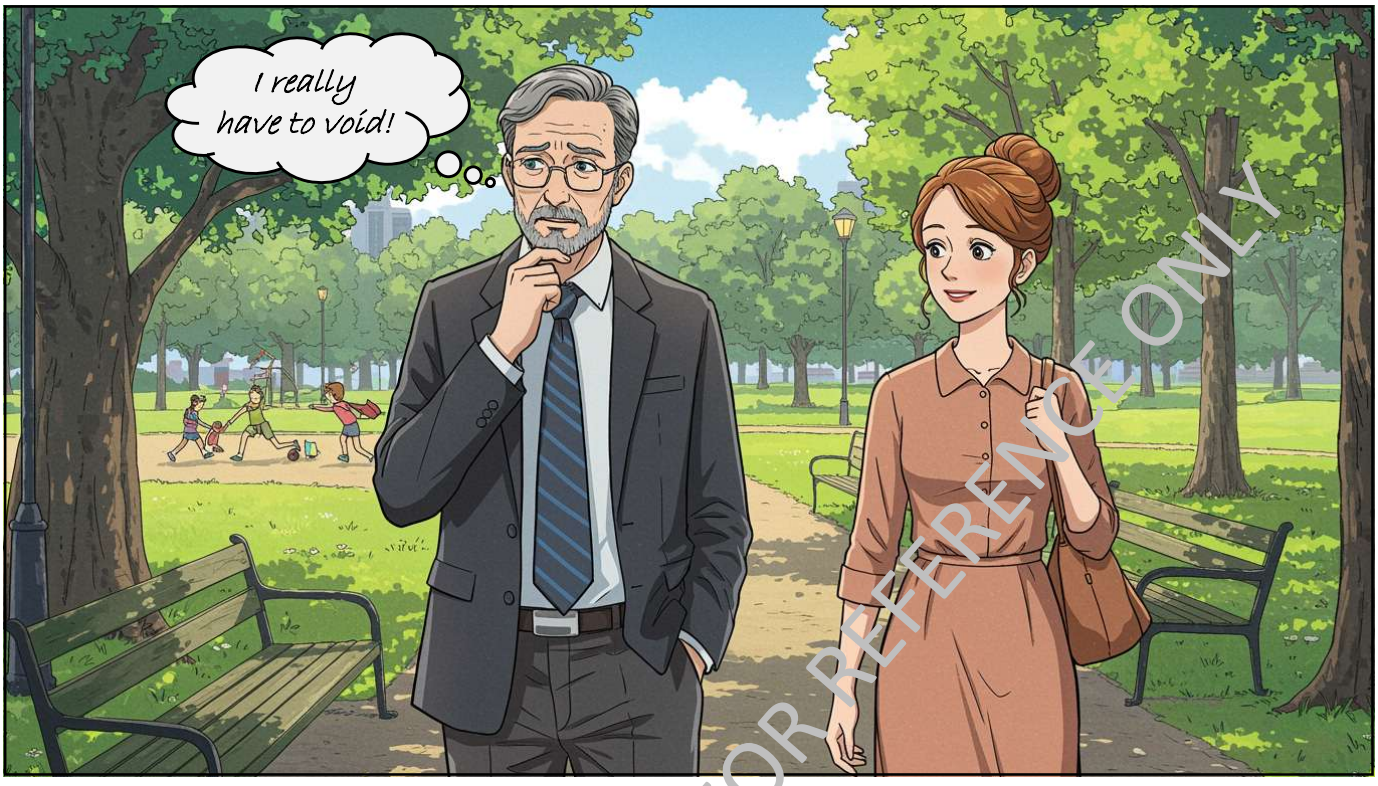


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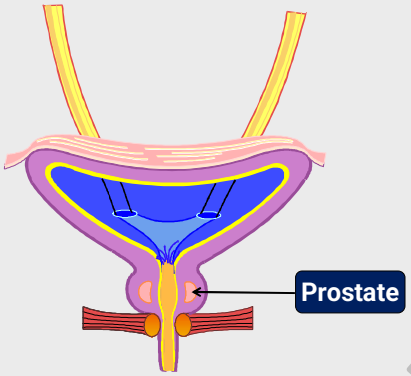
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Symptomatology

14

Why Do We Treat Men Differently Than Women … When It Comes to Bladder Symptoms?



In men and women, the symptoms of OAB are the same

In men, LUTS (Lower Urinary Tract Symptoms) are often considered related to the prostate

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15

Men Also Have LUTS – OAB Symptoms

16

- OAB is equally prevalent in men and women
- OAB symptoms often overlap with conditions of the prostate
- Men with LUTS are more likely to be treated with an α-blocker than with an antimuscarinic or beta-3 agonist
- Many men have persistent storage symptoms following treatment

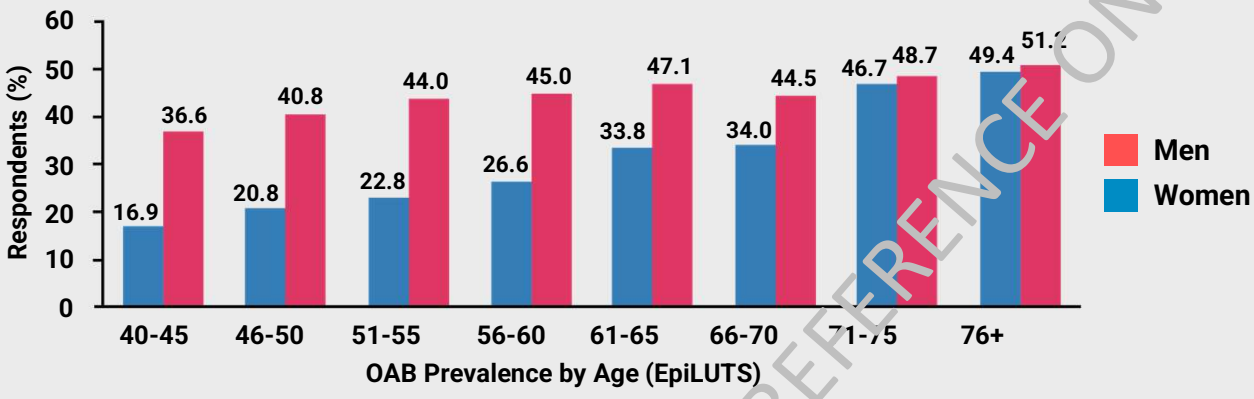
OAB = overactive bladder; LUTS = lower urinary tract symptoms

Stewart WF et al. *World J Urol*. 2003;20:327-336.
Lee JY et al. *BJU Int*. 2004;94:817-820.
Machino R et al. *Neurourol Urodyn*. 2002;21:444-449.
Jumadilova Z et al. *ICS* 2005.
Abrams P et al. *Neurourol Urodyn*. 2001;20:547-548.

16

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Prevalence of OAB Symptoms in US Adults



Coyne et al. *Urology*. 2011;77(5):1081-1087. Coyne et al. *Neurourol Urodyn*. 2013;32(3):230-237

17

Acronyms and Definitions "WORD SOUP"

- **BPH** (benign prostatic hyperplasia) / **BPE** (benign prostatic enlargement)
  - Histologic diagnosis characterized by proliferation of the cellular elements of the prostate, leading to an enlarged prostate gland
- **BOO** (bladder outlet obstruction) / **BPO** (benign prostatic obstruction)
  - Secondary to BPH may lead to OAB, urinary retention, impaired kidney function, recurrent urinary tract infections, gross hematuria, and bladder calculi
- **OAB** (overactive bladder)
  - Urgency, frequency, nocturia +/- urgency incontinence
- **LUTS** (lower urinary tract symptoms)
  - Combination of OAB ("irritative symptoms" (urgency, frequency, nocturia, +/- urgency incontinence) AND/OR BPO ("obstructive symptoms" (hesitancy, straining, incomplete emptying, weak stream, double voiding).

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Defining LUTS

Frequency	▪ Patient considers that he/she voids too often by day ▪ Normal is < 8 times per 24 hours
Nocturia	▪ Waking to urinate during sleep hours ▪ Considered a clinical problem if frequency is greater than twice a night
Urgency	▪ *Sudden* compelling desire to pass urine that is difficult to defer
Urge Urinary Incontinence (UUI)	▪ Involuntary leakage accompanied by, or immediately preceded by, urgency
OAB "Wet"	▪ OAB *with* UUI
OAB "Dry"	▪ OAB *without* UUI
Warning Time	▪ Time from first sensation of urgency to voiding

FOR REFERENCE ONLY

Abrams P, et al. *Neurourol Urodyn*. 2002;21:167-78; Wein A, et al. *J Urol*. 2006;175:S5-10;Zinner N, et al. *Int J Clin Pract*. 2006;60:119-26; Wein AJ. *Am J Manag Care*. 2000;6:S559-64.

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Let's Go Back to the Beginning: Basic Science



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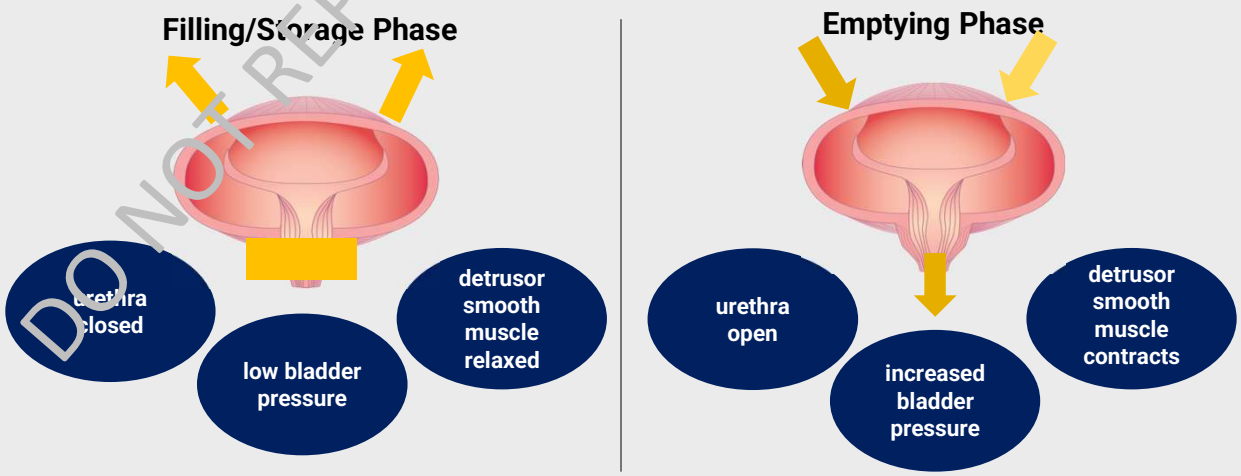
Understanding LUTS means understanding the normal functions of the BLADDER and the PROSTATE

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Normal Bladder Function

Bladder usually holds ~500 mL of urine
Normal voiding occurs near capacity of 300-400 mL



Andersson KE, Anders A. *Physiol Rev*. 2004;84(3):935-986. Ouslander JG. *N Engl J Med*. 2004;350(8):786-799.

22

Abnormal Function of the Bladder

Failure to store or empty

- Voiding frequently small amounts
- Uncontrollable urge (urgency)
- Incomplete emptying
- Hesitancy, poor stream

Wein AJ. Pathophysiology and categorization of voiding dysfunction. In: Wein AJ, Kavoussi LR, Novick AC, et al, eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia, PA: W. B. Saunders/Elsevier; 2007:1973-1985.

23

Function of the Prostate

NORMAL

- Produces fluid for seminal emission
- Does not grow into the urethra thereby allowing unobstructed flow

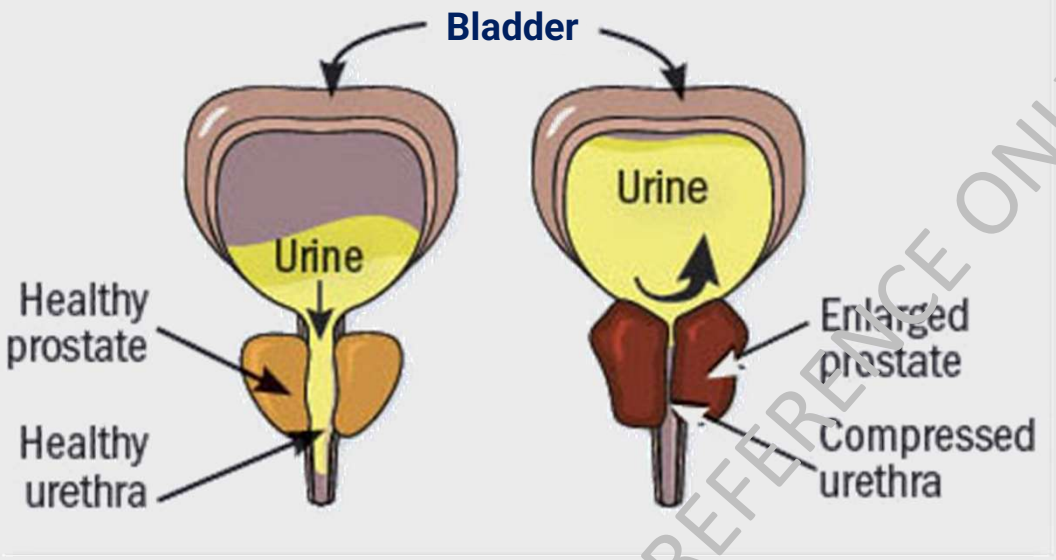
ABNORMAL

- Obstruction of urinary flow
- Poor function seen as failure to void

Rosenberg MT, et al. *Int J Clin Pract*. 2007;61(9):1535-1546.

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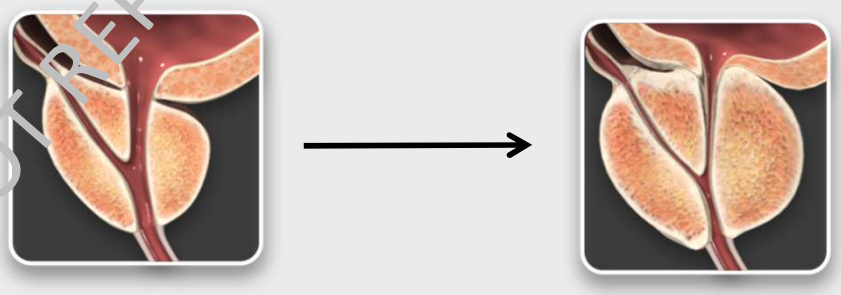


Sloan M. Treatment for Enlarged Prostate. Harvard Health. September 2, 2022. https://www.health.harvard.edu/mens-health/treatment-for-an-enlarged-prostate. Accessed September 5, 2025

25

Natural History of Prostate Growth

Based on data from a study by Roehrborn and colleagues, a 55-year–old man who has a 30 mL prostate volume, is experiencing symptoms, and has a PSA of 1.5 ng/mL can expect his prostate to approximately double in size over the next 15 years.



Age	55 yrs ⟶	60 yrs ⟶	65 yrs ⟶	70 yrs
PV	**30 mL**	**>40 mL**	**>50 mL**	**>61 mL**
PSA	1.5 ng/mL			

Roehrborn C, et al. *J Urol*. 2000;163:13–20.

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Natural History of Prostate Growth

A common condition as men age

- By sixth decade: > 50% of men have some degree of hyperplasia
- By eighth decade: > 90% of males will have hyperplasia

In only a minority of patients (about 10%) with this hyperplasia be symptomatic and severe enough to require medical treatment or surgical intervention

McVary KT, et al. J Urol. 2011;185(5):1793-1803.

27

Risk Evaluation of BPH-LUTS Progression

Baseline Factors as Predictors

Five risk factors

1. Total prostate volume ≥31 mL
2. PSA ≥1.6 ng/mL
3. Age ≥62

Not usually evaluated by the PCP

1. Qmax <10.6 mL/s
2. PVR ≥39 mL

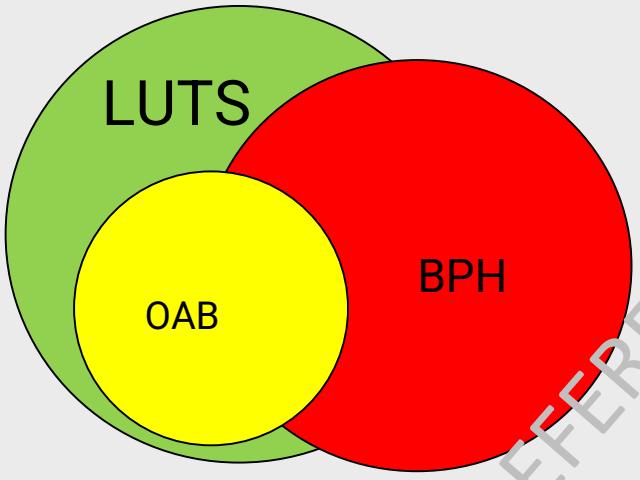
PVR = post-void residual; Qmax, = maximum flow rate.

