CME/CE MONOGRAPH

EARN CME/CE CREDITS

Improving Outcomes in OAB

NEW AND EMERGING STRATEGIES TO REDUCE SYMPTOM BURDEN AND TREATMENT ADVERSE EFFECTS

Visit **https://tinyurl.com/OABOutcomes**
for online testing and instant CME/CE certificate.

Original Release: April 1, 2021
Expiration: April 30, 2022

FACULTY

Roger Dmochowski, MD, MMHC, FACS (Chair)

Benjamin M. Brucker, MD

Kathleen C. Kobashi, MD, FACS

This continuing medical education activity is provided by MedEdicus LLC.

MedEdicus LLC

This continuing medical education activity is supported through an educational grant from Urovant Sciences, Inc.

CONTINUING MEDICAL EDUCATION INFORMATION

ACTIVITY DESCRIPTION AND PURPOSE

Overactive bladder is a common problem among men and women, with bothersome symptoms that can have significant negative physical, social, and emotional consequences. Treatment plans, which should be individualized according to patient needs and assessment of a treatment's benefits and risks, often include pharmacologic therapy with an antimuscarinic and/or a β_3-adrenoceptor agonist. Poor treatment adherence/persistence, however, limits success and patient satisfaction. This activity will review efficacy, safety, and tolerability data for overactive bladder pharmacologic therapies, including a new β_3-adrenoceptor agonist, and their relevance for counseling to improve treatment adherence. The activity will also focus on the effect of pharmacologic therapies on cognitive function, which is of particular concern because older individuals are highly represented in the population with overactive bladder. Finally, case-based discussions will provide insights from experts for practical approaches to optimize patient care. The desired results of this activity are for clinicians to improve their diagnosis and treatment of overactive bladder.

TARGET AUDIENCE

This educational activity is intended for urologists, urogynecologists, physician assistants, nurse practitioners, nurses, and other clinicians caring for patients with overactive bladder.

LEARNING OBJECTIVES

After completing this activity, participants will be better able to:

- Apply efficacy and tolerability clinical data to develop long-term treatment plans for patients with overactive bladder
- Incorporate medication reviews into patient encounters
- Compare the data on central nervous system effects of antimuscarinic overactive bladder medications with those of β_3-adrenoceptor agonists
- Describe the pharmacologic, efficacy, safety, and tolerability profiles of new and emerging treatments for overactive bladder

FOR PHYSICIANS:

ACCME Accreditation Statement

MedEdicus LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

AMA PRA Credit Designation Statement

MedEdicus LLC designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

FOR NURSES:

Interprofessional Joint Accreditation Statement

In support of improving patient care, Amedco LLC is jointly accredited by the ACCME, the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Nursing Credit

Amedco LLC designates this activity for a maximum of 1.5 ANCC contact hours.

INSTRUCTIONS FOR OBTAINING CREDIT

To obtain CME/CE credit for this activity, please read the monograph, consult referenced sources as necessary, and complete the posttest and evaluation online at https://tinyurl.com/OABOutcomes. Upon passing with a score of 70% or higher, a certificate will be made available immediately.

DISCLOSURE POLICY

MedEdicus requires that anyone who is in a position to control the content of this educational activity disclose all relevant financial relationships with any commercial interest. Financial relationship information is collected and resolved prior to the educational activity.

FACULTY

Roger Dmochowski, MD, MMHC, FACS (Chair)
Associate Surgeon in Chief
Professor of Surgery
Professor of Urology
Professor of Obstetrics and Gynecology
Vice Chair, Section of Surgical Sciences
Vanderbilt University Medical Center
Nashville, Tennessee

Benjamin M. Brucker, MD
Associate Professor
Departments of Urology and Obstetrics and Gynecology
Director, Female Pelvic Medicine & Reconstructive Surgery and Neurourology
New York University Langone Health
New York, New York

Kathleen C. Kobashi, MD, FACS
Head, Section of Urology and Renal Transplantation
Virginia Mason Medical Center
Seattle, Washington

DISCLOSURES

Benjamin M. Brucker, MD, is a consultant for Allergan, Click Therapeutics, Inc, and Urovant Sciences, Inc; is on the speakers bureau for Allergan; is a contracted researcher for Boston Scientific Corporation; and has ownership interest (future stock options) in Watkins-Conti Products, Inc.

Roger Dmochowski, MD, MMHC, is a consultant for BlueWind Medical, Caldera Medical, and Viveve; and a medical monitor for BlueWind Medical, Caldera Medical, and Viveve.

Kathleen C. Kobashi, MD, is a consultant for Allergan, Contura Ltd, and Medtronic; is on the speakers bureau for Allergan and Medtronic; and is a contracted researcher for Allergan.

Peer Reviewer

This activity was peer reviewed. The peer reviewer has no relevant commercial relationships to disclose.

Planners and Managers

MedEdicus planners and managers have no relevant commercial relationships to disclose.

DISCLOSURE OF COMMERCIAL SUPPORT

This continuing medical education activity is supported through an educational grant from Urovant Sciences, Inc.

OFF-LABEL DISCUSSION

This educational activity may include discussion of unlabeled and/or investigational uses of drugs or devices. Please refer to the official prescribing information for each drug or device discussed in this activity for approved dosing, indications, and warnings.

PROVIDER CONTACT INFORMATION

For questions about this educational activity, please contact MedEdicus LLC at info@mededicus.com.

DISCLAIMER

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of MedEdicus LLC, Urovant Sciences, Inc, or *Urology Times*.

