OAB Practice Case 1

Epidemiology, Screening, and Diagnosis

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Dr. Shenot is a principal investigator on many ongoing clinical trials involving genitourinary disorders. He has written numerous book chapters and peer-reviewed publications. His research focuses on the treatment of lower urinary tract dysfunction, particularly bladder augmentation, and both electrical and pharmacologic neuromodulation.

He has been recognized in Castle Connolly's " America's Top Doctors" Best Doctors in America®,the Consumers' Research Council of America "Guide to America's Top Surgeons", as well as Philadelphia Magazine's "Top Doctors" list. He has made over 70 presentations at national and international conferences and has been the recipient of awards for excellence in research from the American Spinal Injury Association.

Patient Case
Complaint and Evaluation

- A 53-year-old woman with urinary frequency every 1 to 2 hours, nocturia at least 1–2 times per night
- Worst symptom is strong urinary urgency, often with incontinence episodes

- **Medical History**
  - Hypertension treated with a beta blocker
  - Hypercholesterolemia treated with a statin
  - Overweight (BMI = 29 kg/m^2)
- **Physical Exam and Labs**
  - No abnormalities
  - Urinalysis normal

Audience Question

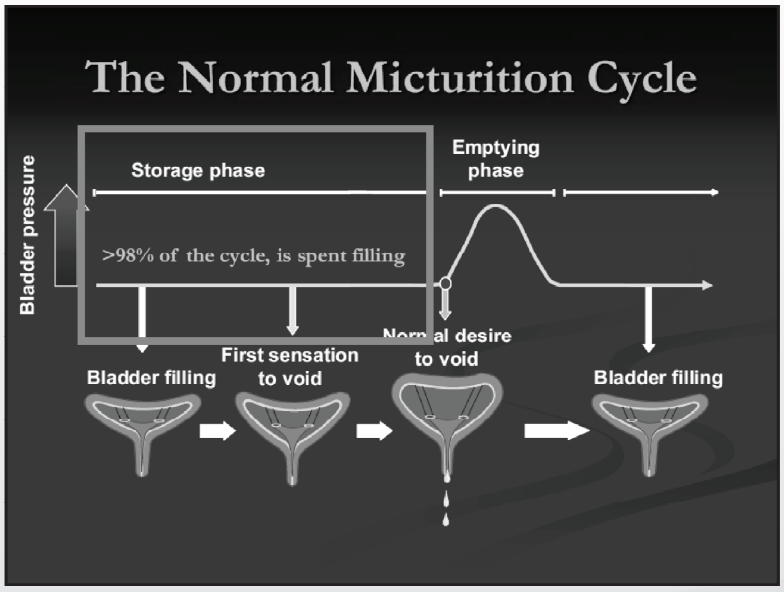
What is your next step for this patient?

1. Urodynamics
2. Cystoscopy
3. Post-void residual evaluation
4. Dietary modification
5. Behavioral therapy
6. Antimuscarinics

Defining Overactive Bladder

- Overactive bladder (OAB) is defined as: "urgency, with or without urge incontinence (UI), usually with frequency and nocturia" in the absence of pathologic or metabolic factors that would explain these symptoms
- Where:
  - Frequency = voiding too often
  - Urgency = sudden compelling desire to pass urine which is difficult to defer
  - Urge incontinence = involuntary urine leakage accompanied by or immediately preceded by urgency which represents a hygiene or social problem
  - Nocturia = wake at night one or more times to void
- Often divided into neurogenic and idiopathic
- Can be wet (with UI) or dry (without UI)

Abrams P, et al. *Urology*. 2003;61:37-49.

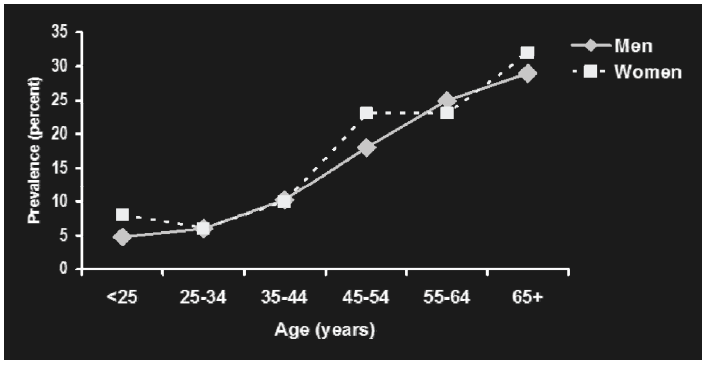


Overactive Bladder

- Large prevalence study for OAB (United States)
  - November 2000–January 2001
  - 17,231 households contacted
  - 5,204 completed interviews
- Conclusions
  - Over 33 million OAB sufferers (16.6% of population)
  - 63% OAB dry; 37% OAB wet
  - OAB significantly impairs health-related quality of life, even in those without urge incontinence

Stewart WF, et al. *World J Urol.* 2003;20:327-336.

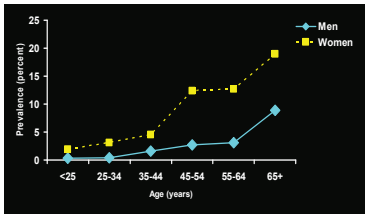
Prevalence of OAB (US)



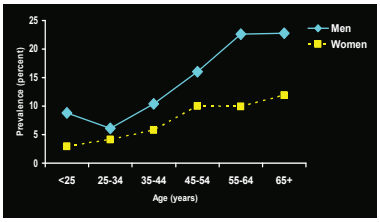
Stewart WF, et al. *World J Urol.* 2003;20:327-336.