Crawford ED, et al. *Urology*. 2006;175(4):1422-1427. Rosenberg MT, et al. Int J Clin Pract. 2010; 64(4):488-496. Rosenberg MT, et al. Current Urology Reports. 2013 Dec;14(6).

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OAB and BPH Can Coexist



Rosenberg MT, et al. *Int J Clin Pract*. 2007;61,9,1535-1546Lee JY et al. *BJU Int*. 2004;94:817. Dmochowski et al. *Urology*. 2003;60(suppl 5A):56-62. Thomas AW et al. *J Urol*. 1999;161:257.

29

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Symptoms when LUTS relates to the Bladder (storage) or Prostate (voiding)

Storage (bladder)	Voiding (prostate)
Urgency	Hesitancy
Frequency	Poor flow/weak stream
Nocturia	Intermittency
Urge incontinence	Straining to void
Stress incontinence	Terminal dribble
Mixed incontinence	Prolonged urination
Overflow incontinence	Urinary retention

Abrams P. et al. Neurourol Urodyn. 2002;21:167-178. Chapple CR, et al. Eur Urol. 2006;49:651-658.

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Differentiating the Etiology of LUTS

- Weak flow – think prostate
- Voiding small amounts – think bladder
- Leakage of urine – think bladder or sphincter

It is all about volume and flow

Rosenberg MT, et al. *Int J Clin Pract*. 2007;61(9):1535-1546.

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Differentiating the Etiology of LUTS

What if....?

- Weak flow – think prostate
- Voiding small amounts – think bladder
- Leakage of urine – think bladder or sphincter
- Good flow, normal volume – think too much fluid production and evaluate accordingly

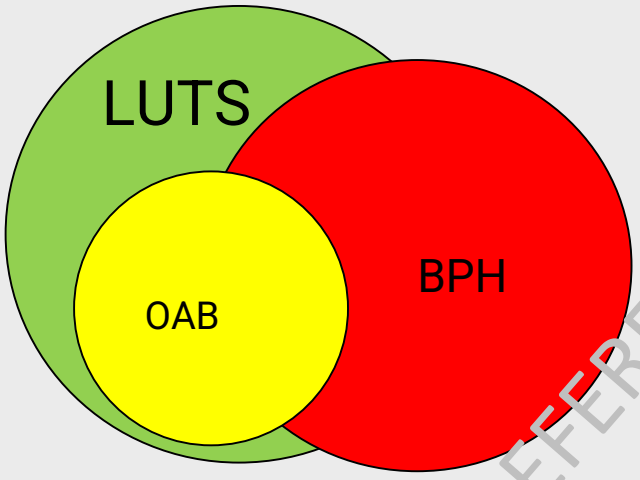
It is all about volume and flow

Rosenberg MT, et al. *Int J Clin Pract*. 2007;61(9):1535-1546.

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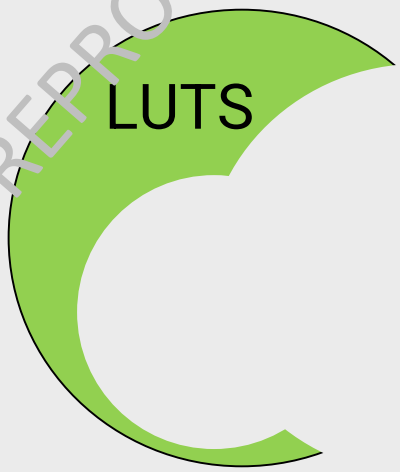
OAB and BPH Can Coexist



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LUTS Not Always Caused by OAB and BPH

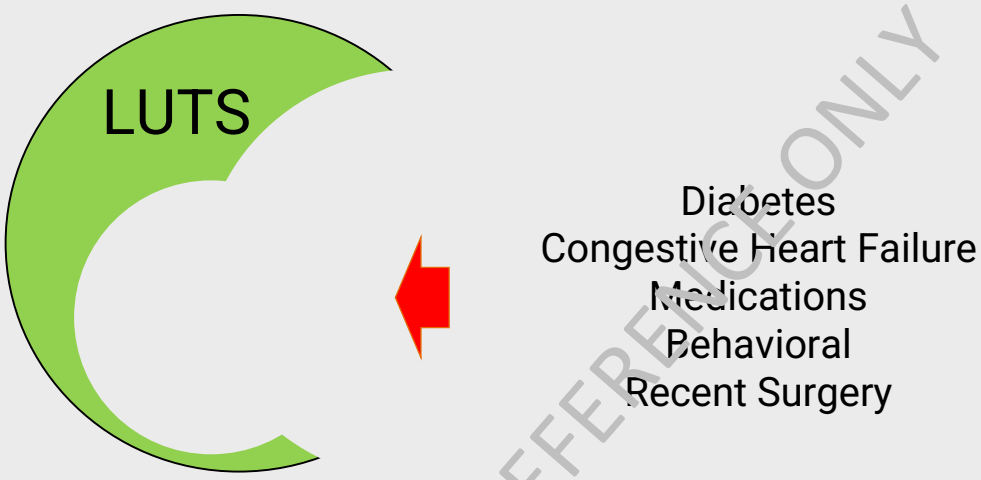


Rosenberg MT, et al. *Int J Clin Pract*. 2007;61,9,1535-1546Lee JY et al. *BJU Int*. 2004;94:817. Dmochowski et al. *Urology*. 2002;60(suppl 5A):56-62. Thomas AW et al. *J Urol*. 1999;161:257.

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LUTS Not Always Caused by OAB and BPH



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The Patient Journey



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Long and Winding Road

Become aware of symptoms

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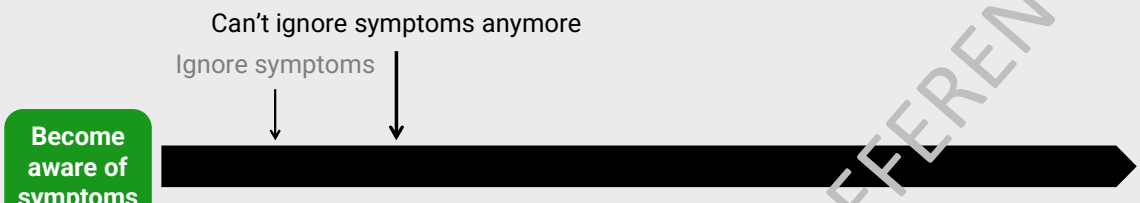
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Long and Winding Road



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Long and Winding Road



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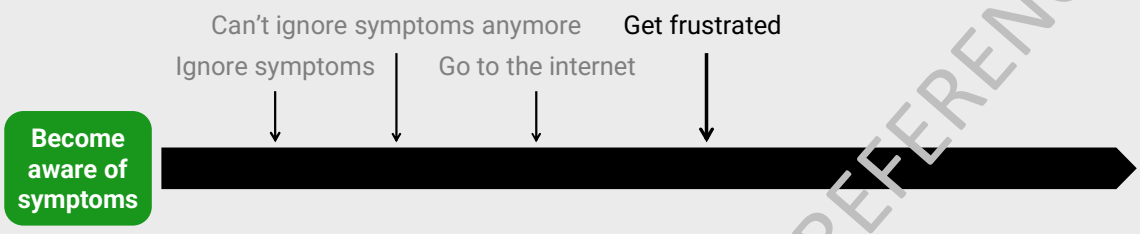
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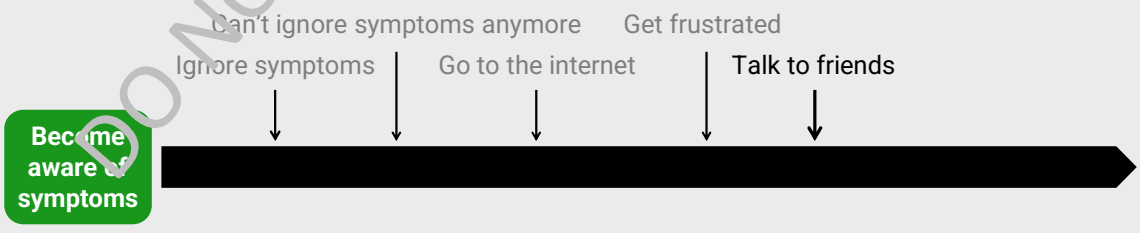
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Long and Winding Road



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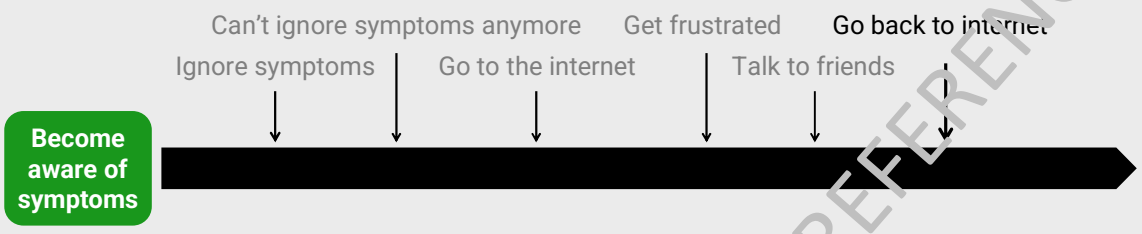
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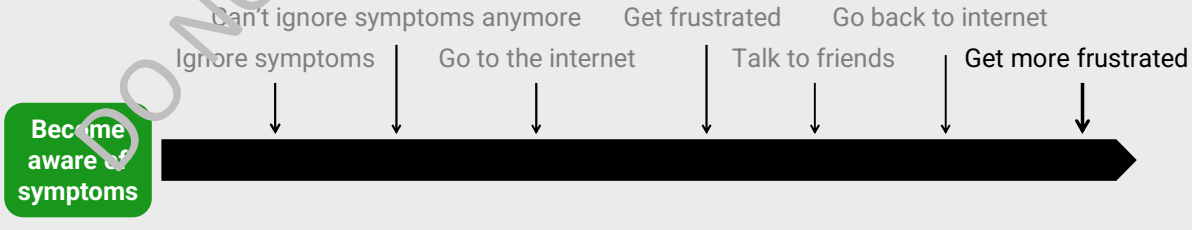
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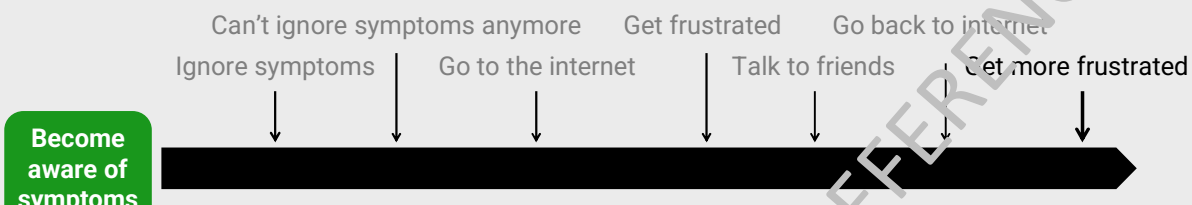
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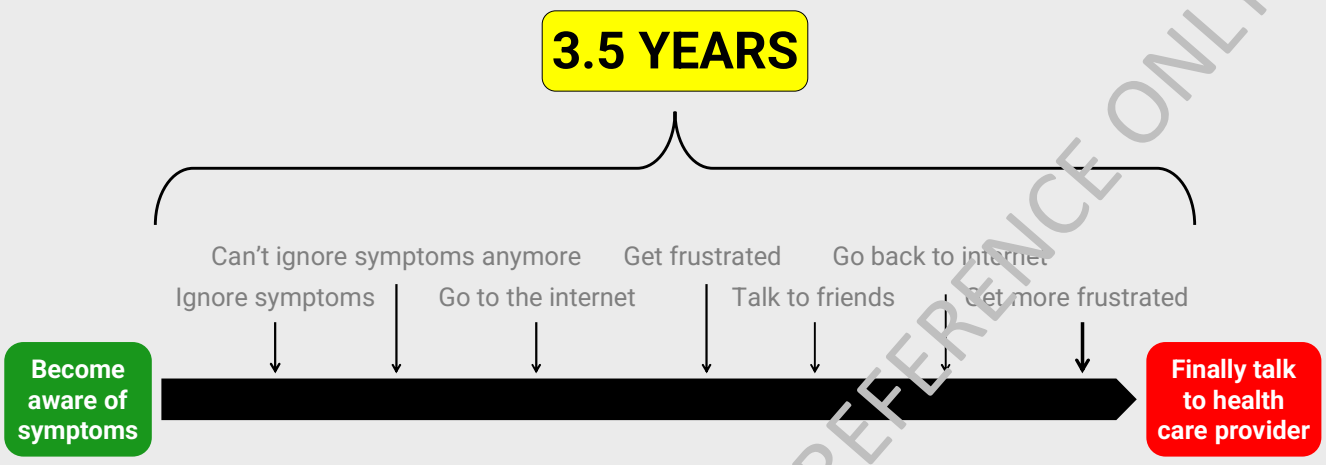
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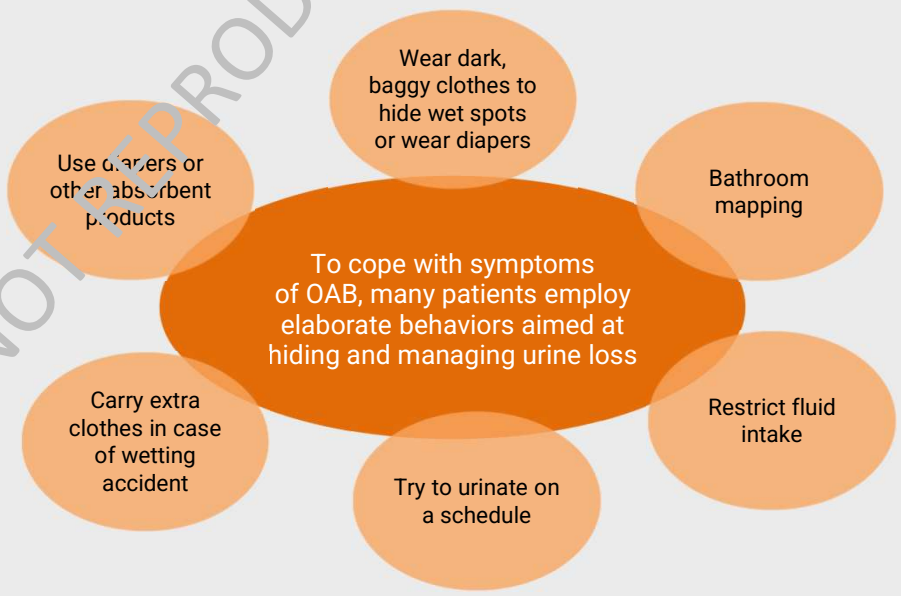
Long and Winding Road



Filipetto FA, et al. BMC Fam Pract. 2014 May 14;15:96

47

Coping (Suffering) in Silence



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

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Evaluation in Primary Care Setting

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AUA/SUFU OAB Guidelines: Diagnostic Workup (Female / Male)

Initial diagnostic process	▪ History ▪ Physical exam ▪ Urinalysis
Optional additional diagnostic measures	▪ Urine culture ▪ Post voiding residual(PVR) assessment ▪ Bladder (voiding) diaries ▪ Symptom questionnaire
Tests for complicated or refractory patients	▪ Urodynamics, cystoscopy, and diagnostic renal and bladder ultrasound should *not* be used in the initial workup of uncomplicated patients

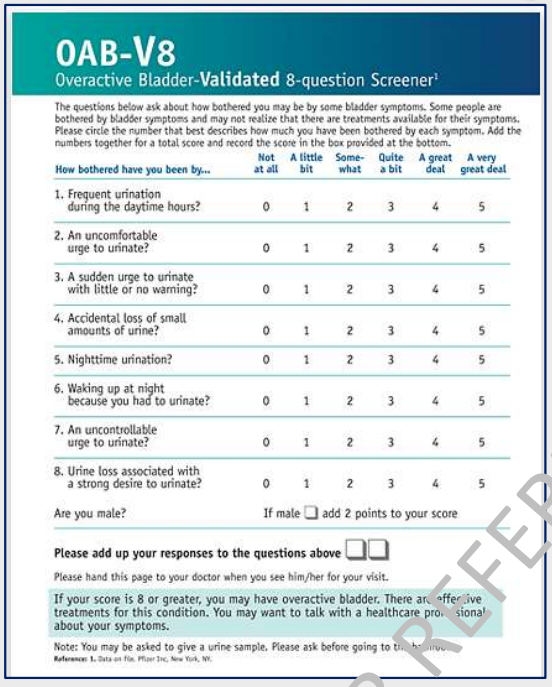
AUA Guideline Management of Lower Urinary Tract Symptoms Attributed to BPH:

ADD FOR MEN / BPH	▪ International Prostate Symptom Score ▪ Flow / PVR (optional)

DO NOT REPRODUCE – FO

Gormley et al. AUA Web site. http://www.auanet.org/guidelines/overactive-bladder-(oab)-(aua/sufu-guideline-2012-amended-2014)#x2903. Accessed April 27, 2020 Sandhu JS, et al. 2023. *J Urol.* 2023;10.1097.