Introduction

Overactive bladder (OAB) is a symptom complex defined as urinary urgency, usually accompanied by frequency, with or without urinary incontinence, in the absence of urinary tract infection or other obvious pathology.[1] It is a common condition, with a reported prevalence of 13% to 43% among women and 11% to 27% among men.[2-4] The data for men, however, may be an underestimation because storage conditions historically attributed to prostate enlargement are increasingly being recognized as primary OAB.[2]

Considering that seniors are the fastest growing segment of the population and because OAB prevalence and symptom severity increase with age,[2-5] OAB is a rising problem. The importance of treating OAB is highlighted by research showing that it negatively impacts multiple dimensions of quality of life. Studies show OAB interferes with social, work, and personal relationships; compromises self-image; is associated with sleep disturbances and depression; and is a risk factor for falls and fracture.[6-11]

Updates in Overactive Bladder Treatment

The goals for treating OAB are to maximize symptom control and patient quality of life while minimizing adverse effects and patient burden.[12] On the basis of these goals, the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) have developed recommendations for OAB treatment and outlined a treatment algorithm that presents a hierarchal scheme of first-, second-, and third-line options.[12] The algorithm is not intended to be used in strict stepladder fashion; rather, it is meant to provide a clinical framework that clinicians can use as a guide for individualizing patient care while taking into account multiple factors.

The guideline identifies behavioral treatments as first-line therapy for OAB and recommends their offering to all patients, but also notes that behavioral treatments can be used with pharmacologic management, with the potential for greater improvement and quality of life.[12] Pharmacologic management using antimuscarinics and/or β_3-adrenoceptor agonists represents second-line therapy. All the available medications for treating OAB can be effective for improving bothersome symptoms, but the 2 classes differ in their safety profiles.

Antimuscarinics

There are 5 subtypes of muscarinic receptors (M_1-M_5) located on various tissues throughout the body.[13] Antimuscarinics used to treat OAB act primarily by blocking the binding of acetylcholine to M_3 receptors in the bladder that are primarily responsible for detrusor contraction. Although the antimuscarinics approved for OAB treatment may differ in their selectivity for the M_3 receptor, there is no evidence in population studies that one is more effective than any other for reducing urgency and urgency incontinence or regarding long-term outcomes, quality of life, or cost.[12,14]

Aside from the bladder, muscarinic receptors are found in the brain, eyes, salivary glands, heart, and gastrointestinal tract.[13] Binding to these receptors accounts for some of the unwanted adverse effects associated with use of antimuscarinics for OAB—eg, cognitive impairment, dry mouth, increased heart rate, and constipation[15]—as well as for contraindications and cautions pertaining to their use in patients with narrow-angle glaucoma or impaired gastric emptying, those with a history of urinary retention, frail individuals, and patients receiving other anticholinergic medications **(Table 1)**.[12,16]

Table 1. Medications With Anticholinergic Activity[16]

Medication Class	Medications
Antiarrhythmics	Disopyramide
Antihistamines	Brompheniramine, chlorpheniramine, clemastine, cyproheptadine, diphenhydramine, hydroxyzine
Antidepressants	Amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, paroxetine, trimipramine
Antiepileptics	Carbamazepine, oxcarbazepine
Antimuscarinic bronchodilators	Glycopyrrolate, ipratropium
Antiparkinson drugs	Benztropine, orphenadrine, procyclidine, trihexyphenidyl
Antipsychotics	Chlorpromazine, clozapine, olanzapine, quetiapine, thioridazine
Antivertigo/Antiemetic drugs	Cyclizine, prochlorperazine, promethazine
Gastrointestinal antispasmodics	Atropine products, dicyclomine, propantheline, scopolamine
Skeletal muscle relaxants	Methocarbamol, tizanidine

The risk of specific adverse events may vary among the available antimuscarinics for OAB owing to differences in muscarinic receptor selectivity and pharmacokinetic profiles.[12,14,15] Compared with an immediate-release formulation, an extended-release version of an antimuscarinic, which lowers medication blood level peaks, is associated with a lower rate of dry mouth.[12] The risk of dry mouth and of constipation appears to vary among the antimuscarinic agents.[15] Darifenacin, solifenacin, and oxybutynin may have less potential to cause cardiovascular adverse effects than other antimuscarinics used to treat OAB.[15]

It has also been suggested that there are differences in risk of central nervous system adverse effects among the antimuscarinics, which have been explained, in part, by differences in molecular and physicochemical properties that affect penetration through the blood-brain barrier.[13,15,17,18] Central nervous system adverse effects are of particular concern in patients with cognitive dysfunction as well as in older patients, who may be more susceptible because of polypharmacy and age- and disease-related changes in blood-brain barrier permeability and in the brain.[15,17,18]

With respect to pharmacokinetics, antimuscarinics also differ in route of elimination. Trospium, fesoterodine, and solifenacin are excreted through the kidneys into the urine, which may contribute to their efficacy via a local tissue effect.[15] Except for trospium, all the antimuscarinics undergo hepatic metabolism via different cytochrome P450 (CYP450) enzymes, with potential implications for drug-drug interactions.[15,19]

β_3-Adrenoceptor Agonists

Commercially available β_3-adrenoceptor agonists for the treatment of OAB include mirabegron, which was approved by the US Food and Drug Administration (FDA) in 2012,[20] and vibegron, which was approved by the FDA in December 2020.[21] Binding of these medications to the β_3-adrenergic receptor in the bladder increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling.[22] The β_3-adrenergic receptor is also found in the kidney, brain, retina, adipose tissue, myocardium, and myometrium, and there is interest in these receptors as therapeutic targets for β_3-adrenoceptor agonists.[23,24]