Prevalence of OAB With and Without Incontinence (US)

Overall prevalence of wet OAB (with incontinence)
Men: 2.4% Women: 9.3%



Overall prevalence of dry OAB (without incontinence)
Men: 13.6% Women: 7.6%



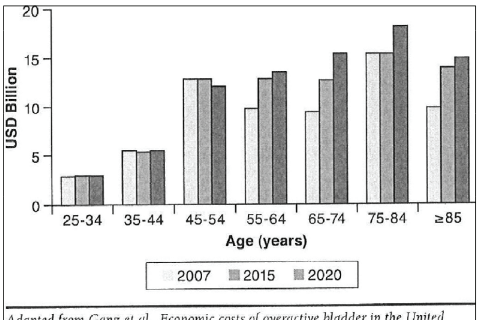
Stewart WF, et al. *World J Urol.* 2003;20:327-336.

Burden of Overactive Bladder

- **Direct Costs**
  - Treatment, routine care (including incontinence pads) and OAB-associated comorbidities/complications
- **Indirect Costs**
  - Lost wages by patients and caregivers and lost work productivity
- Intangible Costs
  - Pain, suffering, and decreased health-related quality of life

Coyne K, et. al. *J Manag Care Pharm.* 2014;20:130-40.

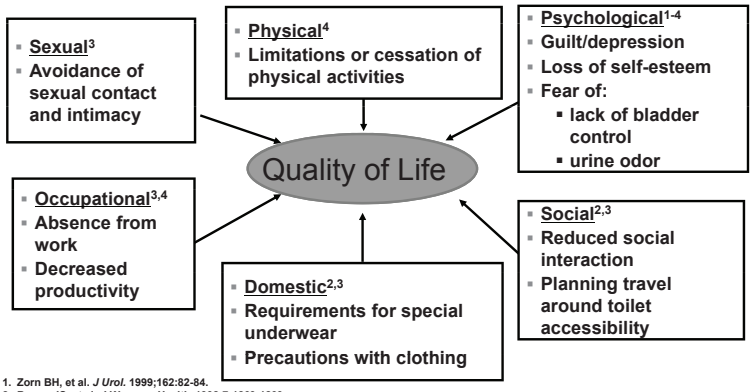
Economic Burden of Urge Urinary Incontinence



Adapted from Ganz et al., Economic costs of overactive bladder in the United States.[20]
USD = U.S. dollars; UUI = urgency urinary incontinence.

Coyne K, et. al. *J Manag Care Pharm.* 2014;20:130-40.

Overactive Bladder: Quality of Life Issues



1. Zorn BH, et al. *J Urol.* 1999;162:82-84.
2. Brown JS, et al. *J Womens Health.* 1998;7:1263-1269.
3. Abrams P, et al. *Am J Manag Care.* 2000;6(suppl):S580-S590.
4. McGhan WF. *Am J Manag Care.* 2001;7:S62-S75.

Voiding Dysfunction

	STORAGE	EMPTYING
BLADDER	Overactive Urgency, urge incontinence	Underactive Retention
OUTLET	Inadequate resistance Stress incontinence	Obstruction Retention

Wein AJ, Barrett DM (1988). *Voiding Function and Dysfunction: A Logical and Practical Approach.* Chicago: Year Book Medical Publishers, Inc.

Types of Urinary Incontinence (UI)

Type	Symptoms	Most Common Cause
Urge (UUI)	Involuntary leakage with urgency	Detrusor overactivity
Stress (SUI)	Involuntary leakage with exertion	Urethral hypermobility; intrinsic sphincter deficiency
Mixed (MUI)	Combination of stress and urge symptoms	Combination

Initiating the Conversation

- Don't assume patient will mention OAB symptoms
- Begin with open-ended questions:
  - *"Do you have any problems with your bladder?"*
- If "no," become specific:
  - "*Do you ever leak urine when you have a strong urge on the way to the bathroom? How often?"*
  - *"How many times do you urinate during the day or night?"*
  - *"Does this problem inhibit any activity or prevent you from doing things you like to do?"*

Diagnostic Guidelines

- Thorough history, physical examination, and urinalysis should be done initially
- If necessary, a urine culture, or postvoid residual assessment, or both can be done, along with use of bladder diaries or symptom questionnaires
- Urodynamic study, cystoscopy, and renal and bladder ultrasonography are not necessary in the initial workup of uncomplicated cases
- Urine cytology is not recommended in the absence of hematuria when the patient responds to therapy

Gormley EA et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. J Urol. 2012/12;188(6 suppl):2455-63.
AUA/SUFU. Available at: https://www.auanet.org/education/guidelines/overactive-bladder.cfm. Amended 2014.

The Physical Exam

- Neurological
- Mental Status
- Weight
- Abdominal
- Genitalia
- Rectal Exam

Differential Diagnosis

Exclude Reversible Causes

- **D** elirium
- **I** nfection
- **A** trophic vaginitis
- **P** harmaceuticals
- **P** sychological problems
- **E** xcessive urination
- **R** estricted mobility
- **S** tool impaction

Also consider urinary stone disease, gastrointestinal (GI) or colonic pathology, gynecologic pathology

Exclude Overflow

Measure Post-Void Residual Urine

- Patient empties bladder
- Catheter or ultrasound to measure PVR
- Patients w/overflow need urodynamic testing and catheter drainage

Summary - Diagnostic Plan for UI/OAB

- Use history to decide on urge vs. stress
- Exclude reversible causes and complicating factors
- Exclude overflow
- Treat

Audience Question

Overactive bladder (OAB) is best characterized as :

1. A condition characterized by frequent urination that is not association with patient age.
2. A symptom syndrome suggestive of lower urinary tract dysfunction, specifically urgency, with or without urge incontinence, usually with frequency and nocturia
3. A syndrome characterized by urge incontinence that is more common in female patients.
4. A symptom complex associated equally with both storage and emptying symptoms

Discussion

The International Continence Society defines OAB as a symptom syndrome suggestive of lower urinary tract dysfunction, specifically urgency, with or without urge incontinence, usually with frequency and nocturia. OAB, thus, is define by the predominance of storage symptoms. OAB is a common condition and may occur in up to 16% of the population. Urge incontinence in association with OAB is the second most common cause of urinary incontinence in women. The incidence increases with age such that urge incontinence in association with OAB is the most common cause of incontinence in the elderly and is equally prevalent in men and women.