50



OAB-V8

Overactive Bladder-**Validated** 8-question Screener[1]

The questions below ask about how bothered you may be by some bladder symptoms. Some people are bothered by bladder symptoms and may not realize that there are treatments available for their symptoms. Please circle the number that best describes how much you have been bothered by each symptom. Add the numbers together for a total score and record the score in the box provided at the bottom.

How bothered have you been by...	Not at all	A little bit	Some-what	Quite a bit	A great deal	A very great deal
1. Frequent urination during the daytime hours?	0	1	2	3	4	5
2. An uncomfortable urge to urinate?	0	1	2	3	4	5
3. A sudden urge to urinate with little or no warning?	0	1	2	3	4	5
4. Accidental loss of small amounts of urine?	0	1	2	3	4	5
5. Nighttime urination?	0	1	2	3	4	5
6. Waking up at night because you had to urinate?	0	1	2	3	4	5
7. An uncontrollable urge to urinate?	0	1	2	3	4	5
8. Urine loss associated with a strong desire to urinate?	0	1	2	3	4	5
Are you male?	If male ☐ add 2 points to your score					

Please add up your responses to the questions above ☐☐

Please hand this page to your doctor when you see him/her for your visit.

If your score is 8 or greater, you may have overactive bladder. There are effective treatments for this condition. You may want to talk with a healthcare professional about your symptoms.

Note: You may be asked to give a urine sample. Please ask before going to the clinic.

Reference: 1. Data on file. Pfizer Inc, New York, NY.

The Clinician's Ultimate Reference GlobalRPh. https://globalrph.com/medcalcs/overactive-bladder-8-question-screener-oab-q/. Coyne et al. The OAB-q. *Qual Life Res* 2002; 11:563-574. Coyne et al *Eur Urol* 2006; 49:1079-1086. Accessed September 5, 2025

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BPH Symptom Score Index

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
Incomplete emptying — It does not feel like I empty my bladder all the way.	0	1	2	3	4	5	
Frequency — I have to go again less than two hours after I finish urinating.	0	1	2	3	4	5	
Intermittency — I stop and start again several times when I urinate.	0	1	2	3	4	5	
Urgency — It is hard to wait when I have to urinate.	0	1	2	3	4	5	
Weak stream — I have a weak urine stream.	0	1	2	3	4	5	
Straining — I have to push or strain to begin urination.	0	1	2	3	4	5	
	None	**1 time**	**2 times**	**3 times**	**4 times**	**5 times or more**	**Your score**
Nocturia — I get up to urinate after I go to bed until the time I get up in the morning.	0	1	2	3	4	5	
						Total AUA Symptom Score	

Total score: 0–7 mildly symptomatic; 8–19 moderately symptomatic; 20-35 severely symptomatic.

Quality of life due to urinary symptoms	**Delighted**	**Pleased**	**Mostly satisfied**	**Mixed: about equally satisfied and dissatisfied**	**Mostly dissatisfied**	**Unhappy**	**Terrible**
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Barry M. MDCalc. https://www.mdcalc.com/calc/10462/american-urological-association-symptom-index-aua-si. Accessed September 5, 2025

52

DO NOT REPRODUCE – FOR REFERENCE ONLY

IPSS Symptom Index

AUA-Symptom Index includes 1 quality of life question (#8)

Urinary symptoms	Not at all	<1 in 5	<1 in 2	About 1 in 2	>1 in 2	Almost always
1. Over the past month, how often have you had a **sensation of not emptying** your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month, how often have you had a **weak urinary stream**?	0	1	2	3	4	5
3. Over the past month, how often have you found you **stopped and started** again several times while urinating?	0	1	2	3	4	5
4. Over the past month, how often have you had **to push or strain** to begin urination?	0	1	2	3	4	5
5. Over the past month, how often have you had to **urinate again** less than 2 hours after you finished urinating?	0	1	2	3	4	5
6. Over the past month, how often have you found **it difficult to postpone urination**?	0	1	2	3	4	5
7. Over the past month, how many times did you typically **get up to urinate** from the time you went to bed until the time you got up in the morning?	Never 0	1 time 1	2 times 2	3 times 3	4 times 4	≥5 times 5
TOTAL FOR URINARY SYMPTOMS						

Barry MJ, et al. *J Urol*. 1992;148(5):1549-1557.

53

Simple Questions the PCP Can Ask

- Do you have a sudden urge to void and can barely make it to the bathroom?
- Do you wear a pad or diaper?
- Can you sit through a movie without going to the bathroom?
- Do you leak urine?
- Do you get up at night?

Rosenberg et al. *Can J Urol*. 2014;21 Suppl 2:2-11

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DO NOT REPRODUCE – FOR REFERENCE ONLY

Examples in the Patient's History That May Cause or Worsen LUTS

Diabetes (new onset or poorly controlled)

- Causing polyuria/polydipsia

Congestive heart failure

- Nighttime fluid mobilization

Recent Surgery

- Catheterization during surgery, immobilization, constipation from pain medications

A recent onset of the symptoms may provide a clue to the etiology

Rosenberg et al. *Can J Urol.* 2014;21 Suppl 2:2-11

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Medications as a Cause of LUTS

Sedatives	Confusion, secondary incontinences
Alcohol, Caffeine, Diuretics	Diuresis
Anticholinergics	Impair contractility, voiding difficulty, overflow inc
α – Agonists	Increased outlet resistance, voiding difficulty
ß - Blockers	Decreased urethral closure, stress incontinence
Calcium-Channel Blockers	Reduce bladder smooth muscle contractility
Angiotensin Converting Enzyme	Induce cough, stress urinary incontinence
First generation antihistamines	Increase outlet resistance
Cholinesterase inhibitors	Precipitate urge incontinence
Opioids	Constipation

Lavelle JP, et al. *Am J Med*. 2006;119(suppl 1):37-40. DeBeau CE. *J Urol*. 2006;175(3 py 2):S11-S15. Gill SS, et al. *Arch Intern Med*. 2005;165:808-813. Wyman JF, et al. *Int I Clin Pract*. 2009;63:1177-1191. Newman DK. *Nurse Pract*. 2009;34:33-45.

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DO NOT REPRODUCE – FOR REFERENCE ONLY

The Focused Physical Examination

Abdominal

- Tenderness, masses, distension

Neurological

- Mental and ambulatory status, neuromuscular function

Genitourinary

- Meatus and testis

Rectal

- Tone
- Prostate size, shape, nodules and consistency

Rosenberg MT ,Staskin DR, Kaplan SA, et al. *Int J Clin Pract*. 2007;61(9):1535-1546.
Rosenberg MT, Newman DK, Tallman CT, et al. *Cleve Clin J Med*. 2007;74(suppl 3):S21-S29.
Rosenberg MT, Miner MM, Riley PA, Staskin DR. *Int J Clin Pract*. 2010; 64(4):488-496.

57

Laboratory Tests

Urinalysis

- Infection, blood
- Urine not an adequate screener for diabetes

A random or fasting blood sugar

- Diabetes

Prostate specific antigen

- Prostate specific not cancer specific
- Excellent as a surrogate marker for prostate size
  - PSA is more accurate than a DRE when estimating prostate size.
  - A PSA of 1.5 ng/ml equates to a prostate volume of at least 30 grams(ml)

Rosenberg MT, Staskin DR, Kaplan SA, et al. *Int J Clin Pract*. 2007;61,9,1535-1546. Bosch J, et al. *Eur Urol*. 2004;46:753-759 Roerborn CG, et al. *Urology*. 1999;53;381-9. American Urological Association (AUA) Guideline. AUA Web site. 2012. http://www.auanet.org/content/media/OAB_guideline.pdf. Accessed March 21, 2014.

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DO NOT REPRODUCE – FOR REFERENCE ONLY

The Purpose of the Voiding Diary

- Identifies voiding frequency and voided volume
- Differentiates behavioral vs LUTS pathology
  - Voiding frequently
    - after drinking the 40 ounce beverage (behavioral)
    - small amounts as a result of always being in a rush (behavioral)
    - small amounts (OAB)
    - large amounts (intake / output)
- Alerts the patients to habits /opportunities to modify
- Can monitor effect of treatment

Wyman JF, et al. *Int J Clin Pract*. 2009; 63(8):1177-91

59

The Post Void Residual (PVR) is Only Needed in Select Patients

- The fear of patients going into retention when treated for OAB leaves many patients untreated
- If PVR residual is less than 50 ml, causing retention when treating OAB is extremely unlikely
  - FACT: Most PCPs will not have bladder scanner and will not want to catheterize a patient
  - FACT: Most PCPs will have access to a ultrasound unit and can order a post void residual

USE COMMON SENSE
If you are treating the patient for voiding too frequently (OAB) and they have not voided in 6–8 hours or have a sense to void but cannot, have them contact you

Rosenberg MT. *Curr Opin Urol.* 2008;9(6):428-32. Rosenberg MT, Staskin DR, Kaplan SA, et al. *Int J Clin Pract*. 2007;61(9):1535-1546.

60

DO NOT REPRODUCE – FOR REFERENCE ONLY

Indications for Referral

- History of recurrent urinary tract infections or other infection
- Pelvic irradiation
- Microscopic or gross hematuria
- Prior genitourinary surgery
- Elevated prostate-specific antigen
- Abnormal genital exam
- Suspicion of neurological cause of symptoms
- Meatal stenosis
- History of genitourinary trauma
- Pelvic pain
- Uncertain diagnosis or patient choice

Rosenberg MT, Staskin DR, Kaplan SA, et al. *Int J Clin Pract.* 2007;61,9,1535-1546

61

Treatment Now Can Be Empiric

- No identifiable etiology
- No reversible causes
- Is patient bothered enough for treatment?
  - No, watchful waiting
  - Yes, consider algorithm
    - Weak flow – think Prostate
    - Poor voiding volumes – think Bladder
    - Incontinence – think Bladder/Outlet

Rosenberg MT. *Cur Uro* 2008, 9:428–432.

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DO NOT REPRODUCE – FOR REFERENCE ONLY

Treatment

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Treatment Guidelines



Behavioral treatment



Pharmacologic management

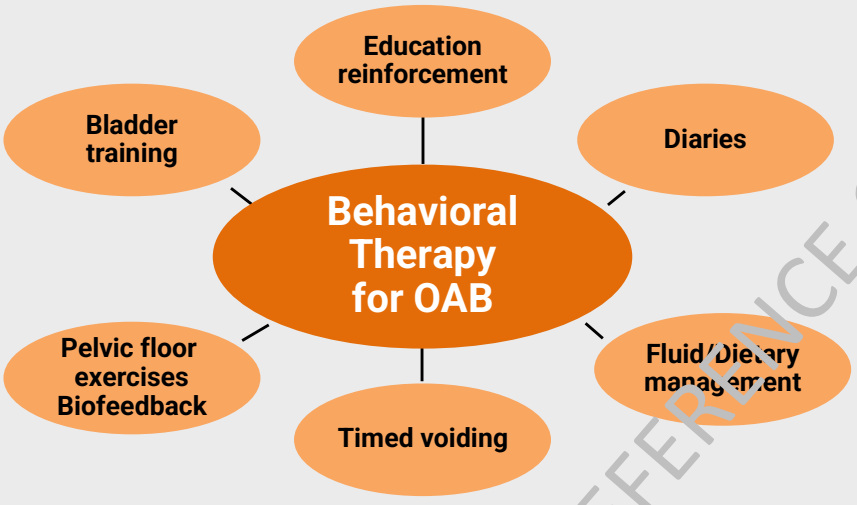


Other (specialist)

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Behavioral Therapy for OAB

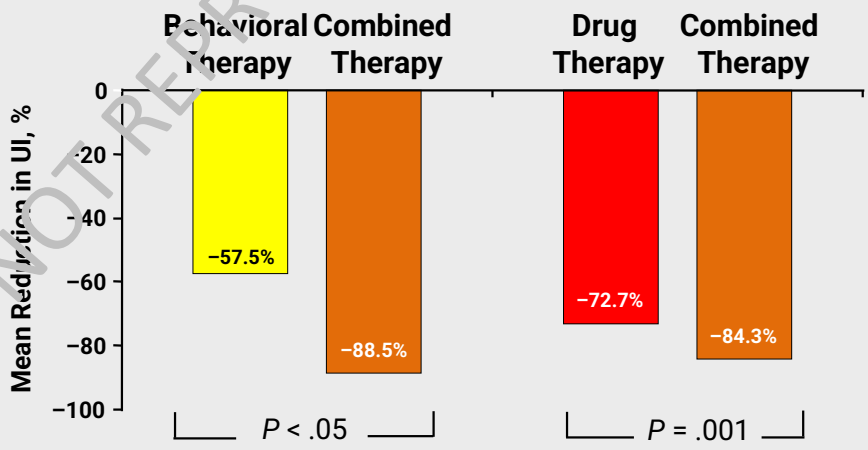


No matter what the treatment course, behavioral modification should be offered to every patient

Burgio KL. *Urology.* 2002;60:(5)suppl 1:72-76. Burgio KL, Goode PS, Locher JL, et al. *JAMA.* 2002;288:2293-2299. Fantl [illegible], Wyman JF, McClish DK, et al. *JAMA.* 1991;265:609-613. Ouslander JG. *N Engl J Med.* 2004;350:786-799. Soda T, et al. *J Urol.* 2010; 184: 1000-1004

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Additive Effect of Combining Behavioral And Drug Therapy

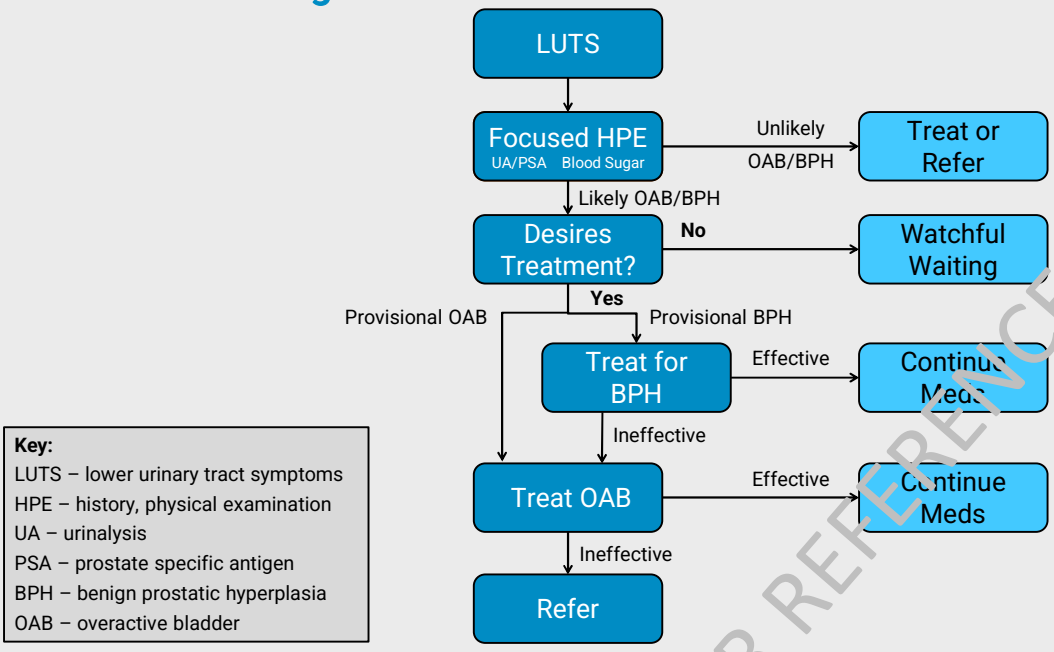


Burgio KL, et al. *J Am Geriatr Soc.* 2000;48:370-374.