Mirabegron

The phase 3 trial supporting the FDA approval of mirabegron for treating OAB showed that mirabegron 25 and 50 mg/d significantly reduced the mean number of daily micturitions (-1.65 and -1.60 vs -1.18, respectively; $P \leq .015$) and incontinence episodes (-1.36 and -1.38 vs -0.96, respectively; $P \leq .005$) compared with placebo at the 12-week primary end point **(Figure 1)**.[25] The benefits vs placebo were seen for mirabegron 50 mg at week 4, but a significant difference for decreasing mean number of micturitions was not seen until week 8 for mirabegron 25 mg. According to these results, mirabegron is recommended to be started at a dose of 25 mg once daily, with titration to 50 mg once daily according to patient response.[26] It is also indicated for use with solifenacin succinate 5 mg once daily. In clinical trials, the combination was associated with significantly greater improvements in micturitions/24 hours, incontinence episodes/24 hours, urgency episodes/24 hours, and volume voided/micturition compared with solifenacin 5-mg monotherapy.[12,27-30] The AUA/SUFU guideline states that clinicians may consider combination antimuscarinic/β_3-adrenoceptor agonist use for patients refractory to either medication alone.[12]

Mirabegron was generally safe and well tolerated in the phase 3 trial investigating its use,[25] and there was no significant increase in adverse events when it was combined with solifenacin.[12,27-30] Mirabegron alone or with solifenacin, however, can increase blood pressure.[26] Therefore, blood pressure monitoring is recommended, especially in patients with hypertension, and mirabegron is not recommended for use in patients with severe uncontrolled hypertension.[26] Pooled data from 12-week phase 3 studies showed that mirabegron 25 mg (n = 432) and 50 mg (n = 1375) were associated with lower rates of dry mouth (1.6% and 0.9% vs 9.5%, respectively), constipation (1.6% and 0.8% vs 1.4%, respectively), and discontinuations for a drug-related adverse event (2.5% and 2.5% vs 4.0%, respectively) vs tolterodine extended release (n = 495), which was included as an active control.[31] There are also warnings/cautions about the potential for urinary retention when using mirabegron in patients with bladder outlet obstruction or in those who are receiving antimuscarinics or drugs metabolized by CYP450 2D6 isozyme (CYP2D6).[26] Mirabegron is a moderate inhibitor of CYP2D6, and monitoring to identify a need for dose adjustment is recommended when using mirabegron with drugs metabolized by CYP2D6 that have a narrow therapeutic index, such as metoprolol, desipramine, and especially thioridazine, flecainide, and propafenone.

Vibegron

The FDA approval of vibegron 75 mg once daily expands the options for β_3-adrenoceptor agonist treatment of OAB.[21] In addition to being administered with a single fixed vs titratable dose, vibegron is distinguished from mirabegron by not having any CYP450-mediated drug interactions or a warning regarding blood pressure monitoring or use in patients with severe uncontrolled hypertension. Data from their respective phase 3 studies show onset of benefit occurred earlier with vibegron than with mirabegron (2 weeks vs 4 weeks), but the 2 medications have not been compared in head-to-head trials.[25,26,32,33]

EMPOWUR, the international phase 3 trial supporting FDA approval of vibegron to treat OAB, randomized 1518 patients 5:5:4 to receive once-daily vibegron 75 mg, placebo, or tolterodine 4 mg extended release.[32] The study met its coprimary end points,