Back to the Case

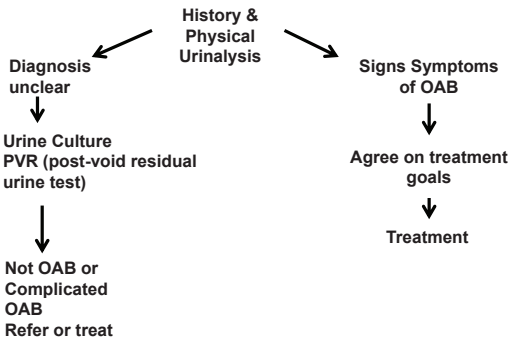
What measures are appropriate as part of a basic diagnostic evaluation of a patient with suspected overactive bladder?

1. Urodynamics
2. Cystoscopy
3. Urine cytology
4. Post-void residual evaluation
5. All of the above

Discussion

Basic evaluation of overactive bladder includes a history, physical examination, and urinalysis. Specialized studies do have a place in the non-responders and complex presentations.

Diagnosis and Evaluation of OAB



PVR, post-void residual urine test
Adapted from: Gormley EA, et al. *J Urol.* 2012;188:2455-63.

Summary

- Overactive bladder is a highly prevalent condition
- Patients will not always volunteer information
- Diagnosis is often simple and can be performed in the physician's office using a straight-forward simple diagnostic algorithm

OAB Practice Case 2
Initiating Treatment

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Dr. Mickey Karram, MD, is the Director of Urogynecology and Reconstructive Surgery at The Christ Hospital in Cincinnati, OH and the Medical Director of The Christ Hospital Pelvic Floor Center. He also serves as a Clinical Professor of Obstetrics and Gynecology at the University of Cincinnati School of Medicine. He is past-chairman of the board of the American Urogynecology Society Foundation, past-president of the American Urogynecology Society, and co-founder and president of the Foundation for Female Health Awareness. Dr. Karram is Board Certified in Obstetrics and Gynecology and completed his fellowship training in Urogynecology and Reconstructive Surgery at Harbor UCLA School of Medicine.

Dr. Karram is Editor-In-Chief of the *International Urogynecology Journal* and the consumer publication *Women's Health Today.* He has published more than 200 scientific articles and book chapters and has co-authored numerous medical textbooks including "Urogynecology and Reconstructive Pelvic Surgery," published by Mosby, the "Atlas of Pelvic Anatomy and Gynecologic Surgery," published by Saunders, and "The Pelvic Surgery Video Atlas," published by Elsevier. Dr. Karram has directed a number of postgraduate teaching courses throughout the United States and abroad. He has been invited to lecture and perform live surgeries throughout the United States, Europe, Asia, South America, and Australia. Dr. Karram has been designated by *Good Housekeeping Magazine* as one of the "Best Doctors in America for Women."

Learning Objectives

After this presentation, the clinician will be better able to:

- Describe the 2014 AUA/SUFU recommendations for behavioral and pharmacologic management of overactive bladder
- Compare the benefits and limitations of currently available therapies
- Discuss how best to initiate behavioral therapy, pelvic floor rehabilitation and role of local hormone therapy
- Discuss how best to select the most appropriate pharmacologic agent
- Review side effect profiles for antimuscarinic agents and review issues of non-adherence
- Discuss new drug class (β3-agonist)
- How best to set patient specific goals and expectations

Patient Case

58-year-old female with OAB
- 3–4 years of increasing frequency, urgency
  - "Just makes it to bathroom"
  - No pain, GU Hx or surgery, GH, dysuria, or UTI
  - Nocturia x 2, no Nocturnal Enuresis
- Medical History: borderline HTN, mild obesity (BMI=30 kg/m^2)
- Surgical History: Total Abdominal Hysterectomy for fibroids
- Gravida 2 Para 2

- Physical examination
  - Mild atrophic vaginitis
  - No significant Pelvic Organ Prolapse
  - No Stress Urinary Incontinence
  - Rectal tone WNL
  - Anal wink +
- Urinalysis is negative
- Behavioral therapy is initiated

UTI, urinary tract infection; WNL, within normal limits

AUA Guideline Statement: Treatment

"No treatment" is an acceptable choice made by some patients and caregivers." ***(Expert Opinion)***

First-line treatments:

1. Behavioral therapies *(Standard)*
   - Bladder training
   - Bladder control strategies
   - Pelvic floor muscle training
   - Fluid management


DIAGNOSIS AND TREATMENT OF OVERACTIVE BLADDER (Non-Neurogenic) IN ADULTS: AUA/SUFU GUIDELINE

E. Ann Gormley, Deborah J. Lightner, Kathryn L. Burgio, Toby C. Chai, J. Quentin Clemens, Daniel J. Culkin, Anurag Kumar Das, Harris Emilio Foster, Jr., Harriette Miles Scarpero, Christopher D. Tessier, Sandip Prasan Vasavada

2. Behavioral therapies may be combined with pharmacologic therapy (*Recommendation)*

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

Key Clinical Questions

- What exactly is your regimen for behavioral therapy? What are the components? Who administers it? When do they see you back in the office?
- In your experience, what is the success rate with behavioral therapy?
- What, if any, is the role of HRT in this patient?

Key Clinical Questions (cont.)

- What are bladder storage strategies?
- What is the role for pelvic floor muscle rehabilitation?
- Do your patients know how to appropriately perform Kegel exercises?