66

DO NOT REPRODUCE – FOR REFERENCE ONLY

The Male LUTS Algorithm

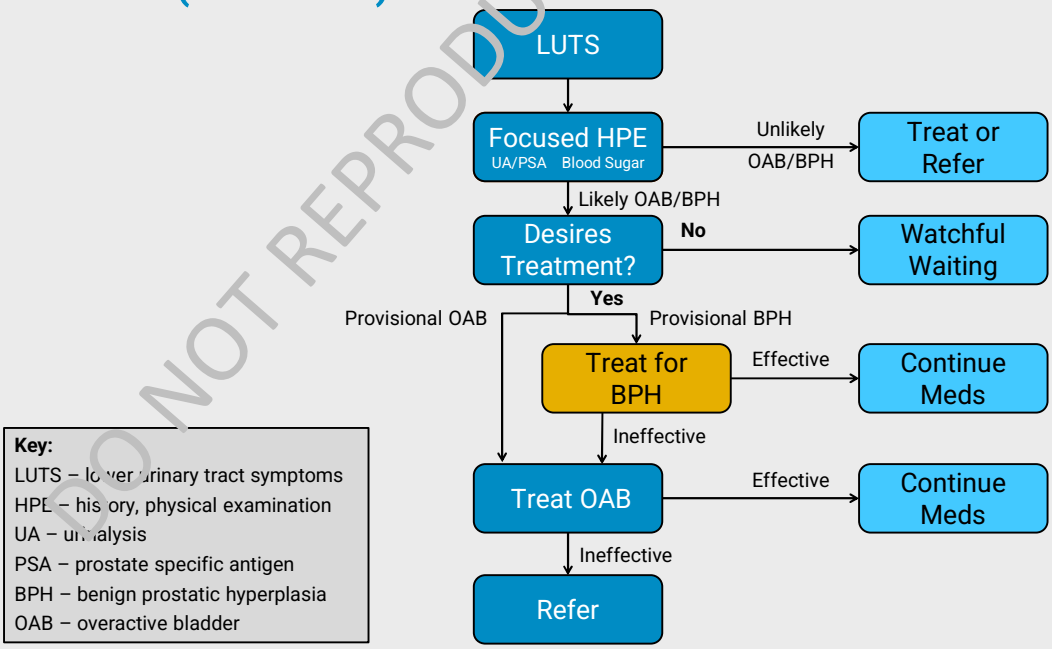


Key:
LUTS – lower urinary tract symptoms
HPE – history, physical examination
UA – urinalysis
PSA – prostate specific antigen
BPH – benign prostatic hyperplasia
OAB – overactive bladder

Modified from Rosenberg MT, Staskin DR, Kaplan SA, et al. *Int J Clin Pract*. 2007;61(9):1535-1546.

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The Male (or Prostate) Dilemma



Key:
LUTS – lower urinary tract symptoms
HPE – history, physical examination
UA – urinalysis
PSA – prostate specific antigen
BPH – benign prostatic hyperplasia
OAB – overactive bladder

Modified from Rosenberg MT, Staskin DR, Kaplan SA, et al. *Int J Clin Pract*. 2007;61(9):1535-1546.

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DO NOT REPRODUCE – FOR REFERENCE ONLY

Common Types of Male Patients We Encounter the "Simplified Staskin Method"

Patients with:

Poor flow (BPH med)	and	no OAB symptoms
Poor flow (BPH med)	and	+ OAB symptoms
Good flow (OAB med)	and	+ OAB symptoms
Flow treated (OAB BPH combo)	and	+ OAB symptoms persist

One of a million conversations discussing how to simplify the process

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– FOR REFERENCE ONLY

Pharmacological Treatment for OAB

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Pharmacologic Management

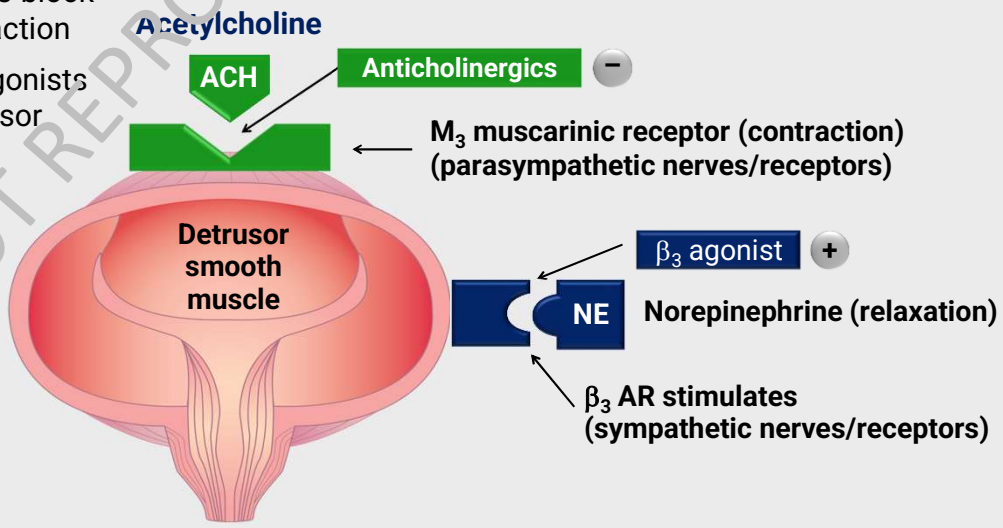
- 8 antimuscarinics to choose from, 6 are oral and 2 are topical
- 2 beta-3 adrenergic agonists
- All medications have been proven effective for OAB treatment
- Choice is based of efficacy, dose flexibility, adverse event profiles and drug interactions
- Trying several medications before referral is appropriate

Finney SM, et al. *BJU Int.* 2006;98:503-507. Chapple C, et al. *Eur Urol.* 2005;48:5-26. Rosenberg M, Newman DK, Tallman CT, et al. *Cleve Clin J Med.* 2007;74(suppl 3):S21-S29. *Physicians' Desk Reference.* 64st ed. Montvale, NJ: Thomson PDR; 2010. The AUA/SUFU Guideline on the Diagnosis and Treatment of Idiopathic Overactive Bladder - American Urological Association OAB Guidelines. https://www.auanet.org/guidelines-and-quality/guidelines/idiopathic-overactive-bladder#x21313

71

Receptor Pathways for OAB Treatment

- Anticholinergics block detrusor contraction
- Sympathetic agonists stimulate detrusor relaxation



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

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DO NOT REPRODUCE – FOR REFERENCE ONLY

Antimuscarinics – Immediate Release

Drug	Brand Name	Dose	Dosing
Darifenacin	Enablex	7.5 mg, 15 mg	Daily
Fesoterodine	Toviaz	4 mg, 8 mg	Daily
Oxybutynin ER	Ditropan XL	5 – 30 mg	Daily
Oxybutynin TDS	Oxytrol	3.9 mg	Twice per week
Oxybutynin 10% gel	Gelnique	100 mg	Daily
Solifenacin	Vesicare	5 mg, 10 mg	Daily
Tolterodine ER	Detrol LA	2, 4mg	Daily
Trospium Chloride	Sanctura XR	60 mg	Daily

Physcians' Desk Reference. 64st ed. Montvale, NJ: Thomson PDR; 2010.

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Antimuscarinics – Extended Release

Drug	Brand Name	Dose	Dosing
Oxybutynin IR	Ditropan	5 mg	2 – 4 times per day
Tolterodine IR	Detrol	1–2 mg	Twice per day
Trospium Chloride	Sanctura	20 mg	Twice per day

Physcians' Desk Reference. 64st ed. Montvale, NJ: Thomson PDR; 2010.

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Common Side Effects of Antimuscarinics

- Dry Mouth
- Constipation
- Headaches
- Blurred vision

✓ Clinicians should manage constipation and dry mouth before abandoning effective antimuscarinic therapy

✓ Patient must decide if the efficacy of the medication is worth side effects

✓ Some patients have symptoms that are severe enough they would tolerate significant problems, whereas that may not be the same for others

Balance of efficacy and tolerability should be considered and discussed with each patient

Steers WD. *Urol Clin North Am*. 2006;33:475-482. Erdam N, et al. *Am J. Med* 2006;119(suppl 1):29-36. Gormley EA, et al. American Urological Association (AUA) Guideline. AUA Web site. 2012. http://www.auanet.org/content/media/OAB_guideline.pdf. Accessed March 21, 2014.

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Contraindications, Warnings and Precautions for Antimuscarinics

Contraindications

- Urinary or gastric retention
- Uncontrolled narrow angle glaucoma

Warnings and Precautions

- Angioedema of face, lips, tongue and/or larynx
- Clinically significant bladder outlet obstruction
- Decreased gastrointestinal motility
- Treated narrow angle glaucoma
- May have CNS effects i.e. somnolence
- Use with caution in patients with myasthenia gravis

Physicians' Desk Reference. 64st ed. Montvale, NJ: Thomson PDR; 2010. Oelke M, et al. *Eur Urol*. 2013;64(1):118-140.

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DO NOT REPRODUCE – FOR REFERENCE ONLY

ACH Drugs: Potentially Inappropriate Use in Older Adults

2019 AGS Beers Criteria[1]

Avoid ACH drugs in patients with dementia or cognitive impairment

- Evidence quality: Moderate
- Recommendation strength: Strong

Minimize number of ACH drugs according to increased risk of cognitive decline

- Evidence quality: Moderate
- Recommendation strength: Strong

Drug Class	Drugs With Strong Anticholinergic Properties[1]
Antiarrhythmics	Disopyramide
Antidepressants	Amitriptyline, amoxapine, clomipramine, desipramine, doxepin (> 6 mg), imipramine, nortriptyline, paroxetine, protriptyline, trimipramine
Antihistamines	Promethazine, pyrilamine, triprolidine
Antimuscarinics (urinary incontinence)	Darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, *trospium*

AUA White Paper on Beers Criteria[2]
"We strongly encourage clinicians, payers, pharmacy benefits managers, and policy makers to educate themselves about the reasoning and recommendations contained within the Beers Criteria as they apply to urologic medications and practice with older adults."

AGS = American Geriatrics Society.

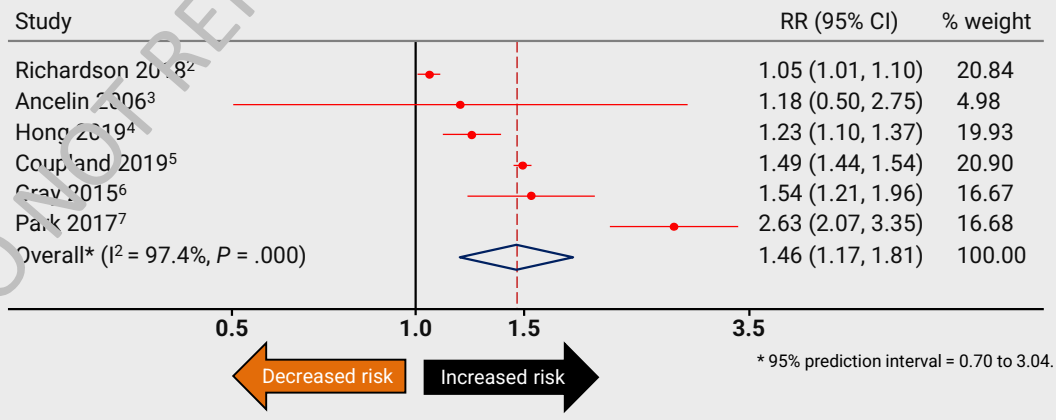
1. 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. *J Am Geriatr Soc*. 2019;67(4):674-694. 2. Gr...ling TL, et al. *Urol Pract*. 2016;3(2):102-111.

Abbreviation: AGS, American Geriatrics Society.

77

Meta-Analysis Demonstrates Association ≥3 Months' ACH Use and Incident Dementia

Estimated RRs for the 6 studies included in the meta-analysis; 2 included ACH medications for OAB[1]



* 95% prediction interval = 0.70 to 3.04.

RR = rate ratio.

1. Reprinted with permission from Dmochowski RR, et al. *Neurourol Urodyn*. 2021;40(1):28-37. © 2021 by the Authors. 2. Richardson K, et al. *BMJ*. 2018;361:k1315. 3. Ancelin ML, et al. *BMJ*. 2006;332(7539):455-459. 4. Hong C-T, et al. *Parkinsonism Relat Disord*. 2019;65:224-229. 5. Coupland CAC, et al. *JAMA Intern Med*. 2019;179(8):1084-1093. 6. Gray SL, et al. *JAMA Intern Med*. 2015;175(3):401-407. 7. Park H-Y, et al. *PLoS One*. 2017;12(1):e0169463.

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DO NOT REPRODUCE – FOR REFERENCE ONLY

Beta-3 Adrenergic Agonists

Drug	Dose	Dosing
Mirabegron	25 mg, 50 mg	Daily
Vibegron	75 mg	Daily

Mirabegron prescribing information, Astellas Pharma US, Inc. June 2012. Gemtesa prescribing information, Sumitomo Pharma America, Inc. May 2025

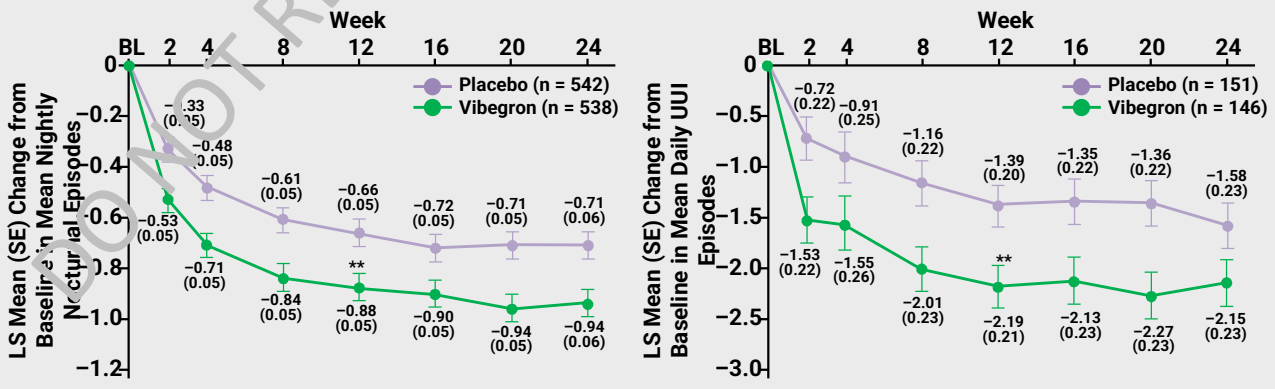
79

Vibegron

Unique patient population

- Risk of retention if treating storage symptoms, Elderly

Vibegron decreases frequency, urge episodes and nocturia, compared to placebo[31]



Staskin D, et al. Efficacy and Safety of Vibegron for Persistent Symptoms of Overactive Bladder in Men Being Pharmacologically Treated for Benign Prostatic Hyperplasia: Results From the Phase 3 Randomized Controlled COURAGE Trial. *J Urol*. Volume 212, Issue 2 Aug 202

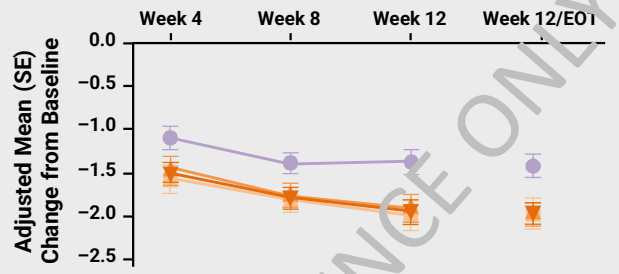
80

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Mirabegron

- Decreases frequency, urge and incontinence episodes[28]
- Can be used in combination w/ anticholinergics[29]
  - Mirabegron commonly paired w/ solifenacin
- Particularly effective / safe in older patients[30]