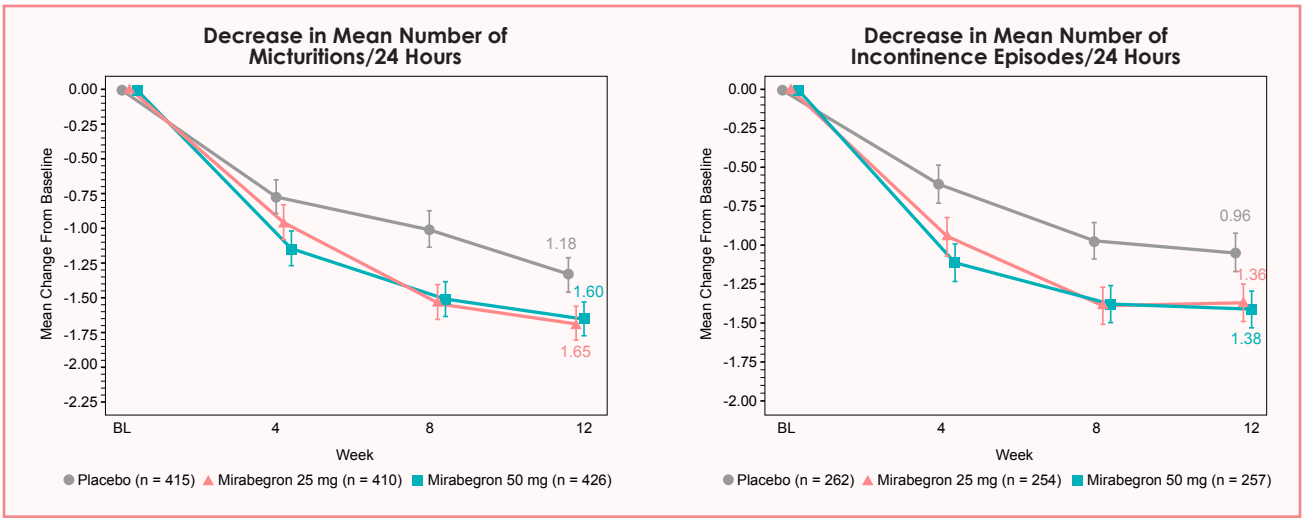


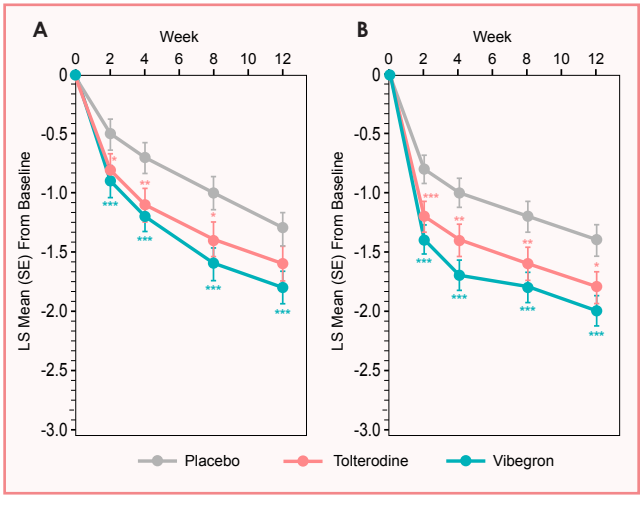
Figure 1. Pivotal trial results show mirabegron met its coprimary efficacy end points[25]

Abbreviation: BL, baseline.

showing statistically significant differences favoring vibegron over placebo in mean change from baseline to week 12 in daily micturitions (1.8 vs 1.3; $P < .001$) and urge urinary incontinence episodes (2.0 vs 1.4; $P < .0001$) **(Figure 2)**. Statistical superiority of vibegron to placebo was achieved for both end points at week 2 and in key secondary end points measuring frequency of urgency episodes, volume voided per micturition, and proportion of incontinent patients with a ≥ 75% reduction in urge urinary incontinence episodes. Compared with patients receiving placebo, those receiving vibegron also had significantly greater improvements in total health-related quality of life, coping, concern, sleep, and symptom bother domains from baseline to week 12 ($P \leq .0039$ for all comparisons).[34] Although statistical analyses were not performed, comparisons with tolterodine showed numerical differences favoring vibegron for reductions in urgency episodes, incontinence episodes, volume voided per micturition, and quality of life end points.[32,34] Results from an extension of EMPOWUR showed that patients treated with vibegron had further improvements in urgency and incontinence episodes when followed for up to 52 weeks **(Figure 3)**.[35] The results of EMPOWUR are consistent with the outcomes of phase 3 studies of vibegron conducted in Japan.[36-38]

Vibegron demonstrated favorable safety and tolerability during the 12-week placebo-controlled study period and the extension phase, and its safety profile was similar in patients regardless of age.[32,35] During the 12-week placebo-controlled period, rates of adverse events of clinical interest—ie, hypertension, increased blood pressure, urinary tract infection, and urinary retention—were similar for vibegron and placebo, and the rate of dry mouth was lower in the 545 patients receiving vibegron than in the 430 patients receiving tolterodine (1.7% vs 6.5%).[32]

The rate of discontinuations related to adverse events was lower with vibegron than with tolterodine (1.7% vs 3.3%). Patients treated with vibegron, especially those with bladder outlet obstruction or those taking an antimuscarinic antagonist, should be monitored for urinary retention.[33]



* $P < .05$, ** $P < .01$, *** $P < .001$

Figure 2. In the EMPOWUR study, vibegron met its coprimary end points assessing changes from baseline to week 12 in daily micturitions (A) and urge urinary incontinence episodes (B) and showed superiority vs placebo for both end points at week 2[32]

Abbreviations: LS, least squares; SE, standard error.

Emerging Therapies for Overactive Bladder

Solabegron is an investigational β_3-adrenoceptor agonist that has shown benefits for treating OAB in two phase 2 trials.[39,40] In a 12-week study enrolling 435 women, solabegron demonstrated statistically significant superiority to placebo for reducing mean daily micturitions, urgency episodes, and urge urinary incontinence episodes.[39] The second study included

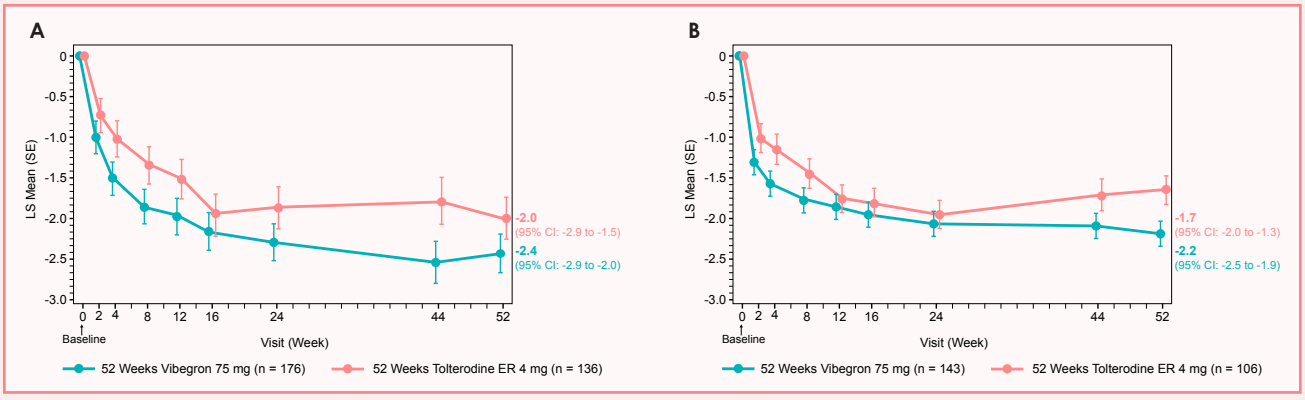


Figure 3. In an extension to the EMPOWUR study, treatment with vibegron between weeks 12 and 52 resulted in further improvements in daily micturitions (A) and urge incontinence episodes (B)[35]

Abbreviations: CI, confidence interval; LS, least squares; SE, standard error.