Audience Question

Your patient, who originally initiated behavioral therapy, now returns and wants drug therapy.
Your agent of choice (regardless of cost) is:

1. Oxybutynin
2. Tolterodine
3. Solifenacin
4. Darifenacin
5. Trospium
6. Mirabegron

AUA Guideline Statement: Second-line Treatment

1. **Oral antimuscarinics *(standard)***
   - tolterodine
   - fesoterodine
   - darifenacin
   - oxybutynin
   - solifenacin
   - trospium

   No hierarchy or preference

2. **β3-Agonist**
   - Mirabegron

3. **ER formulations preferred over IR formulations**
   - Lower rates of dry mouth. (Standard)

Audience Question

The patient returns with effective relief of OAB but has bothersome constipation on the lowest dose of a once-daily antimuscarinic. The next step is:

1. Discontinue medication and discuss PTNS
2. Discontinue medication, initiate intensive behavioral modification
3. Change to qod dosing
4. Change to a different antimuscarinic
5. Manage the constipation

PTNS, peripheral tibial nerve stimulation

AUA Guideline Statement: Treatment

- **Manage constipation and dry mouth before abandoning effective antimuscarinic therapy *(clinical principle)***
  - bowel management
  - fluid management
  - dose modification
  - alternative antimuscarinic

  (Clinical principle)
- **If refractory to behavioral and medical therapy:**
  - Refer to specialist if desires additional therapy

    (*Expert Opinion*)


DIAGNOSIS AND TREATMENT OF OVERACTIVE BLADDER (Non-Neurogenic) IN ADULTS: AUA/SUFU GUIDELINE

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

Audience Question

One month later your patient returns to the office and reports a great response to the medication and no further constipation. She is better and wants to stop the medication. You counsel her that she will require:

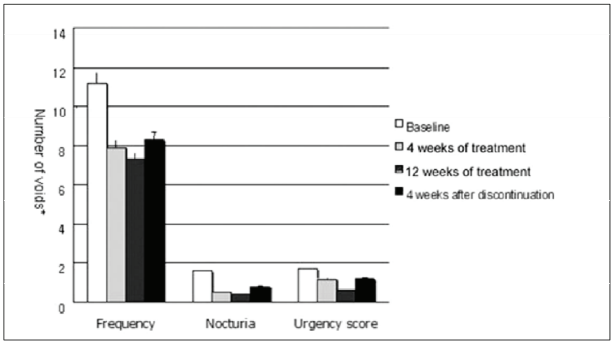
1. 8–12 weeks of Rx and then can discontinue
2. 6 months of Rx and then can discontinue
3. 1 year of Rx and then can discontinue
4. Lifetime therapy
5. Compliance with behavioral modification will permit discontinuing Rx in 4–8 months

Discontinuance of Antimuscarinics

- Multiple reports of poor persistence
- Common to see only 20% still on antimuscarinic
- 68 selected females with good response to OAB
  - Treated with propiverine x 8 weeks
  - Meds discontinued and reevaluation 4 weeks later
    - Diary, IUSS, questionnaire
    - Do you want to restart propiverine?

IUSS, Indevus Urgency Severity Score
Choo MS, et al. *J Urol.* 2005;174:201-204.

Discontinuance of Antimuscarinics



35% desired re-treatment 4 weeks after discontinuation

Choo MS, et al. *J Urol.* 2005;174:201-204.

Discontinuation After Combination Therapy

- Be-Dri study (NIDDK)
- 307 women (237 completed)
  - UUI or urge predominant MUI
  - Randomized to:
    - Drug only (tolterodine)
    - Drug + structured behavioral regimen
      - *(PFEs, urge suppression, timed voiding, etc.)*
  - Treated for 10 weeks, then all therapy stopped
  - Re-evaluation at 8 months: diary, questionnaire, etc.

UUI, urgency urinary incontinence; MUI, mixed urinary incontinence; PFE, pelvic floor exercises
Burgio KL, et al. *Ann Intern Med.* 2008;149:161-169.

Discontinuation After Combination Therapy (cont.)

- Primary outcome at 8 months
  - >70% reduction in UUI episodes AND
  - No use of antimuscarinics or other UUI Rx
- Methods
  - 4 visits over 10-week treatment period
  - Fluid management instructions given to both groups
  - Combo group told to continue therapy for all 8 months

Burgio KL, et al. *Ann Intern Med.* 2008;149:161-169.

10-Week Data (Phase I)

Table 4. Adjusted Mean Incontinence Episodes per Week*

Variable	Incontinence Episodes, *n*	
	Combination Therapy (*n* = 154)	Drug Therapy Alone (*n* = 153)
Pretreatment	23.1	23.2
End of stage 1	2.7	4.7
Mean reduction	20.4	18.5
Difference between groups (95% CI), *percentage points*	1.9 (−2.0 to 5.9)	

* Computed from mixed-model analysis of variance, controlling for randomization stratum and site.

Burgio KL, et al. *Ann Intern Med.* 2008;149:161-169.

8-Month Data (Phase II)

Table 2. Outcome Status at 8-Month Follow-up

Outcome Status	Combination Therapy (n = 154)	Drug Therapy Alone (n = 153)	Difference, *percentage points*
Failure, *n (%)*	75 (49)	78 (51)	–
Success, *n (%)**	43 (28)	41 (27)	–
Missing, *n (%)*†	36 (23)	34 (22)	–
8-month success rate (95% CI), %			
Life-table analysis estimate	41 (32 to 50)	41 (33 to 50)	0 (−12 to 12)

Burgio KL, et al. *Ann Intern Med.* 2008;149:161-169.