Number of urgency incontinence episodes/24 h



Difference (SE) vs placebo at EOT

Mirabegron total	−0.56 (0.14) 95% CI: -0.83, −0.29, p < .001
Mirabegron 25 mg	−0.54 (0.17) 95% CI: -0.88, −0.21, p = .001
Mirabegron 50 mg	−0.57 (0.17) 95% CI: -0.91, −0.24, p < .001

Placebo · Mirabegron 25 mg · Mirabegron 50 mg · Mirabegron Total

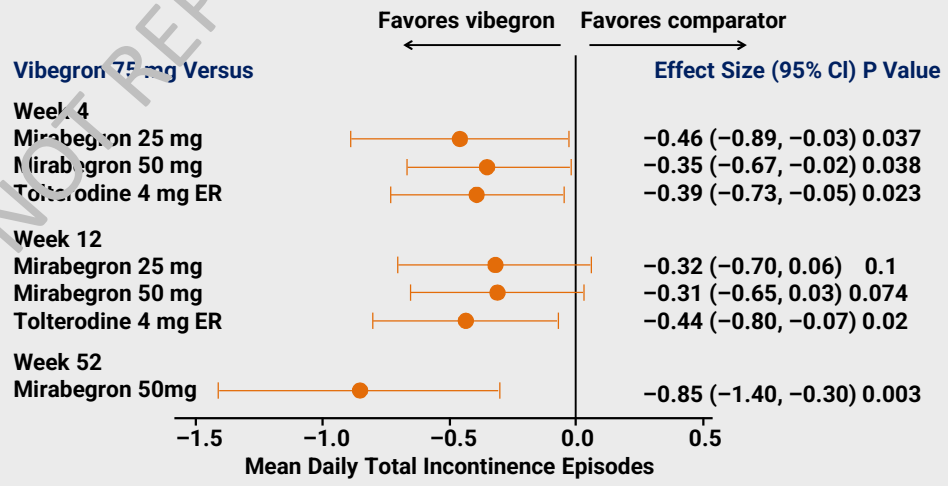
Herschorn S, et al. A Phase III, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicentre Study to Assess the Efficacy and Safety of the β3 Adrenoceptor Agonist, Mirabegron, in Patients With Symptoms of Overactive Bladder – ScienceDirect *Urology.* Volume 82, Issue 2, August 2013, Pages 313-320
Abrams P, et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder: efficacy and safety results from a randomised, double-blind, dose-ranging, phase 2 study (Symphony). *Eur Urol.* 2015 Mar;67(3):577-88.
Wagg A, et al. Efficacy, safety, and tolerability of mirabegron in patients aged ≥65yr with overactive bladder wet: a phase IV, double-blind, randomised, placebo-controlled study (PILLAR). *Eur Urol* . 2020 Feb;77(2):211-220.

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Vibegron Indirect Comparison to Mirabegron

No direct head-to-head analysis

Indirect comparison show greater decrease in total incontinence episodes w/ Vibegron[32]



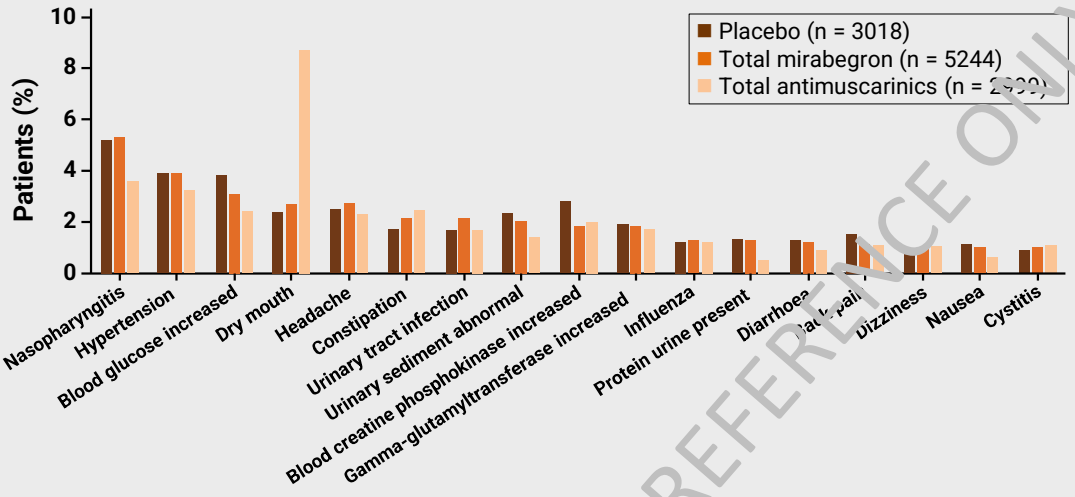
Kennelly MJ, et al. Efficacy of Vibegron and Mirabegron for Overactive Bladder: A Systematic Literature Review and Indirect Treatment Comparison. *Adv Ther.* 2021 Sep 18;38(11):5452–5464.

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DO NOT REPRODUCE – FOR REFERENCE ONLY

Mirabegron: Post Approval Safety Data

Common TEAEs (Frequency ≥ 1%)



TEAE = trreatment-emergent adverse event.

Reprinted with permission from Chapple CR, et al. *Eur Urol.* 2020;77(1):119-128. © 2020 .

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Vibegron: Adverse Events (total population)

Adverse Event by Preferred Term	Number of Patients (%)		
	Placebo	Vibegron	Tolterodine
Urinary tract infection	33 (6.1)	27 (5.0)	25 (5.8)
Headache	13 (2.4)	22 (4.0)	11 (2.6)
Nasopharyngitis	9 (1.7)	15 (2.8)	11 (2.6)
Diarrhea	6 (1.1)	12 (2.2)	9 (2.1)
Nausea	6 (1.1)	12 (2.2)	5 (1.2)
Upper respiratory tract infection	4 (0.7)	11 (2.0)	2 (0.5)
Constipation	7 (1.3)	9 (1.7)	6 (1.4)
Dry mouth	5 (0.9)	9 (1.7)	28 (6.5)
Hypertension	9 (1.7)	9 (1.7)	11 (2.6)
Dizziness	6 (1.1)	5 (0.9)	4 (0.9)
BP increased	5 (0.9)	4 (0.7)	8 (1.9)
Urinary retention	2 (0.4)	3 (0.6)	3 (0.7)
Fatigue	5 (0.9)	2 (0.4)	6 (1.4)

Staskin D, et al. *J Urol.* 2020;204(2):316-324.

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DO NOT REPRODUCE – FOR REFERENCE ONLY

Similarities / Differences: (Based on Package Inserts)

	Mirabegron	Vibegron
Dosing and Administration		
Dosing: General	Titration: Start at 25 mg, ↑ to 50 mg according to efficacy/tolerability; do not chew, divide, or crush	Fixed: 75 mg; may crush, mix with apple sauce
Renal impairment	Severe: Do not exceed 25 mg ESRD: Not recommended*	Mild to severe: No adjustment ESRD: Not recommended*
Hepatic impairment	Moderate: Do not exceed 25 mg Severe: Not recommended*	Mild to moderate: No adjustment Severe: Not recommended*
Warnings/Precautions		
Drug interactions	Use with appropriate monitoring and possible dose adjustment of drugs metabolized by CYP2D6	Does not inhibit or induce CYP450 enzymes
Patients with hypertension	Periodic BP determinations recommended; not recommended if severe uncontrolled hypertension	No warnings/precautions re:BP
Angioedema	Reported on face, lips, tongue, and/or larynx	No warnings/precautions

* Not studied in this population

ESRD = end-stage renal disease.

US National Library of Medicine. Accessed September 22, 2023. https://dailymed.nlm.nih.gov/dailymed/

85

Follow Up: Patient Treated for OAB

Review the patient after 2–4 weeks

- Be prepared to titrate as studies show > 50 % will increase dose if given the option
- Be prepared to try different agent or class

Consider checking PVR to ensure volume not increasing significantly in the complex patient

- Studies on medication usage in males show safety and minimal increase in post void residual over time of follow up
- The risk of urinary retention (although low) is highest during the first 30 days of treatment

DO NOT REPRODUCE – FOR REFERENCE ONLY

Chapple CG, Rosenberg MT, Brenes FJ. *Brit J Urol.* 2009;104(7):960-7. Rosenberg MT, Staskin DR, Kaplan SA, et al. *Int J Clin Pract.* 2007;61(9):1535-1546. Martin-Merino E, et al. J Urol. 2009; 182(4):1442-8. Rosenberg M, Newman DK, Tallman CT, et al. *Cleve Clin J Med.* 2007;74(suppl 3):S21-S29. Myrbetriq™ (mirabegron) prescribing information, Astellas Pharma US, Inc. June 2012.

86

What Defines Refractory OAB?

- Failure of behavioral therapy
- Lack of efficacy with oral medications
- Lack of tolerability of medications
  - Adverse effects
  - Contraindications to use
  - Drug interaction/polypharmacy

Vasdev N, et al. *Indian J Urol.* 2010;26(2):263-9

87

Options for the Unsatisfied Patient

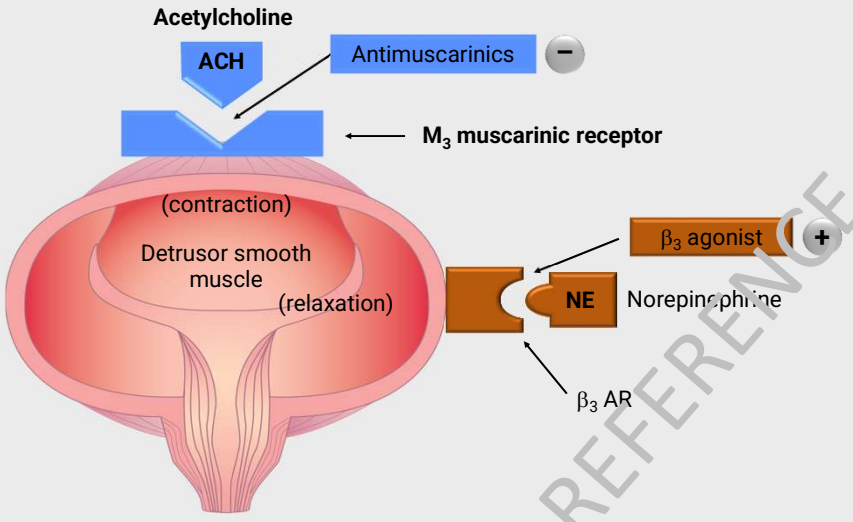
- Combination Therapy:
  - Antimuscarinic + β3-Agonist
- Percutaneous Tibial Nerve Modulation
- Sacral Nerve Stimulation
- Onabotulinum Toxin A

Gormley EA, et al. American Urological Association (AUA) Guideline. AUA Web site. 2012. http://www.auanet.org/content/media/OAB_guideline.pdf. Accessed March 21, 2014

88

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If We Have 2 Receptors Why Not Use Them?

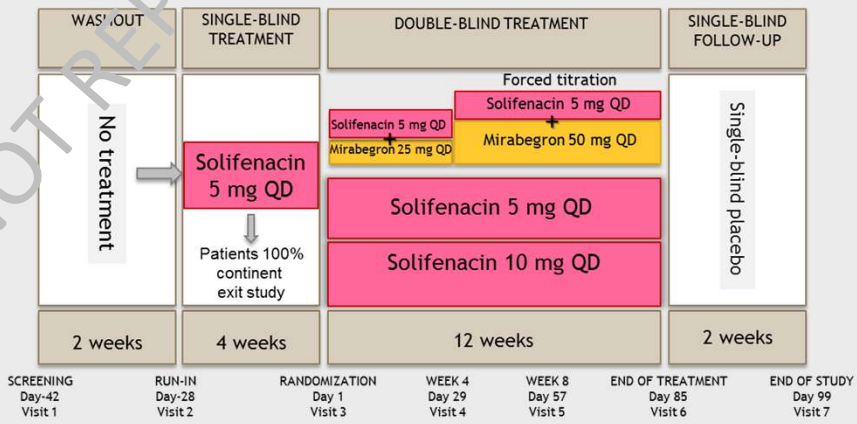


Takeda M, et al. *J Pharmacol Sci.* 2010;2110:121-127. Fowler CJ, et al. Nat Rev Neurosci. 2008;8:453-466.

89

The BESIDE Trial: A Study in Combination Therapy

Patients aged ≥18 years with OAB symptoms for ≥3 months and who remained incontinent after 4 weeks of solifenacin 5 mg daily were eligible for double-blind treatment



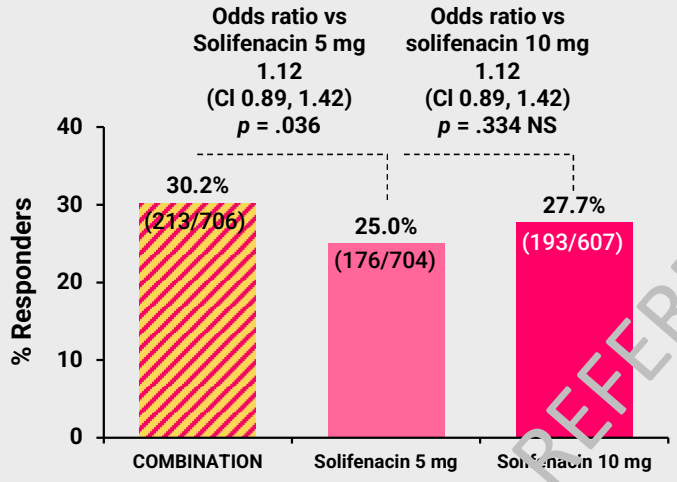
Drake MJ, Chapple C, Esen AA, et al: Efficacy and safety of mirabegron add-on therapy to solifenacin in incontinent overactive bladder patients with an inadequate response to initial 4-week solifenacin monotherapy: a randomised double-blind multicentre phase 3B study. (BESIDE) Eur Urol 2016; Published on-line March 8, 2016, DOI: 10.1016/j.eururo.2016.02.030

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DO NOT REPRODUCE – FOR REFERENCE ONLY

Efficacy in Combination Therapy

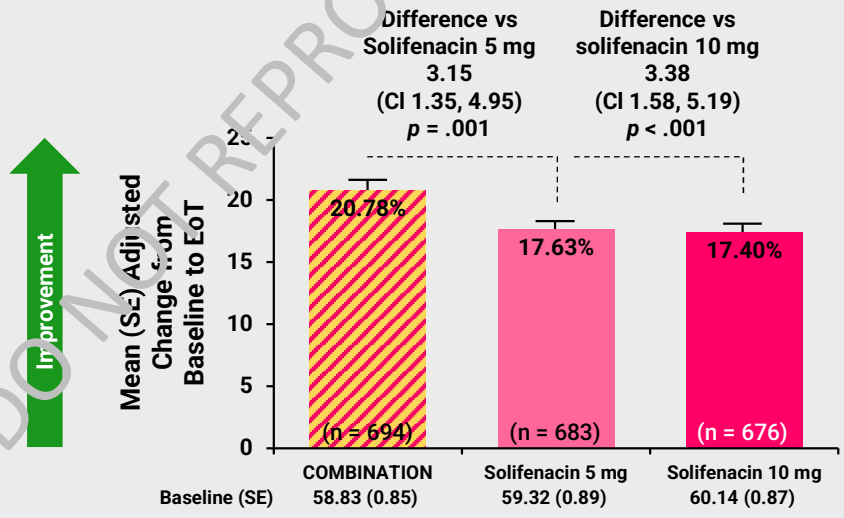
Percentage of patients achieving an average of <8 micturitions/24 h at EoT



Drake MJ, Chapple C, Esen AA, et al: 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) Eur Urol 2016; Published on-line March 8, 2016, DOI: 10.1016/j.eururo.2016.02.030

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Improvement in Health-Related Quality of Life Using Combination Therapy



Drake MJ, Chapple C, Esen AA, et al: 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) Eur Urol 2016; Published on-line March 8, 2016, DOI: 10.1016/j.eururo.2016.02.030

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Safety Results of Combination Therapy: Incidence and Frequency of TEAEs*

	Solifenacin 5 mg (n=728)	COMBINATION (n=725)	Solifenacin 10 mg (n=719)
TEAEs, n (%)			
Any TEAE	241 (33.1)	260 (35.9)	283 (39.4)
Any drug-related TEAE	125 (17.2)	141 (19.4)	161 (22.4)
Any TEAE leading to death	0	0	0
Any serious TEAE	10 (1.4)	13 (1.8)	15 (2.1)
Any TEAE leading to withdrawal	11 (1.5)	11 (1.5)	11 (1.5)
Common TEAEs* occurring in ≥2% of patients in any treatment group, n (%)			
Dry mouth	41 (5.6)	43 (5.9)	68 (9.5)
Constipation	22 (3.0)	33 (4.6)	34 (4.7)
Oedema peripheral	16 (2.2)	6 (0.8)	2 (0.3)

*TEAEs = treatment-emergent adverse events.