258 women with moderate to severe OAB and found statistically significant differences favoring solabegron over placebo for decreasing incontinence episodes and daily micturitions.[40]

Gene therapy with URO-902, a plasmid vector expressing the human BK channel α subunit, is being developed as a bladder-selective treatment of OAB.[41] It aims to induce overexpression of the BK channel in urinary bladder smooth muscle cells to reduce detrusor muscle overactivity. In 2 double-blind, placebo-controlled, randomized phase 1 trials, URO-902 administered by direct bladder wall injection or intravesical instillation had no dose-limiting toxicities or significant adverse events. At 1 week following intradetrusor injection, URO-902 significantly reduced the number of urgency episodes and number of voids compared with placebo. Recruitment is ongoing in a phase 2 trial investigating intradetrusor URO-902 in patients with urge urinary incontinence associated with OAB.[42]

Overactive Bladder Medication Adherence/Persistence

Available evidence shows that better adherence/persistence with OAB medication translates into better patient outcomes and reduced costs.[43,44] Multiple studies, however, show that adherence to antimuscarinic medications for OAB is poor.[45,46] A systematic review of studies with long-term follow-up found that rates of adherence to antimuscarinic treatment of OAB ranged from just 12.0% to 39.4% at 1 year and decreased to between 6.0% and 12.0% at 2 years.[45] At 3 years, adherence to darifenacin and trospium was 0% and 16.0%, respectively. Results were similar in a more recent analysis of Medicare claims data, which found an adherence rate of only 14.2% at 1 year.[46]

Compared with antimuscarinics, the β_3-adrenoceptor agonist mirabegron has been shown to be associated with higher rates of adherence/persistence.[47-52] For example, in a retrospective study of approximately 22,000 patients, median time to discontinuation and 12-month persistence rates were significantly greater ($P < .0001$) for mirabegron than for all antimuscarinics.[51] According to the investigators of these comparative studies, the difference favoring the β_3-adrenoceptor agonist may be explained, at least in part, by a more tolerable adverse effect profile.[47-49,51] Nevertheless, there is a need to improve adherence/persistence to all OAB medications.

Understanding the reasons for poor adherence/persistence provides a foundation for addressing the problem **(See Sidebar: Expert Tips for Follow-Up on p 7)**. In a survey of 5392 patients who discontinued antimuscarinic OAB medications, 46.2% cited failure to meet expectations for efficacy as a reason, and 21.1% of participants identified adverse effects as a cause.[53] These findings underscore the importance of medication counseling that sets appropriate expectations for treatment benefit and informs patients of potential adverse events and strategies for their mitigation. Patient and provider materials accompanying a SUFU clinical care pathway for OAB can assist with these efforts to improve medication adherence.[54]

Overactive Bladder Medications, Cognitive Effects, and Frailty: Evidence for Understanding the Risks

The AUA/SUFU OAB guideline recommendations highlight the need to consider frailty and cognitive impairment in treatment decisions for patients with OAB and notes that medications in frail patients may have a lower therapeutic index and a higher adverse drug event profile.[12] As defined in the guideline, frailty is a composite of multiple factors, including mobility deficits, weight loss, weakness without medical cause, and cognitive deficits. The guideline recommends that clinicians conduct a Mini-Mental State Examination on all patients who may be at risk for cognitive impairment to

Expert Tips for Follow-Up

Dr Dmochowski: Clinicians need to be aware of the high discontinuation rates with overactive bladder (OAB) medications and take actions to improve adherence and persistence that determine patient benefit. One thing to keep in mind is that individuals vary in their response to any one medication, so follow-up with a medication review is important to determine the need for modifications based on efficacy and tolerability. Clinicians have to recognize that adverse effects are a leading reason for patient discontinuation of OAB medications, particularly antimuscarinics. Even if a medication substantially improves symptoms, long-term treatment persistence can be compromised if the medication is causing bothersome adverse effects. Therefore, patients should be counseled on the potential for constipation or dry mouth before starting antimuscarinic treatment and advised on mitigation strategies, such as ensuring adequate fiber and fluid intake to minimize constipation or using oral lubricants, sugar-free hard candies, or sugar-free gum to relieve dry mouth. Dose reduction or switching to another antimuscarinic may be options when patients develop bothersome adverse effects.

In addition, it is essential that clinicians counsel patients to establish appropriate expectations for treatment outcomes. Patients need to understand that OAB is a chronic condition. Although medications can improve OAB symptoms, they are not a cure and maintaining benefit depends on continued use.

Dr Kobashi: Dry mouth and constipation might seem like minor problems, but patients are often already experiencing these issues and an existing problem can become intolerable when it is worsened by medication-induced adverse effects.

A multimodal approach for OAB management can be valuable. Use of behavioral interventions with medications can result in better outcomes and engage patients in their care.

Nevertheless, patients must realize that similar to hypertension, OAB is a chronic condition requiring ongoing treatment for control, and clinicians must be proactive with follow-up. We may tell a patient to call or come back if a treatment is not working, but this approach might not provide the patient and the clinician with the opportunity for a meaningful medication review. In my practice, I instruct patients starting on a new treatment to schedule a return visit soon after they start the medication so I can review their response and determine if something else is needed to improve things for them.