Be-Dri Results

The addition of behavioral therapy to drug therapy and subsequent CESSATION of drug therapy at 10 weeks:

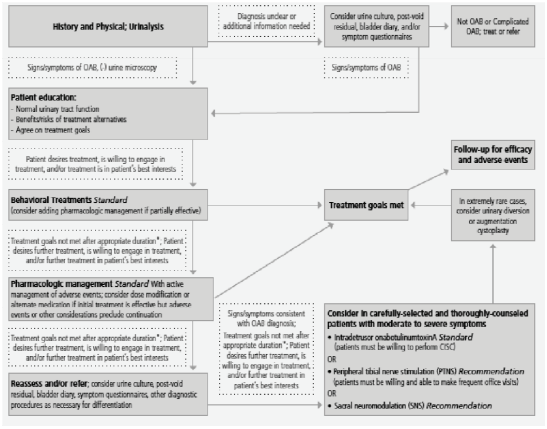
- DID result in
  - Improved UUI at 10 weeks
  - Better UDI, OAB-q scores, self-reported improvement at 10 weeks and 8 months
- Did NOT result in differences in
  - UUI at 8 months
  - Need for drug therapy at 8 months

Burgio KL, et al. *Ann Intern Med.* 2008;149(3):161-169.

Success with Drug Therapy

- What is the definition of “success”?
- What do you quote your patients as “success” rates with drug therapy?
- What is dry rate with current drug therapies?

Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline



AUA. Available at https://www.auanet.org/common/pdf/education/clinical-guidance/Overactive-Bladder-Algorithm.pdf. Amended 2014.

Agent Selection Considerations

- Clinical efficacy & safety
- Possible CNS side effects (cognitive impairment, sleep disturbance, photophobia)
- Drug-drug interactions
- Cost
- Convenience
- ER formulations associated with less dry mouth than corresponding IR formulations
- With the exception of trospium, most antimuscarinic agents easily pass the blood-brain barrier
- Differences in receptor selectivity among agents do not appear to correlate with clinical efficacy

Back to Our Case

This 58-year-old female has been on pelvic floor exercises and solifenacin 5 mg daily for three months and returns for a follow-up evaluation. She reports diminished urgency, somewhat diminished frequency (decreased from 18 to 11 voids per day), and urgency incontinence (decreased from 1 to 2 episodes per day to 2 to 3 episodes per week). She has mild but tolerable constipation. She also acknowledges that she had hoped to see greater improvement in her OAB symptoms.

Audience Question

How would you best optimize management of this patient at this time?

1. Stop antimuscarinic therapy and refer to a urologist
2. Discontinue current antimuscarinic therapy and switch to a different antimuscarinic drug
3. Titrate up the antimuscarinic agent dose and advise increase of fluid and fiber intake to manage constipation
4. Discontinue pelvic floor exercises because they add no benefit to pharmacologic therapy

Answer

When monitoring patients being treated for OAB who develop minor adverse effects, AUA Guidelines recommend that AEs such as constipation and dry mouth be managed before abandoning effective therapy.

Because she is noting improvement and the side effect is tolerable, the dose of her antimuscarinic drug should be titrated up.

Adjusting Pharmacologic Therapy for OAB Lack of Efficacy vs. Tolerability

- Consider the goals of the individual
- Balance efficacy against 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
  - If possible, manage adverse effects before stopping an effective therapy

Adjusting Pharmacologic Therapy for OAB Lack of Efficacy

- Change medication
  - Within class
  - Other class
  - Combine classes
    - ? Increased risk of retention
- Refer to specialist

Adjusting OAB Therapy: Excess Adverse Effects

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

Gormley EA, et al. *J Urol*. 2012;188(6 Suppl):2455-2463.
AUA/SUFU. Available at: https://www.auanet.org/education/guidelines/overactive-bladder.cfm. Amended 2014.

Antimuscarinic Alternative: β3-Agonists

- Non-antimuscarinic option (i.e., mirabegron) approved by the FDA June 2012
- Only medication with FDA-indication for OAB that is not an antimuscarinic
- Development of selective β3-agonists for OAB
  - Avoids activation of the β1 and β2-AR (and undesirable adverse effects such as increased heart rate and muscle tremors
- Mirabegron
  - Once daily, two doses (25 and 50 mg)
  - Lower incidence of dry mouth or constipation
  - Hypertension

Strategies for Improving Adherence to Pharmacologic Treatments

- Discuss potential side effects with all classes to the patient
- Weigh whether the benefits of a given therapy outweigh its negative aspects
- Different agents within a class and different classes may offer different benefits to various patients
- Try different agents to improve adherence

Significant Barriers to the Optimal Management of Patients with OAB

- Poor patient adherence to OAB therapy
- Insufficient physician time for communicating with patients about OAB and its management
- Limited physician awareness of different therapeutic options
- Difficulties assessing the need for referrals to a urology specialist
- Lack of a urology specialist within reasonable time or proximity

Summary Considerations for OAB Management

- Focus on meeting reasonable expectations
  (e.g., <100% dryness may be reasonable)
- Tailor therapy to the patient's needs
- Patient education about the specifics of their condition
- Consider using behavioral and pharmacologic interventions in combination
- Regimens may need to be altered over time
- Decrease incontinent episodes, frequency of urination & improve control

OAB Practice Case 3
When Patients Do Not Reach Treatment Goals: What Do You Do?

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Dr. Scott MacDiarmid is the Director of the Alliance Urology Specialists Bladder Control and Pelvic Pain Center in Greensboro, NC. He completed fellowships in reconstructive urology and urodynamics at Duke University Medical Center in Durham, NC; the University of Otago in Christchurch, New Zealand; and the University of Sheffield in England.

Dr. MacDiarmid's clinical, educational, and academic expertise is in male and female voiding dysfunction, neurogenic bladder, and complex lower urinary tract and pelvic floor reconstruction, and he has lectured extensively on these topics. He has authored or coauthored numerous book chapters and journal articles, and is recognized nationwide as a leader in his field. He has been instrumental both clinically and academically in advancing the field of neuromodulation in the treatment of overactive bladder.

Case Study: Ms. Smith

- 55-year-old women with urgency incontinence
- Cannot sit through a two hour movie
- Daily incontinence episodes
- Medical co-morbidities
- Failed two antimuscarinic agents
  - Inadequate response and complaints of dry mouth

Case Study

Which Treatment Option Would You Consider for Ms. Smith?