Drake MJ, Chapple C, Esen AA, et al: 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) Eur Urol 2016; Published on-line March 8, 2016, DOI: 10.1016/j.eururo.2016.02.030

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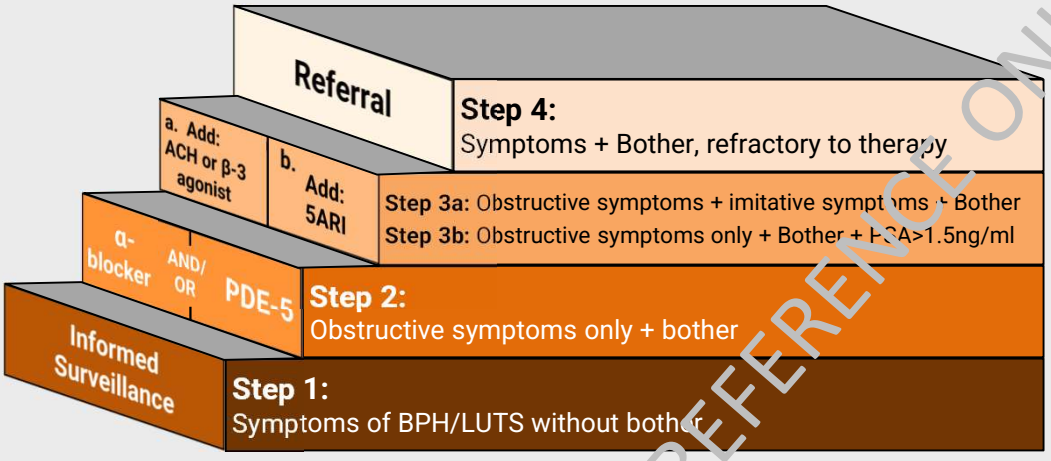
FOR REFERENCE ONLY

Pharmacological Treatment for BPH

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For the Patient with BPH

The Next STEP

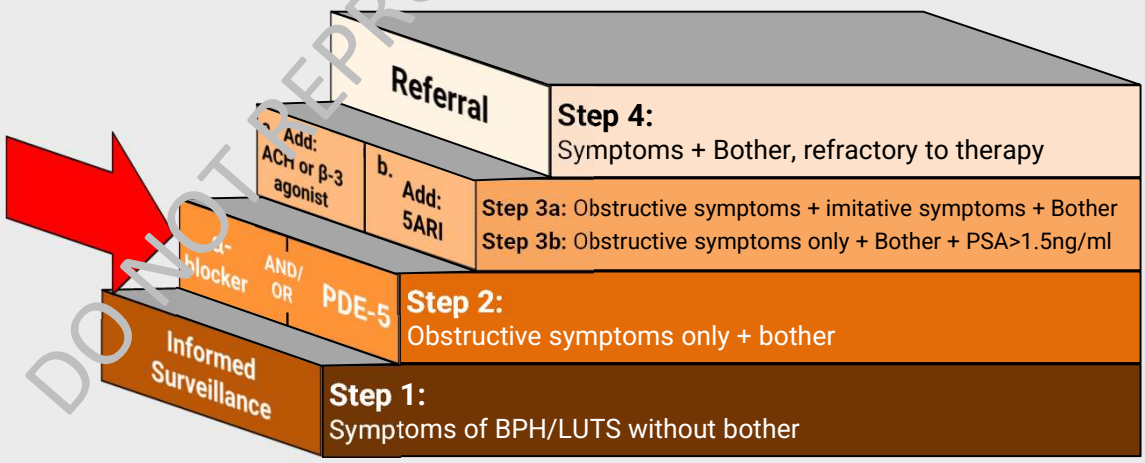


Rosenberg MT, et al. *Current Urology Reports*. 2013 Dec;14(6).

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The Next STEP:

STEP 2

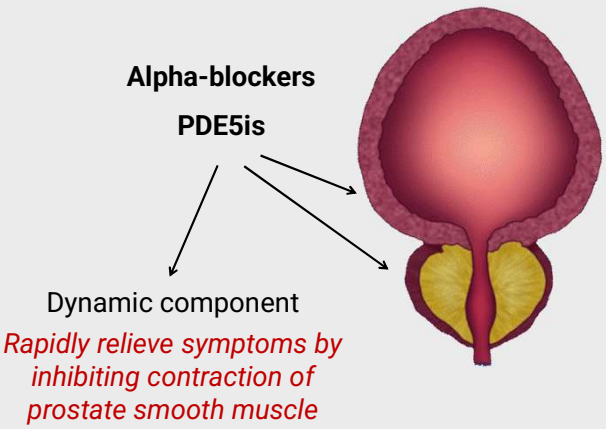


Rosenberg MT, et al. *Current Urology Reports*. 2013 Dec;14(6).

96

DO NOT REPRODUCE – FOR REFERENCE ONLY

Rationale for Alpha-Blocker or PDE5i Therapy



Rosenberg MT, et al. *Int J Clin Pract*. 2010; 64(4):488-496. Rosenberg MT, et al. *Current Urology Reports*. 2013 Dec;14(6). Roehrborn CG. *Rev Urol*. 2009;11(Suppl 1):S1-8 Rosenberg MT, et al. *Current Urology Reports*. 2013 Dec;14(6).

97

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Alpha Blockers (AB)

Single medication therapy with an AB is appropriate for the symptomatic patient who has identified bother and has a PSA of < 1.5 ng/mL

- Generally fast acting, relieving symptoms within days
- Does not affect progression of prostate growth

Rosenberg MT, et al. *Int J Clin Pract*. 2010; 64(4):488-496.

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DO NOT REPRODUCE – FOR REFERENCE ONLY

Alpha – Blockers

Non - Uroselective	Uroselective
Terazosin 1, 2, 5, 10 mg daily	Tamsulosin 0.4 mg daily
Doxazosin 1, ,2, 4, 8 mg daily	Alfuzosin 10 mg daily
	Silodosin 8 mg daily

Potential side effects (decreased incidence with uroselective agents)

- Asthenia, fatigue, dizziness
- Postural hypotension
- Congestion, rhinitis, cough
- Abnormal ejaculation
- Edema
- Headache

Physician's Desk Reference, 64 ed. Montvale, NJ:Thomson PDR; 2010. Lepor H. *Rev Urol*. 2007;9:181-190. Roehrborn [illegible] *Rev Urol*. 2009;11(Suppl 1):S1-8.

99

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Step2: Phosphodiesterase 5 Inhibitors(PDE5i)

Single medication therapy with a PDE5-I is appropriate for the symptomatic patient who has identified bother and has a PSA of < 1.5 ng/ml. The potential impact of this therapy on male sexual function should be considered

- It is believed that the PDE5i increase the signaling of the NO/cGMP pathway, which reduces smooth muscle tone in the lower urinary tract
- It is not believed that use of a PDE5i will reduce progression of prostate cancer growth

Roehrborn CG, et al. *J Urol*. 2008;180(4):1228-1234. Rosenberg MT, et al. *Current Urology Reports*. 2013 Dec;14(6).

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Phosphodiesterase type 5 Inhibitors

Medication	Dose	Indication
Tadalafil	2.5 mg per day	BPH
Tadalafil	5.0 mg per day	BPH and ED

Common side effects: headache, back pain, myalgia, dizziness, flushing and dyspepsia.

Contraindicated in patients who use nitrates, potassium channel openers, or non-selective 2nd generation ABs. Cardiac status must be assessed for patient risk before taking this medications.

Roehrborn CG, et al. *J Urol.* 2008;180(4):1228-1234. Oelke M, et al. *Eur Urol.* 2013;64(1):118-140. Nehra A, et al. *Mayo Clin Proc.* 2012;87(8):766-778. Cialis (product insert). Indianapolis, IN; Eli Lilly and Company, 2011.

101

What About PDE5is and ABs?

Studies show benefit of PDE5i/AB combination therapy over AB monotherapy

- Improvement in IPSS
- No added benefit in urodynamic parameters

Concerns over hemodynamics effects of combination therapy not demonstrated

Bechara A, et al. *J Sex Med.* 2008;5:2170–2178. Giuliano F, et al. *Urology.* 2006;67:1199–1204. Liguori G, et al. *J Sex Med.* 2009;6:544–552. Kaplan SA, et al. *Eur Urol.* 2007;51:1717–1723. Gacci M, et al. Eur Urol. 2012;61(5):994-1003.

102

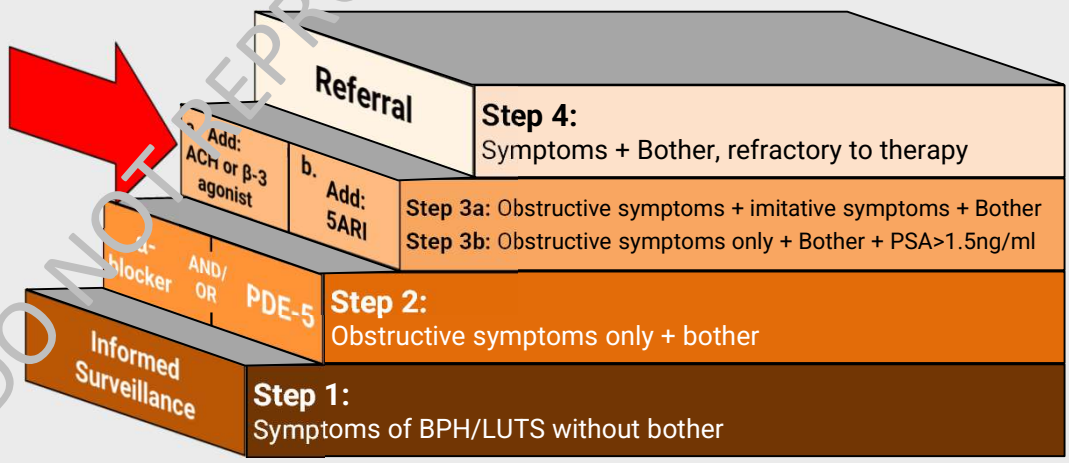
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Pharmacological Treatment for OAB and BPH

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The Next STEP:

STEP 3a

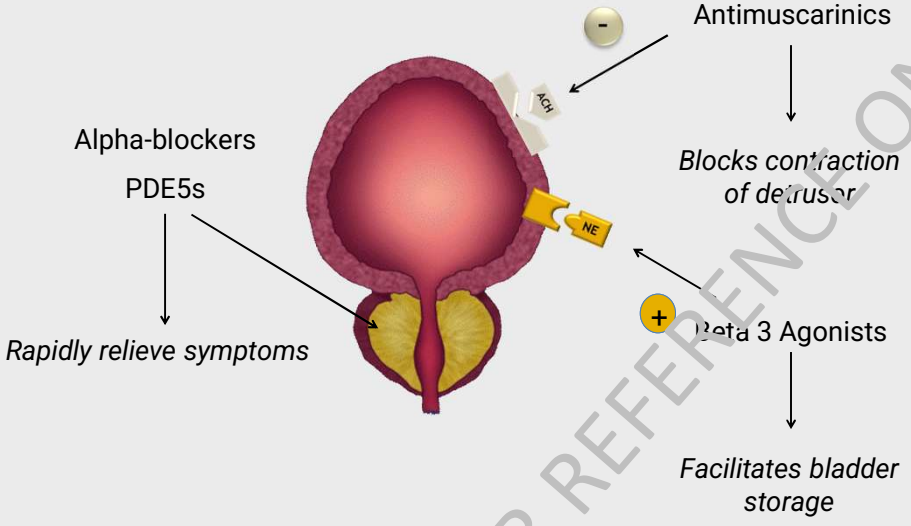


Rosenberg MT, et al. *Current Urology Reports*. 2013 Dec;14(6).

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Rationale for Combining AB/PDE5i with Antimuscarinic/Beta - 3



Rosenberg MT, et al. *Int J Clin Pract*. 2010; 64(4):488-496. Rosenberg MT, et al. *Current Urology Reports*. 2013 D[illegible].

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DO NOT REPRODUCE – FOR REFERENCE ONLY

Voiding Dysfunction

Efficacy and Safety of Mirabegron versus Placebo Add-On Therapy in Men with Overactive Bladder Symptoms Receiving Tamsulosin for Underlying Benign Prostatic Hyperplasia: A Randomized, Phase 4 Study (PLUS)

Steven A. Kaplan,*,† Sender Herschorn,‡ Kevin T. McVary,§ David Staskin,‖ Christopher Chapple,¶ Steve Foley,# Javier Cambronero Santos,** Rita M. Kristy,† Nurul Choudhury,† John Hairston† and Carol R. Schermer†

THE JOURNAL OF UROLOGY® 2020 by AMERICAN UROLOGICAL ASSOCIATION
Vol. 203, 1163-1171, June 2020

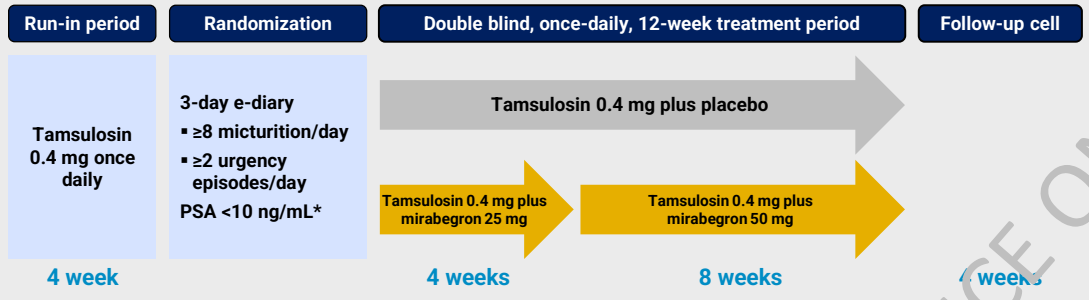
Efficacy and Safety of Vibegron for Persistent Symptoms of Overactive Bladder in Men Being Pharmacologically Treated for Benign Prostatic Hyperplasia: Results From the Phase 3 Randomized Controlled COURAGE Trial

David Staskin, Janet Owens-Grillo, Elizabeth Thomas, et al.