Dr Brucker: I agree. If we strive to understand patient perceptions of their condition and the effects of the treatment, we can better personalize treatment. It is also important to update our care algorithms as new therapeutic options and information emerge. For example, cognitive issues with antimuscarinics were not something I thought much about 2 or 3 years ago, but it has been brought to the forefront by accumulating evidence.

determine if their symptoms could be aggravated by cognitive problems, ensure that they will be able to follow directions for behavioral therapy, and/or determine the degree of risk for cognitive decline with antimuscarinic therapy. In addition, the guideline states that clinicians should use caution in prescribing antimuscarinics or β_3-adrenoceptor agonists in frail patients and in prescribing antimuscarinics in patients who are using other medications with anticholinergic properties. Furthermore, the American Geriatrics Society Beers Criteria of medications that are potentially inappropriate for use in older adults strongly recommends the avoidance of antimuscarinics, which are identified as having strong anticholinergic properties, in patients with cognitive impairment or dementia.[55]

Despite these cautions and recommendations, results of a study investigating bladder antimuscarinic use among Medicare recipients provide evidence that failure to consider cognitive impairment leading to inappropriate prescribing is common.[56] Analyzing data from 698 community-dwelling subjects, the study found that of the 9% who filled a prescription for an antimuscarinic, 35% were identified as having dementia and 76% experienced a serious fall or delirium, 32% were on a cholinesterase inhibitor for dementia, and 19% were on another medication with strong anticholinergic activity.

Research Evidence

In discussing its recommendation for using caution when prescribing antimuscarinics or β_3-adrenoceptor agonists in frail patients, the AUA/SUFU guideline cites studies on the adverse cognitive effects of antimuscarinics and a lack of data on the use of β_3-adrenoceptor agonists.[12] Since the last update to the guideline, however, evidence has emerged that is consistent with the hypothesis that β_3-adrenoceptor agonists are a safer choice for treating OAB than are antimuscarinics, with respect to cognitive effects and dementia risk.[57,58]

Research investigating the effects of medications with anticholinergic activity on the risk of cognitive impairment and dementia comprises several studies with varying designs, patient populations, follow-up durations, and measured outcomes. **Table 2** summarizes a few of these studies.[16,59,60]

A recently conducted systematic literature review and quantitative meta-analysis assessed the risk of incident dementia associated with ≥ 3 months of exposure to anticholinergics.[61] Six studies representing 645,865 patients met the rigorous criteria for inclusion in the meta-analysis; 2 of the 6 studies included data specific for bladder antimuscarinics.[16,59,60,62-64] The results showed that use of anticholinergics significantly increased the risk of dementia by 46% compared with nonuse **(Figure 4)**.[61] The relationship was consistent

Table 2. Select Studies Investigating Impact of Anticholinergic Use on Cognition and Dementia Risk

Study	Participants	Follow-Up/ Study Duration, Years	Main Findings
Longitudinal			
Ancelin[59]	372 adults aged > 60 years without dementia	8	Significantly increased risk (5-fold) of mild cognitive impairment in subjects with a 1-year history of continuous anticholinergic use prior to testing vs nonusers
Gray[60]	3434 adults aged ≥ 65 years without dementia	7.3	Significant 10-year cumulative dose-response relationship between anticholinergic use and incident dementia Dose stratification showed risk was significantly increased (1.54-fold) at the highest cumulative dose exposure
Nested case-control study			
Coupland[16]	Adults aged ≥ 55 years; 58,769 with dementia matched to 225,574 without dementia	Not applicable	Anticholinergics associated with dose-related increased risk for dementia Risk increased significantly at all anticholinergic dose levels (1.06- to 1.49-fold) and in the subgroup using bladder antimuscarinics (1.65-fold)

in the studies assessing bladder antimuscarinics. In addition, a stratified analysis of data from 3 studies with dose information showed the risk of dementia increased with increasing anticholinergic medication dose and was statistically significant even at the lowest dose exposure level.

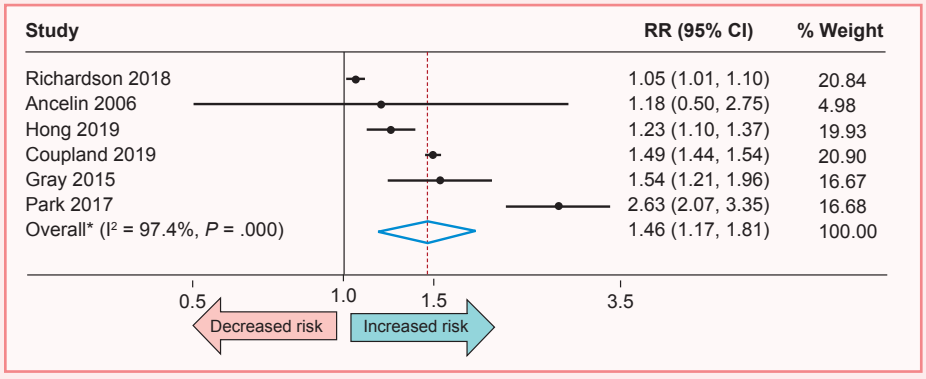


Figure 4. Forest plot of estimated rate ratios for the association between ≥ 3 months of anticholinergic use and incident dementia.[61] On average, anticholinergics increased the risk by 46% vs nonuse.

* 95% prediction interval = 0.70 to 3.04

Abbreviations: CI, confidence interval; RR, rate ratio.