1. Alternative antimuscarinic
2. β3-agonist
3. Combination therapy
4. Referral to a specialist to consider refractory therapies
5. Live with her condition

Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline

Second-Line Treatments

- Clinicians should offer oral antimuscarinics* or beta3 (β3)-adrenoceptor agonists
- If an immediate-release (IR) and extended-release (ER) formulations are available, ER formulations preferential (lower dry mouth rate)
- Transdermal (TDS) oxybutynin may be offered
- If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one antimuscarinic:
  - Dose modification
  - Different antimuscarinic medication
  - β3-agonist

*** Listed in alphabetical order: darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine & trospium**

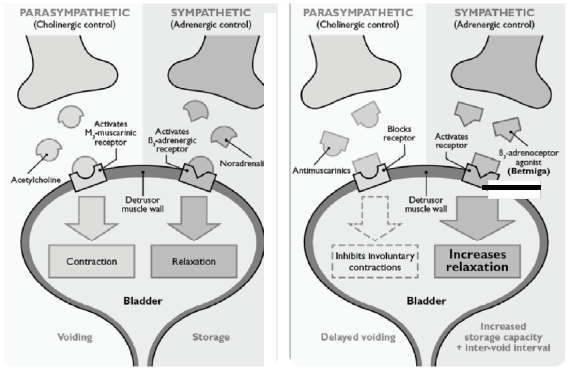
AUA/SUFU. Available at: https://www.auanet.org/education/guidelines/overactive-bladder.cfm. Amended 2014.

Antimuscarinic Alternative: β3-agonist

- Development of selective β3-agonists for OAB
  - Avoid activation of the β1 and β2-AR (and undesirable adverse effects such as increased heart rate and muscle tremors)
- Mirabegron
  - Approved for OAB in Japan, US, Europe & Canada
  - In US: once daily, two doses (25 and 50 mg)
  - Lower incidence of dry mouth or constipation
  - Hypertension

Antimuscarinics vs. β3-Agonists

Nerve pathways in normal bladder control | **Mode of action of OAB treatments**



Adapted from Chu FM, Dmochowski R. *Am J Med* 2006;119(3 Suppl 1):3–8.

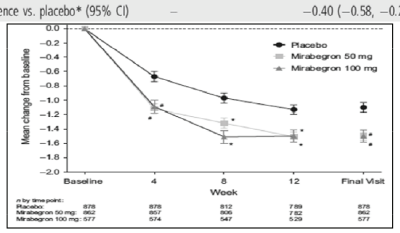
Adherence/Safety Issues With β3-Agonists

- Most common AEs: hypertension, nasopharyngitis, and urinary tract infection
  - The increase in blood pressure associated with mirabegron in clinical trials was ≤1 mm Hg.
  - In healthy volunteers, the 24-hr average increases in SBP/DBP of mirabegron versus placebo were 3.5/1.5 mm Hg.
- Incidence of dry mouth similar to placebo and five-fold less than tolterodine 4 mg.
  - Could be a useful treatment option for patients experiencing dry mouth.
- No studies specific to vulnerable older population or on cognitive effects.
  - Theoretically should not affect cognition, unlike potential of most antimuscarinics.

Astellas Pharma US Inc. MYRBETRIQ Prescribing Information. Available at: https://www.astellas.us/docs/Myrbetriq_WPI.pdf Accessed July 17, 2014.
Chapple CR, et al. *Neurourol Urodyn.* 2014 Jan;33(1):17-30.

Mirabegron Pooled Analysis of 3 Phase III Studies

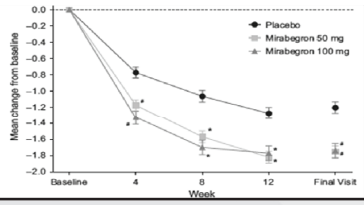
	Placebo	Mirabegron 50 mg
Co-primary end-points		
Change from baseline to Final Visit in the mean number of incontinence episodes/24 h (FAS-I)		
Baseline	2.73 (0.09)	2.71 (0.09)
Final Visit	1.64 (0.09)	1.23 (0.08)
Change from baseline	−1.09 (0.09)	−1.48 (0.08)
Adjusted change from baseline* (95% CI)	−1.10 (−1.23, −0.97)	−1.49 (−1.63, −1.36)
Adjusted difference vs. placebo* (95% CI)	–	−0.40 (−0.58, −0.21)†



Nitti VW, et al. *IJCP.* 2013; 67: 619-32.

Mirabegron Pooled Analysis of 3 Phase III Studies

	Placebo	Mirabegron 50 mg
Co-primary end-points		
Change from baseline to Final Visit in the mean number of micturitions/24 h (FAS)		
Baseline	11.58 (0.09)	11.70 (0.09)
Final Visit	10.39 (0.09)	9.93 (0.09)
Change from baseline	−1.18 (0.08)	−1.77 (0.08)
Adjusted change from baseline* (95% CI)	−1.20 (−1.34, −1.06)	−1.75 (−1.89, −1.61)
Adjusted difference vs. placebo* (95% CI)	–	−0.55 (−0.75, −0.36)†



Nitti VW, et al. *IJCP.* 2013; 67: 619-32.