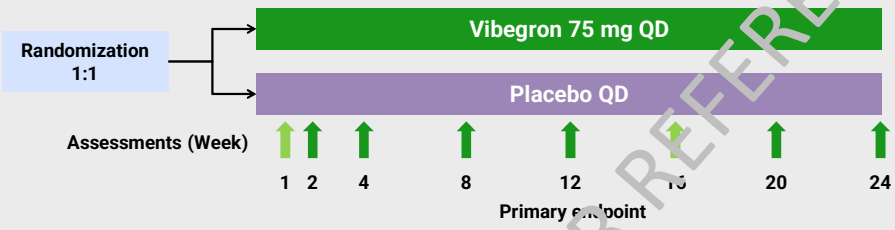
THE JOURNAL OF UROLOGY® 2024 by AMERICAN UROLOGICAL ASSOICIATION
Vol. 212, 256-266, August 2024

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"PLUS" STUDY: MIRABEGRON a Beta-3 agonist



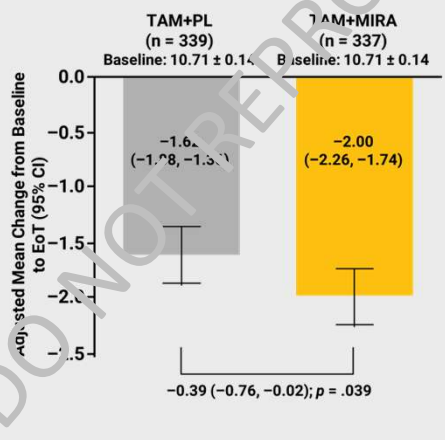
"COURAGE" STUDY VIBEGRON beta-3 (NCT03902080)



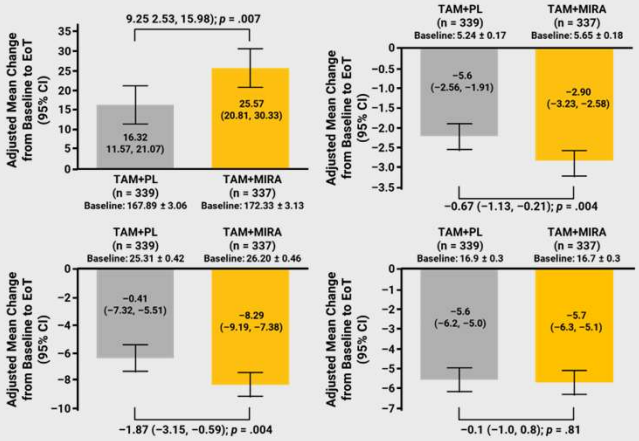
PSA = prostate-specific antigen. Kaplan SA, et al. *J Urol*. 2020;203(6):1163-1171.

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Efficacy and Safety of Mirabegron vs Placebo Add-On Therapy in Men With Overactive Bladder Symptoms Receiving Tamsulosin for Underlying Benign Prostatic Hyperplasia: A Randomized, Phase 4 Study (PLUS)



Primary endpoint of change from baseline to end of treatment (EoT) in mean number of micturitions per day..



Key secondary endpoints of changes from baseline to EoT in mean MVV per micturition (a), mean number of urgency episodes per day (grade 3/4) (b), mean TUFS (c) and mean total I-PSS (d).

Kaplan SA, et al. *J Urol*. 2020;203(6):1163-1171.

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DO NOT REPRODUCE – FOR REFERENCE ONLY

Efficacy and Safety of Mirabegron vs Placebo Add-On Therapy in Men With Overactive Bladder Symptoms Receiving Tamsulosin for Underlying Benign Prostatic Hyperplasia: A Randomized, Phase 4 Study (PLUS)

Mirabegron adverse events

TEAES of Special Interest

TEAEs of special interest, n (%)	TAM + PL (N = 354)	TAM + MIRA (N = 352)
Urinary retention	4 (0.3)	6 (1.7)
Infections and infestations	2 (0.6)	2 (0.6)
Urinary tract infection enterococcal	1 (0.3)	1 (0.3)
Escherichia urinary tract infection	0	1 (0.3)
Urinary tract infection	0	1 (0.3)
Urinary tract infection bacterial	4 (0.3)	0
Investigations	3 (0.8)	1 (0.3)
Blood pressure increased	2 (0.6)	1 (0.3)
Heart rate increased	1 (0.3)	0
Cardiac disorders	2 (0.6)	1 (0.3)
Acute myocardial infarction	0	1 (0.3)
Arrhythmia	1 (0.3)	0
Cerebral infarction	0	1 (0.3)
Lacunar stroke	4 (0.3)	0
Non-APTC/MACE	1 (0.3)	0
Arrhythmia, no evidence of ischemia	1 (0.3)	0
APTC/MACE	0	0
BPO requiring surgery	0	0

TEAEs (Urodynamic)

TEAEs of special interest, n (%)	TAM + PL (N = 354)	TAM + MIRA (N = 352)
Number of overall TEAEs (%)	111 (31.4)	352
Drug related	21 (5.9)	91 (25.9)
Serious	8 (2.3)	42 (11.9)
Drug related serious	1 (0.3)	10 (2.8)
Leading to treatment discontinuation	4 (1.1)	2 (0.6)
Drug related leading to treatment discontinuation	2 (0.6)	7 (2.0)
	1 (0.3)	6 (1.7)
Number with urinary retention (%)*		6 (1.7)
# requiring catheterization (%)	0	2 (0.6)
PVR vol (mL):		
Mean baseline (SD)	30.2 (40.3)	30.6 (41.5)
Mean change to Week 12/EoT (95% CI) [N]	3.8 (−0.9, 8.4) [331]	14.7 (8.5, 21.0) [321]
Q_{max} (mL/sec):		
Mean screening (SD)	15.7 (7.9)	16.3 (15.9)
Mean change to Week 12/EoT (95% CI) [N]	0.0 (−1.1, 1.1) [319]	−18 (−3.8, 0.1) [309]

Data shown for the SAF.

*Mean + SD (range) age of patients who experienced urinary retention was 68.1 + 7.1 (57 to 74) years. Of these, 5 (85.7%) patients were White and 1 (14.3%) was Black or African American.

Kaplan SA, et al. *J Urol.* 2020;203(6):1163-1171.

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Vibegron Is Effective in Men With OAB Symptoms Receiving Pharmacologic Therapy for BPH

- Results from the phase 3 URO-901-3005 clinical study of vibegron
- 1105 men with OAB symptoms participated over 24 weeks
- Study met its coprimary end points at week 12 compared with placebo
  - Reduction in daily micturitions and urgency episodes were both statistically significant
- Secondary end points at week 12 were also met
  - Significant reduction in nocturia episodes
  - Significant reduction in UUI episodes
  - Significant improvement in International Prostate Symptom Storage score
  - Significant increase in average volume voided per micturition
- No new safety signals compared with prior OAB studies

PRNewswire. September 11, 2023. Accessed September 22, 2023. https://www.prnewswire.com/news-releases/sumitomo-pharma-announces-positive-topline-results-from-phase-3-clinical-studies-evaluating-vibegron-in-men-with-overactive-bladder-symptoms-receiving-pharmacological-therapy-for-benign-prostatic-hyperplasia-301923356.html

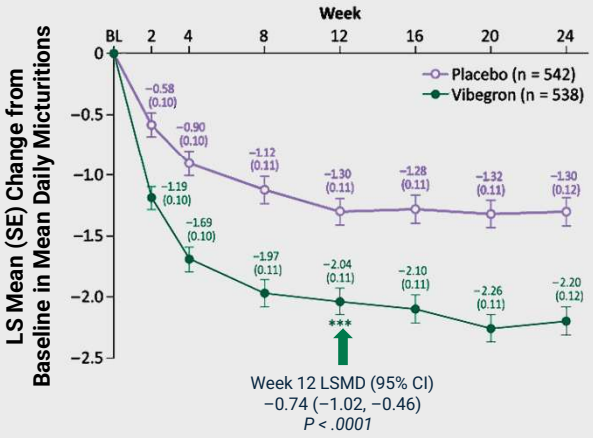
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VIBEGRON: Men with BPH (treated) and Persistent OAB

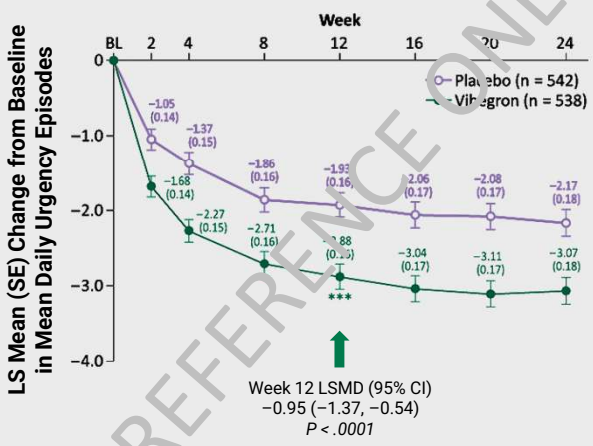
Significant Reductions in both Mean Daily Micturitions and Urgency Episodes at Week 12

Micturitions



Week 12 LSMD (95% CI)
−0.74 (−1.02, −0.46)
P < .0001

Urgency Episodes



Week 12 LSMD (95% CI)
−0.95 (−1.37, −0.54)
P < .0001

BL = baseline; LS = least squares; LSMD = LS mean difference.

Staskin D, et al.. J Urol. 2024;212(2):256-266.

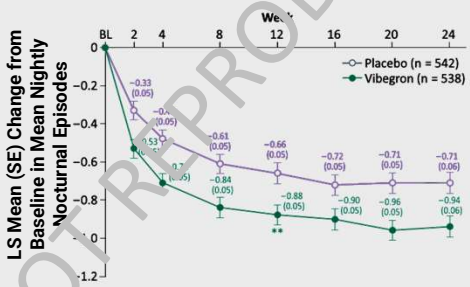
DO NOT REPRODUCE – FOR REFERENCE ONLY

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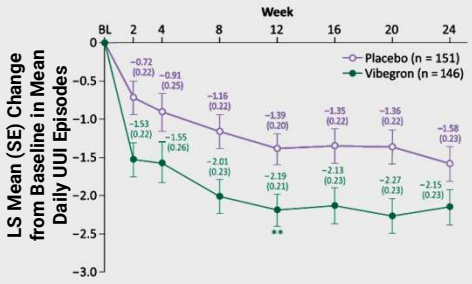
VIBEGRON: Men with BPH (treated) and Persistent OAB

Significant Improvement in Secondary Endpoints at Week 12

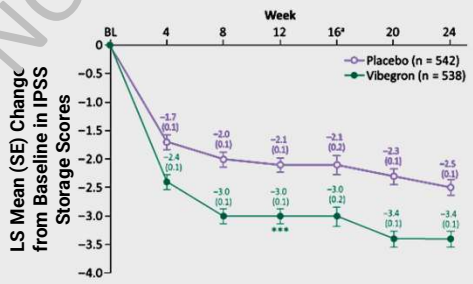
Nocturia Episodes



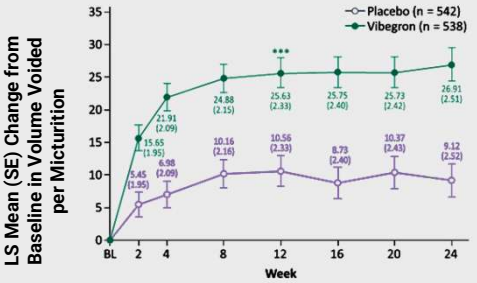
UUI Episodes



IPSS Storage Scores



Volume Voided per Micturition



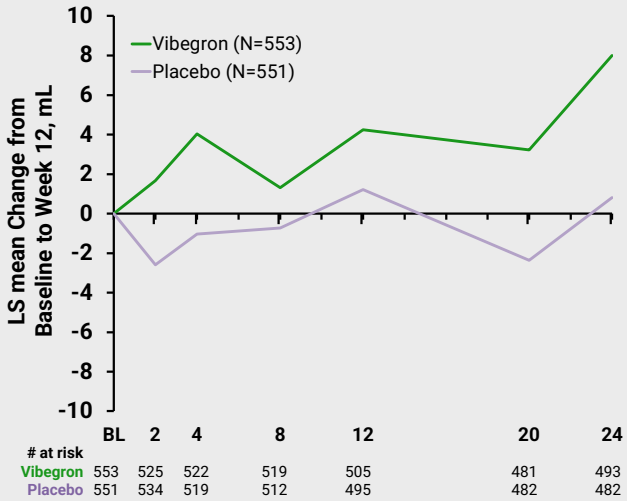
BL = baseline; IPSS = International Prostate Symptom Score; LS = least squares; LSMD = LS mean difference; UUI = urge urinary incontinence.

Staskin D, et al.. *J Urol*. 2024;212(2):256-266.

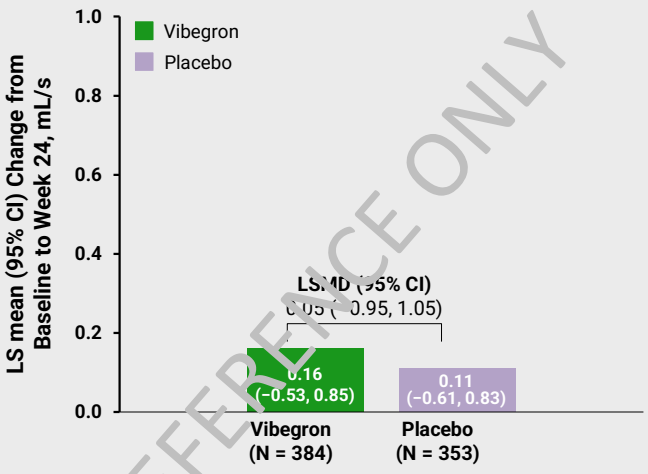
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Change From Baseline in Safety Assessments*

PVR urine volume



Peak flow rate (uroflow Q_{max})



BL = baseline; LS = least squares; LSMD = LS mean difference; PVR = postvoid residual; SAF = safety analysis set; Uroflow Qmax = maximum urinary flow rate.

*Assessed in the safety analysis set (SAF) consisting of all participants who received ≥1 dose of double-blind study medication. Significant improvements in coprimary efficacy parameters were observed by Week 2 and maintained through Week 24. Vibegron was well tolerated with a safety profile comparable to that of placebo and previously published results on vibegron (Staskin D, et al. *J Urol*. 2020;204(2):316-324).

Staskin D, et al. *J Urol*. 2024;212:256-266.

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Summary of Safety and Conclusions

Patients, n (%)	Placebo (N=551)	Vibegron (N=553)
Any TEAE	215 (39.0)	249 (45.0)
Any treatment-related TEAE	52 (9.4)	55 (9.9)
Any serious TEAE	16 (2.9)	24 (4.3)
Any treatment-related serious TEAE	0	0
Any TEAE leading to treatment discontinuation	15 (2.7)	16 (2.9)
TEAEs occurring in ≥2% of participants in any treatment arm		
Hypertension†	46 (8.3)	50 (9.0)
COVID-19‡	17 (3.1)	22 (4.0)
Urinary tract infection	12 (2.2)	14 (2.5)
Hematuria	14 (2.5)	11 (2.0)
TEAEs of special interest		
Cystitis or urinary tract infection	13 (2.4)	14 (2.5)
Urinary retention	3 (0.5)	5 (0.9)
Neoplasms	1 (0.2)	6 (1.1)
Potential major cardiac and cerebrovascular events	3 (0.5)	2 (0.4)
Elevated serum AST or ALT requiring study drug discontinuation	0	1 (0.2)
Orthostatic hypotension	0	1 (0.2)

- In the phase 3 COURAGE trial of men experiencing persistent OAB symptoms with pharmacologically treated BPH, treatment with vibegron 75 mg was associated with significant, clinically meaningful improvements in all coprimary and secondary efficacy endpoints
- Significant improvements in coprimary efficacy parameters were observed by week 2 and maintained through week 24
- Vibegron was well tolerated with a safety profile comparable to that of placebo and previously published results on vibegron (Staskin et al. *J Urol*. 2020;204(2):316-324)

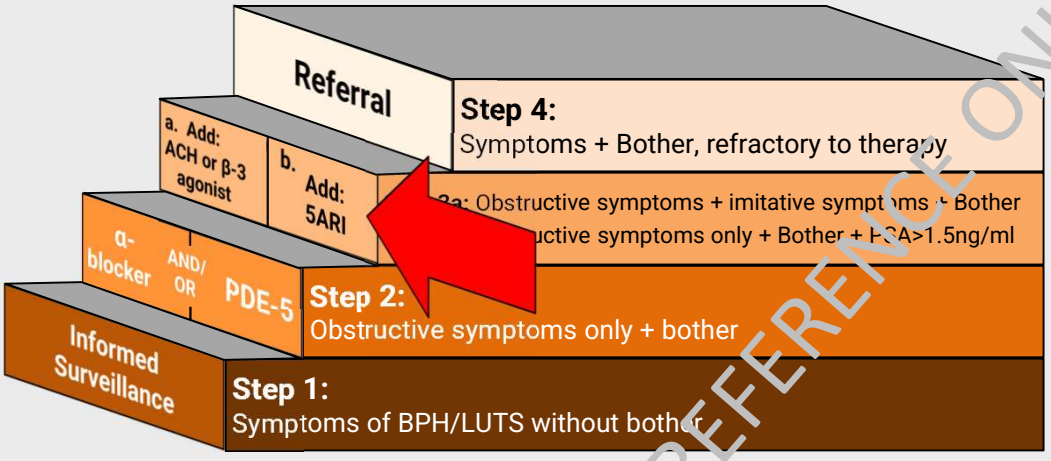
ALT = alanine transaminase; AST = aspartate aminotransferase; COVID-19 = coronavirus disease; TEAE = treatment-emergent adverse event. *Safety analysis set, consisting of all randomized patients who received ≥1 dose of double-blind study treatment; 2 patients randomized to placebo mistakenly received vibegron and were therefore analyzed in the vibegron group for the purposes of safety. †Hypertension was also analyzed as an AESI. ‡The COVID-19 global pandemic developed during the conduct of the study. There was no association between experiencing COVID-19 and taking vibegron.