Data on risk of dementia associated with β_3-adrenoceptor agonist treatment of OAB is available from a retrospective Canadian study examining 47,324 patients starting treatment with an antimuscarinic and a matched group of 23,662 patients starting treatment with a β_3-adrenoceptor agonist.[58] The analysis showed that the antimuscarinic group had a statistically significant 1.23-fold increased risk of dementia compared with the β_3-adrenoceptor agonist group. The results were similar in a secondary analysis restricted to patients with at least 3 months of continuous medication use who had not developed dementia during their first 3 months of treatment. A post hoc analysis conducted to explore a possible differential risk depending on medication received found that oxybutynin, solifenacin, tolterodine, and other antimuscarinics (fesoterodine, trospium, darifenacin) all carried a similar risk. Interestingly, patients aged ≤ 75 years and males receiving antimuscarinics had a higher risk of dementia relative to similar users receiving β_3-adrenoceptor agonists.

Prospectively collected data on the effect of treatment of OAB with a β_3-adrenoceptor agonist is available from the 12-week, randomized phase 4 PILLAR trial comparing mirabegron 25 and 50 mg with placebo for the treatment of wet OAB in 887 community-dwelling patients aged ≥ 65 years.[57] Analyses of data collected at baseline and at study end showed no changes in either the mirabegron or placebo group in mean Montreal Cognitive Assessment scores or percentages of patients with a Montreal Cognitive Assessment score indicating mild cognitive impairment **(Figure 5)**.

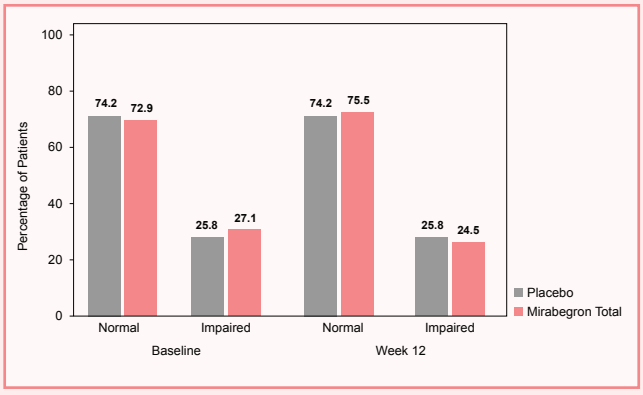


Figure 5. Montreal Cognitive Assessment score at baseline and at week 12/end of treatment in the PILLAR study[57]

Reproduced with permission from Griebling TL, et al. Effect of mirabegron on cognitive function in elderly patients with overactive bladder: MoCA results from a phase 4 randomized, placebo-controlled study (PILLAR). *BMC Geriatr.* 2020;20(1):109. Copyright 2020 by The Authors.

Case Discussions

Case 1
From the Files of Roger Dmochowski, MD, MMHC, FACS

A 54-year-old woman who was a forensic accountant at a leading accounting firm complained, "I can't deal with my bladder anymore!" Her symptom diary showed urinary frequency (14 micturitions/d), bothersome urgency, and minimal but daily incontinence.

The patient had early-onset Parkinson's disease with dystonia, medically controlled chronic obstructive pulmonary disease, and atopic dermatitis. Her medications included ipratropium, benztropine, and diphenhydramine. She had no remarkable findings on physical examination or urinalysis. Postvoid residual urine volume was 10 mL.

The patient had already reduced fluid consumption, tried urge reduction behavioral therapy, and had been doing pelvic floor exercises for approximately 20 years. She researched medications that could impact cognitive dysfunction and said she could not agree to any medication that might impact her mentation.

Dr Dmochowski: Patients we see today have often researched their symptoms and possible treatments on the internet and may request specific treatments or have concerns about treatment risks. How would you treat this patient?

Dr Brucker: Each of the patient's existing medications has anticholinergic activity, which raises concern about cognition. I would choose a β_3-adrenoceptor agonist and avoid an antimuscarinic that would add to her anticholinergic burden.

Dr Kobashi: In addition to her medications, this patient is at risk for cognitive impairment because of her Parkinson's disease. Therefore, I would also favor a β_3-adrenoceptor agonist. Although concern about cognitive impairment is greater in patients who are older than in those who are younger, patients who start antimuscarinic treatment of OAB at a younger age will potentially have longer-term exposure that increases their risk. Unfortunately, because of insurance coverage, patients often have to start on an antimuscarinic, but I schedule an early follow-up to review efficacy and safety. Then, I document adverse effects, intolerance, lack of response, and/or concerns about polypharmacy as supporting evidence to gain approval for a class switch. My discussions of OAB management always incorporate a review of factors that could be contributing to symptoms, including comorbidities, medications, and dietary and behavioral issues, and I discuss behavioral therapies.

Dr Dmochowski: The patient was started on a β_3-adrenoceptor agonist after making behavioral modifications and is benefitting with symptomatic improvement.

Case 2
From the Files of Benjamin M. Brucker, MD

An 84-year-old woman was seen for follow-up 12 weeks after starting OAB treatment with tolterodine. She noted some improvement and denied stress or urgency incontinence, but reported persistent urinary urgency, frequency, and nocturia. She presented a newsletter that discussed risks of anticholinergic use in the elderly, and asked, "Doctor, what are you trying to do to me?"

The patient recently moved to an assisted living facility located 1 block from the practice's office. She had vision impairment from age-related macular degeneration and painful spinal stenosis. Current medications included intraocular bevacizumab injections and acetaminophen and lidocaine patches.

Findings on physical examination included significant atrophy, no pelvic organ prolapse, ability to contract pelvic floor muscles appropriately, and no leaking on cough or Valsalva maneuver. Other pertinent data included a Mini-Mental State Examination score of 23, indicating mild cognitive impairment, a postvoid residual of 0 mL, and a bland urinalysis with no abnormalities. Daily fluid intake was 1 cup of decaffeinated coffee, 16 oz each of cranberry juice and water, and 1 vodka martini every Saturday night. Per her diary, the patient had no leaks and voided 40 oz/24 hours in 12 small volume voids during the day in addition to 3 voids at night.