Mirabegron Pooled Analysis of 3 Phase III Studies

Number of patients (%)	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Mirabegron Total (n = 2736)	Tolterodine ER 4 mg (n = 495)
Any TEAE	658 (47.7)	210 (48.6)	647 (47.1)	402 (43.3)	1259 (46.0)	231 (46.7)
Drug-related TEAE	232 (16.8)	87 (20.1)	256 (18.6)	172 (18.5)	515 (18.8)	131 (26.5)
TEAE leading to discontinuation	46 (3.3)	17 (3.9)	53 (3.9)	34 (3.7)	104 (3.8)	22 (4.4)
Drug-related TEAE leading to discontinuation	27 (2.0)	11 (2.5)	35 (2.5)	25 (2.7)	71 (2.6)	20 (4.0)
SAE	29 (2.1)	7 (1.6)	29 (2.1)	26 (2.8)	62 (2.3)	11 (2.2)
Drug-related SAE	6 (0.4)	3 (0.7)	7 (0.5)	3 (0.3)	13 (0.5)	6 (1.2)
Common TEAEs by preferred term (reported by ≥ 3% in total mirabegron group)						
Hypertension	105 (7.6)	49 (11.3)	103 (7.5)	48 (5.2)	200 (7.3)	40 (8.1)
Nasopharyngitis	35 (2.5)	15 (3.5)	54 (3.9)	25 (2.7)	94 (3.4)	14 (2.8)
Urinary tract infection	25 (1.8)	18 (4.2)	40 (2.9)	25 (2.7)	83 (3.0)	10 (2.0)
Antimuscarinic AEs of interest by preferred term (reported by ≥ 2% in any group)						
Headache	43 (3.1)	10 (2.3)	47 (3.4)	23 (2.5)	80 (2.9)	18 (3.6)
Dry mouth	29 (2.1)	8 (1.9)	23 (1.7)	23 (2.5)	54 (2.0)	50 (10.1)
Constipation	20 (1.4)	7 (1.6)	22 (1.6)	15 (1.6)	44 (1.6)	10 (2.0)
Drug-related* TEAEs by preferred term (reported by ≥ 2% in any group)						
Hypertension	63 (4.6)	30 (6.9)	65 (4.7)	32 (3.4)	127 (4.6)	30 (6.1)
Headache	18 (1.3)	4 (0.9)	28 (2.0)	12 (1.3)	44 (1.6)	11 (2.2)
Dry mouth	22 (1.6)	7 (1.6)	13 (0.9)	20 (2.2)	40 (1.5)	47 (9.5)

SAF, safety analysis set; ER, extended release; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

Nitti VW, et al. *IJCP.* 2013; 67: 619-32.

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Nitti VW, et al IJCP 2013; 67: 619-32

Maximizing Oral OAB Agents? Combo Antimuscarinic & β3-Agonist

Symphony Trial

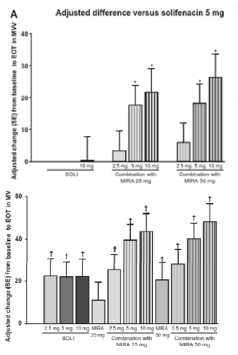
- Phase 2
- 1306 patients with OAB
- Anticholinergic – solifenacin
- Beta3-agonist – mirabegron
- 12 treatment groups
  - Placebo
  - 6 combinations (soli 2.5, 5 or 10 mg + mirabegron 25 or 50 mg)
  - 5 monotherapy (solifenacin 2.5, 5 or 10 mg or mirabegron 25 or 50 mg)

Abrams P, et al. *Eur Urol.* 2014;[Epub ahead of print]

Combination Therapy for OAB: Mean Volume Voided

MVV (primary end point)

- Four combo groups superior to solifenacin 5 mg
  - solifenacin 5 + mirabegron 25
  - solifenacin 10 + mirabegron 25
  - solifenacin 10 + mirabegron 50
  - solifenacin 10 + mirabegron 50
- All arms except mirabegron 25 mg superior to placebo

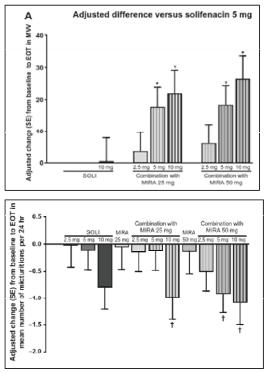


MVV, mean volume voided
Abrams P, et al. *Eur Urol.* 2014;[Epub ahead of print]

Combination Therapy for OAB: Micturitions

Micturitions

- Three combo groups superior to solifenacin 5 mg
  - solifenacin 5 + mirabegron 25
  - solifenacin 10 + mirabegron 50
  - solifenacin 10 + mirabegron 50
- Same three superior to placebo



Abrams P, et al. *Eur Urol*. 2014;[Epub ahead of print]

Combination Therapy for OAB: Incontinence Episodes

Incontinence

- All treatment groups (including placebo) demonstrated decreased incontinence episodes
- No treatment group superior to placebo
- Only solifenacin 5 mg + mirabegron 25 mg superior to solifenacin 5 mg monotherapy

At study entry – 21.5% UI; mean 1.35 episodes/day

Abrams P, et al. *Eur Urol*. 2014;[Epub ahead of print]

Combination Therapy for OAB: Adverse Events

Adverse events

- No significant impact on PVR (one retention pt*)
- Two most common AEs – dry mouth & hypertension
- Anticholinergic side effect (dry mouth, constipation, etc.) – dose relationship with solifenacin monotherapy
  - No increase with combo therapy
- Hypertension – negligible, decreased in some groups

*Patient taking solifenacin 2.5 mg plus mirabegron 25 mg
PVR, post-void residual urine
Abrams P, et al. *Eur Urol*. 2014;[Epub ahead of print]

There is a New Disease in Town?

Refractory OAB

"ROAB"

The AUA Guideline Panel Definition Defines the Refractory Patient as One Who has Failed….

- Behavioral therapy
- At least one antimuscarinic due to lack of efficacy and/or inability to tolerate adverse drug effects
- Consider combining therapies or try alternative antimuscarinics

Gormley EA, et al. American Urological Association (AUA) Guideline. AUA Web site. http://www.auanet.org/content/media/OAB_guideline.pdf. Accessed August 20, 2012.