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The Next STEP:

STEP 3b



Rosenberg MT, et al. *Current Urology Reports*. 2013 Dec;14(6).

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Risk Evaluation of BPH-LUTS Progression

Baseline Factors as Predictors

Five risk factors

1. Total prostate volume ≥31 mL
2. PSA ≥1.6 ng/mL
3. Age ≥62

Not usually evaluated by the PCP

1. Q_{max} <10.6 mL/s
2. PVR ≥38 mL

PVR = post-void residual; Qmax = maximum flow rate.

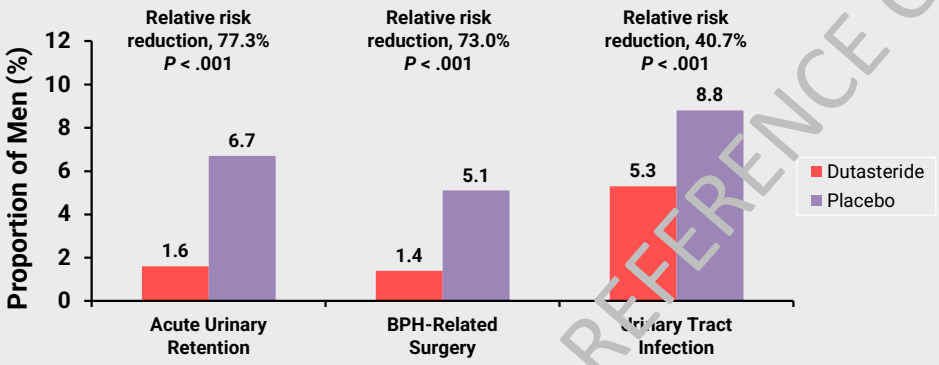
Crawford ED, et al. *Urology*. 2006;175(4):1422-1427. Rosenberg MT, et al. *Int J Clin Pract*. 2010; 64(4):488-496. Rosenberg MT, et al. *Current Urology Reports*. 2013 Dec;14(6).

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5ARIs

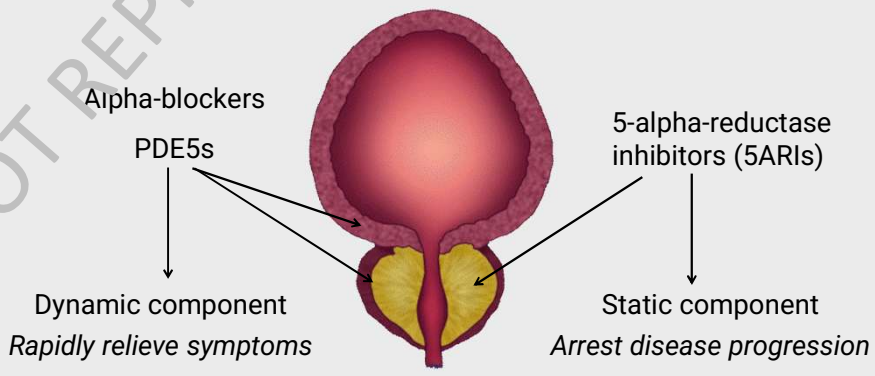
- Monotherapy – prostate > 30g or PSA > 1.5[9]
- Mono or Combination therapy – Prevent progression of BPH
- Reduced risk of urinary retention and need for BPH surgery[15,16]



Benign Prostatic Hyperplasia (BPH) Guideline - American Urological Association https://www.auanet.org/guidelines-and-quality/guidelines/benign-prostatic-hyperplasia-(bph)-guideline#x8190
McConnell JD. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. *NEJM*. 1998 Feb 26;338(9):557-63.
Andriole GL, et al. Effect of Dutasteride on the Risk of Prostate Cancer *NEJM*. 2010;362:1192-1202.

117

Rationale for Combining AB/PDE5i with 5ARI



Rosenberg MT, et al. *Int J Clin Pract*. 2010; 64(4):488-496. Rosenberg MT, et al. *Current Urology Reports*. 2013 Dec;14(6).

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Step3b: Adding a 5 Alpha Reductase Inhibitor (5ARI)

The addition of a 5ARI is appropriate for the symptomatic patient with BPH-LUTS who has identified bother and has a PSA of 1.5 ng/ml or greater

- Prostate growth may result in symptoms progression and other complications
- Prostate growth is stimulated by dihydrotestosterone (DHT) with is converted from testosterone by the 5-alpha reductase enzyme
- Decreasing DHT may induce prostatic epithelial apoptosis and atrophy which can lead to approximately 18% – 28% reduction in prostate size and approximately a 50% reduction in PSA levels after 6 - 12 months

Naslund MJ, et al. *Clin Ther*. 2007;29(1):17-25. Rosenberg MT, et al. *Int J Clin Pract*. 2010; 64(4):488-496.

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5ARIs Blocks Conversion of Testosterone to Dihydrotestosterone, Thereby Inhibiting Prostate Growth

Drug	Dosage
Finasteride	5 mg daily
Dutasteride	0.5 mg daily

Potential side effects

– Diminished ejaculatory volume
– Erectile dysfunction
– Decreased libido
– Gynecomastia
– Increase risk of high-grade prostate cancer *

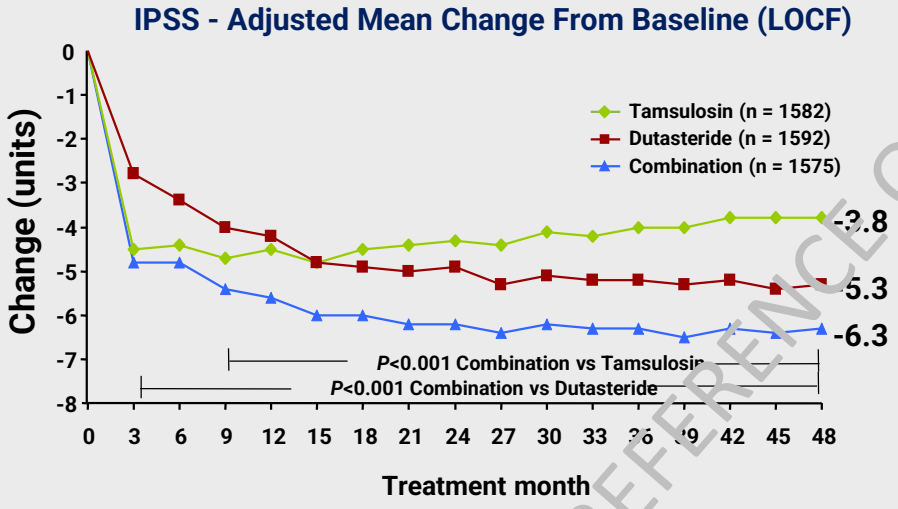
* Conflicting data in the literature

Physicians' Desk Reference. 64th ed. Montvale, NJ: Thomson PDR; 2010. Andriole G, et al. *J Urol*. 2004;172(4 Pt 1):1399-1403.Thompson, IA, et al. N Engl J Med. 2013;369(7):603-610.

120

DO NOT REPRODUCE – FOR REFERENCE ONLY

Combination Therapy of an AB with a 5 ARI Outperforms Either Monotherapy Alone

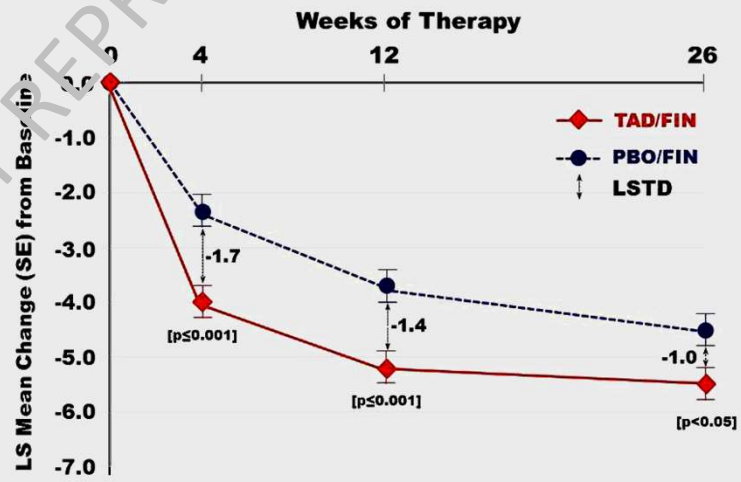


IPSS = International Prostate Symptom Score; LOCF = last observation carried forward.

Roehrborn CG, et al. *Eur Urol*. 2010;57(1):123-31

121

Combination Therapy of a PDE5i and a 5 ARI Outperforms Monotherapy with a 5 ARI



Roehrborn CG, et al. 28TH Annual EAU Congress; Milan, Italy; 15-19 March 2013

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Combination Therapy

- Starting with combination therapy may allow immediate symptom relief from the AB or a PDE51 while facilitating prostate reduction from the 5ARI
- Two prolonged studies (MTOPS and CombaT) using a AB and a 5ARI have shown that combination therapy is better than either monotherapy alone
- One 26 week study showed that use of tadalafil with finasteride was better than finasteride alone
- Expert opinion supports the long term use of combination therapy in the patient with an enlarged prostate

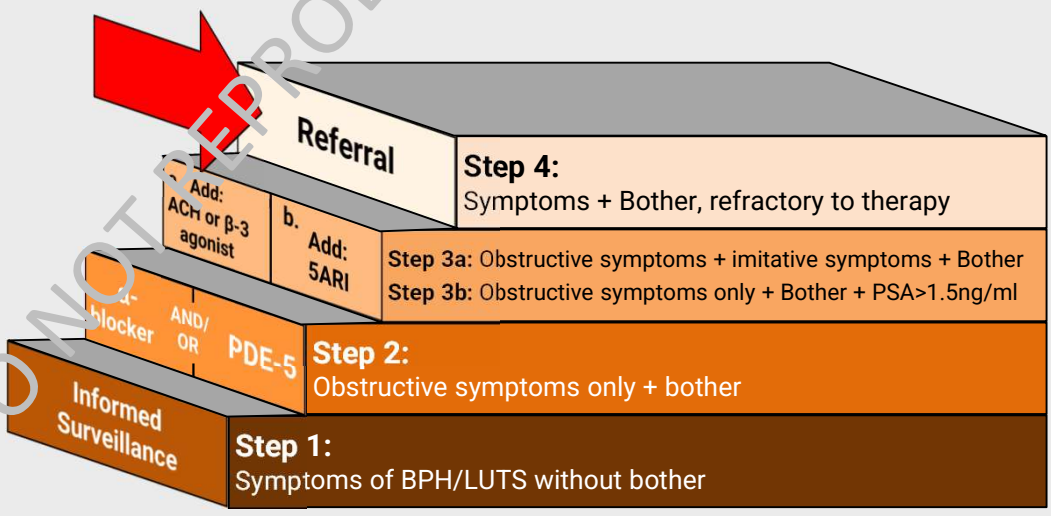
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Crawford ED, et al. *Urology.* 2006;175:1422-1427. Roehrborn CG, et al. *Eur Urol.* 2009;55(2): 461-471. Kaplan S. J *Urol.* 2006;175:217-220. Roehrborn CG, et al. 28TH Annual EAU Congress; Milan, Italy; 15-19 March 2013

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The Next STEP:

STEP 4



Rosenberg MT, et al. *Current Urology Reports*. 2013 Dec;14(6).

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Step 4: Referral

For the patient with symptoms and bother who is refractory to therapy

- "Alarm symptoms" or "red flags"
- Failure to respond in a reasonable amount of time warrants reevaluation and possible referral
  - Alpha blockers, PDE5is, antimuscarinics and β3 agonists should work quickly
  - 5 ARIs work slowly

Rosenberg MT, et al. *Int J Clin Pract.* 2010; 64(4):488-496. Rosenberg MT, et al. *Current Urology Reports*. 2013 Dec;14(6) [illegible] Pending

125

A few last thoughts



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An Unfortunate Truth

Discontinuation Rate for Pharmacologic OAB Therapy is High

- Over 80% of patients discontinue therapy after 12 months
- 0nly 9% of patients reports being "very satisfied" with current treatment plan
  a) A few top reasons for discontinuing therapy
  b) Did not work as expected
  c) Learned to get by without medication
- Side effects
- Follow up on treatment rarely occur after initial diagnosis and treatment

Song YS, et al. *J Urol*. 2021;205(6):1595-1604. Filipetto FA, et al. *BMC Fam Pract*. 2014;15:96. Chancellor MB, et al. *Clin Ther*. 2013;35(11):1744-1751. Benner JS, et al. *BJU International*. 2009;105:1276-1282.

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Tenets of Shared Decision Making

Provision of information

- Balanced and evidence based
- Harms and benefits of each option

Elicitation of patient's perspective

- Asking about prior experiences
- Understanding and discussing concerns
- Delineating preferences regarding screening options

Guiding final decision making (without directing)

Feng B, et al. *Ann Fam Med*. 2013 Jul-Aug;11(4):315-23.

128

DO NOT REPRODUCE – FOR REFERENCE ONLY



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Brian's Journey

Detailed History

- Reasonable flow
- Urgency, frequency, and nocturia
- Physical exam labs normal

What should we do next?

- Specialist
- TURP
- Bladder log
- Start an anti-muscarinic
- Start a beta-3 agonist
- Consider a 5 ARI

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Next Steps

Bladder Log

Time	Volume
9:00 am	80mL
11:00 am	90mL
1:30 pm	50mL
3:45 pm	70mL
6:15 pm	60mL
7:40 pm	80mL
9:20 pm	70mL

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What Would You Do Next?

- Specialist
- TURP
- Start an anti-muscarinic
- Bladder log
- Start a beta-3 agonist
- Consider a 5 ARI

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Take Home Message/Conclusion

- BPH/OAB doesn't take your life — it steals it from you
- The untreated 85% is in the PCP office
- LUTS can be diagnosed efficiently by the PCP
- The armamentarium of treatment options for primary care is extensive
  - Behavioral therapy
  - PDE-5's, alpha blockers, 5 ARI's
  - antimuscarinics and/or β3-agonists
- More extensive options are available for the specialist

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We Will Now Watch a Whiteboard Animation

https://youtu.be/JIWM99XFzcM

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Thank you!

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DO NOT REPRODUCE – FO

Enhancing Diagnostic Pathways and Personalized Care for BPH and OAB in the Primary Care Setting

Toolkit

Resource	Address
A Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002;21(2):167-178. doi: 10.1002/nau.10052	https://pubmed.ncbi.nlm.nih.gov/11857671/
Abrams P, Kelleher C, Staskin D, et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder: efficacy and safety results from a randomised, double-blind, dose-ranging, phase 2 study (Symphony). *Eur Urol*. 2015;67(3):577-588. doi: 10.1016/j.eururo.2014.02.012	https://pubmed.ncbi.nlm.nih.gov/24612659/
Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. *Physiol Rev*. 2004;84(3):935-986. doi: 10.1152/physrev.00038.2003.	https://pubmed.ncbi.nlm.nih.gov/15269341/
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Barry M. MDCalc. American Urological Association Symptom Index (AUA-SI)/International Prostate Symptom Score (IPSS)	https://www.mdcalc.com/calc/10462/american-urological-association-symptom-index-aua-si
Benner JS, Nichol MB, Rovner ES, et al. Patient-reported reasons for discontinuing overactive bladder medication. *BJU Int.* 2010;105(9):1276-1282. doi: 10.1111/j.1464-410X.2009.09036.x	https://pubmed.ncbi.nlm.nih.gov/19912188/
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Cialis (product insert). Indianapolis, IN; Eli Lilly and Company, 2011.	https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021368s20s21lbl.pdf

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