A Real World Definition of ROAB

Patients who fail medical therapy (1-2-3-3+)	Patients who cannot tolerate medication	Patients who cannot afford medication
Patients who have contraindications to medication	Patients who prefer not to take medication	Defined by the third-party payer
	"The millions of partial responders"	

AUA/SUFU 2014 OAB Treatment Guidelines

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

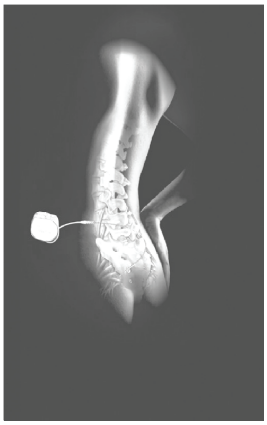
2nd Line
- Oral antimuscarinics
- β_3-agonist (mirabegron)
- Transdermal preparations
- Dose modification or switch to different antimuscarinic/β3-agonist if inadequate efficacy or poor tolerability

3rd Line
- Sacral Nerve Stimulation
- Urgent PC
- Intradetrusor onabotulinum toxin A

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

Sacral Nerve Stimulation

Sacral nerve stimulation provides an effective alternative for voiding dysfunction patients who have not been helped- or could not tolerate- more conventional treatments, including pharmacotherapy.



Sacral Nerve Stimulation: Indications

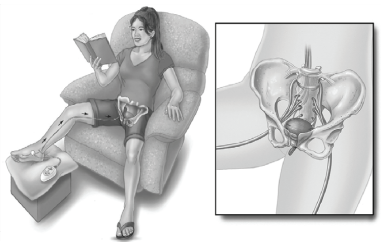
- Refractory OAB
  - Failed or not sufficiently improved by drugs and behavioral therapy
- Urinary Retention
  - Idiopathic non-obstructive
- Non-neurogenic etiology
- Fecal Incontinence

Sacral Nerve Stimulation

- InterStim
- Implantable, programmable neuromodulation system
- Two stage therapy
  - **PNE:** Test stimulation procedure – 3 to 7 days, temporary
  - **Staged Lead Implant:** Placement of potentially permanent lead for up to 4 weeks
  - **Chronic Implant:** Implantation neurostimulator (and lead when not done as a staged procedure)

Percutaneous Tibial Nerve Stimulation (PTNS)

- Urgent® PC is a minimally invasive neuromodulation system
- Retrograde electrical stimulation of sacral nerve plexus
- Targets specific neural tissue and "jams" the pathways transmitting unwanted signals

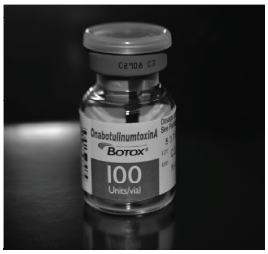


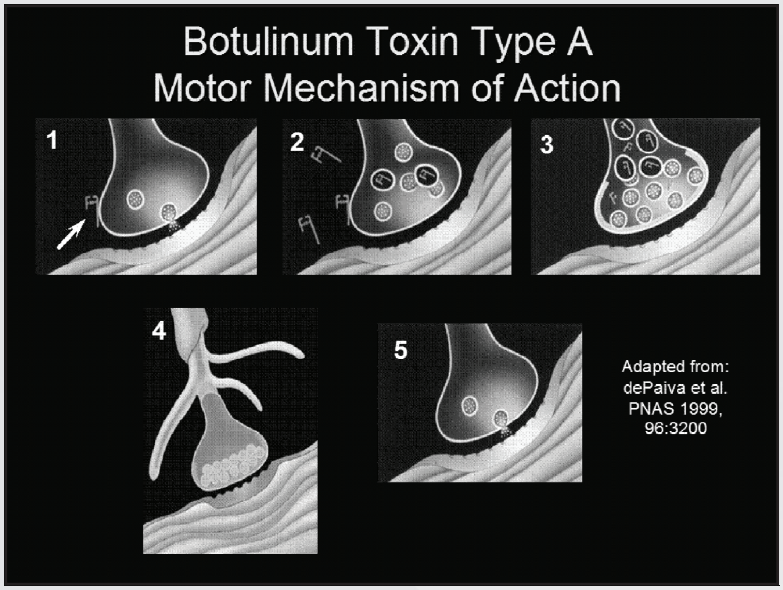
PTNS Clinical Effectiveness

- 50+ US and other peer reviewed publications demonstrate safety and clinical efficacy*
  - Reduces urgency, urge incontinence & frequency
  - Rare, mild adverse events
  - Improved Quality of Life
  - 3 RCTs compared PTNS to drugs & placebo
  - 12-, 24- and 36-month durability data
  - Observational, "real-world" studies support positive conclusions of RCTs

*Staskin D, et al. *Curr Urol* Rep. 2012;13:327-34.

BOTOX® (onabotulinumtoxinA) for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.





Botulinum Toxin: Efficacy

- Proven efficacy and safety in treating refractory OAB
- In-office, minimally invasive procedure
- 6-month durability

Most Common Adverse Events

During the first 12 weeks post-injection adverse reactions reported by ≥2% of BOTOX® (onabotulinumtoxinA) treated patients and more frequently than placebo-treated patients

Adverse reactions	BOTOX® 100 U (N= 552)	Placebo (N= 542)
UTI	18%	6%
Dysuria	9%	7%
Urinary retention† (elevated PVR ≥ 200 mL requiring CIC)	6%	0%

BOTOX® (onabotulinumtoxinA) Prescribing Information. Allergan, Inc., 2013.[91]

What is the Role of the Primary Care Provider?

- Screen patients for voiding dysfunction
- Important role in treating patients with OAB
- Be aware of refractory therapies
- Refer when appropriate

Assessing Therapeutic Response

- Quantitate response to therapy
- Be a cheerleader
- Set your goals high

When to Consider Referral

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

Case Study: Ms. Smith

- Treated with β3-agonist and behavioral therapy
- Significantly improved quality of life
- Wears one pad daily