Dr Brucker: What is your level of concern about the potential effect of tolterodine on mentation in this patient? With that in mind and considering her response so far, how would you treat this patient?

Dr Dmochowski: When assessment of a patient yields concern about cognitive status, the use of antimuscarinics must be balanced against potential safety concerns related to the impact of cumulative exposure and higher faculty central nervous system dysfunction. One of the abiding concerns with the management of OAB is the ability of patients to respond to bladder stimuli for social toileting. If patients are unable to respond or are simply not impacted by their voiding dysfunction, it is reasonable to avoid intervention with medical therapy, given the likelihood that the intervention will be unsuccessful. If antimuscarinic therapy is the only option because of expense, such as with the patient in this case, it would be best to avoid pharmacologic therapy in the interest of avoiding complications.

Dr Brucker: Given the persistence of symptoms and the fact that the patient is already dealing with mild cognitive impairment, I think this is a patient who

would benefit from switching classes of drugs. At this point, she should receive a β_3-adrenoceptor agonist.

The scenario presented—a patient bringing up concerns about drug adverse effects—is more common in my practice today than ever before. We also need to consider aspects such as drug-drug interactions and other unique patient characteristics that might make us favor suggesting one treatment over another.

Take-Home Points

There are many effective treatment options for OAB:

- The AUA/SUFU OAB guideline recommends first- (behavioral), second- (pharmacologic), and third-line (interventional) therapies, but it is not imperative to follow the algorithm in a stepwise fashion
- Behavioral measures can be helpful alone and in combination with other therapies
- Antimuscarinics appear to be equally effective for improving OAB signs and symptoms but vary in their potential to cause specific adverse events because of pharmacologic and pharmacokinetic differences
- β_3-adrenoceptor agonists have demonstrated similar efficacy to antimuscarinics but may have a more favorable adverse effect profile

Vibegron is a new β_3-adrenoceptor agonist for treating OAB.

- Vibegron requires no dose titration and carries no cautions or warnings about blood pressure measurement, use in patients with severe uncontrolled hypertension, or CYP450-mediated drug interactions
- Pivotal trial data show that vibegron has a rapid onset of benefit and sustained efficacy and safety for at least 1 year

Emerging treatments for OAB include another β_3-adrenoceptor agonist and an intradetrusor gene therapy.

Pharmacologic treatment of OAB has been associated with low rates of persistence/adherence.

- Multiple studies show higher persistence rates with β_3-adrenoceptor agonists than with antimuscarinics
- Medication reviews and thorough counseling on efficacy and safety can promote OAB medication adherence/persistence

Frailty, cognitive status, and anticholinergic load should all be considered in treatment decisions for patients with OAB.

- Retrospective and limited prospective data from studies of cognitive impairment and dementia suggest that β_3-adrenoceptor agonists may be a safer alternative to antimuscarinics

References

1. Haylen BT, de Ridder D, Freeman RM, et al; International Urogynecological Association; International Continence Society. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn.* 2010;29(1):4-20.
2. Eapen RS, Radomski SB. Review of the epidemiology of overactive bladder. *Res Rep Urol.* 2016;8:71-76.
3. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol.* 2003;20(6):327-336.
4. Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol.* 2006;50(6):1306-1314.
5. Milsom I, Kaplan SA, Coyne KS, Sexton CC, Kopp ZS. Effect of bothersome overactive bladder symptoms on health-related quality of life, anxiety, depression, and treatment seeking in the United States: results from EpiLUTS. *Urology.* 2012;80(1):90-96.
6. Tubaro A. Defining overactive bladder: epidemiology and burden of disease. *Urology.* 2004;64(6)(suppl 1):2-6.
7. Coyne KS, Payne C, Bhattacharyya SK, et al. The impact of urinary urgency and frequency on health-related quality of life in overactive bladder: results from a national community survey. *Value Health.* 2004;7(4):455-463.
8. Szabo SM, Gooch K, Schermer C, et al. Association between cumulative anticholinergic burden and falls and fractures in patients with overactive bladder: US-based retrospective cohort study. *BMJ Open.* 2019;9(5):e026391.
9. Szabo SM, Gooch KL, Walker DR, Johnston KM, Wagg AS. The association between overactive bladder and falls and fractures: a systematic review. *Adv Ther.* 2018;35(11):1831-1841.
10. Suehs BT, Caplan EO, Hayden J, Ng DB, Gaddy RR. The relationship between anticholinergic exposure and falls, fractures, and mortality in patients with overactive bladder. *Drugs Aging.* 2019;36(10):957-967.
11. Reynolds WS, Fowke J, Dmochowski R. The burden of overactive bladder on US public health. *Curr Bladder Dysfunct Rep.* 2016;11(1):8-13.
12. Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of non-neurogenic overactive bladder (OAB) in adults: an AUA/SUFU guideline (2019). American Urological Association. Accessed March 1, 2021. https://www.auanet.org/guidelines/overactive-bladder-(oab)-guideline
13. Abrams P, Andersson K-E, Buccafusco JJ, et al. Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. *Br J Pharmacol.* 2006;148(5):565-578.
14. Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJC. Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database Syst Rev.* 2012;1:CD005429.
15. Cetinel B, Onal B. Rationale for the use of anticholinergic agents in overactive bladder with regard to central nervous system and cardiovascular system side effects. *Korean J Urol.* 2013;54(12):806-815.
16. Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic drug exposure and the risk of dementia: a nested case-control study. *JAMA Intern Med.* 2019;179(8):1084-1093.
17. Marcelissen T, Rademakers K. Treatment of elderly patients with overactive bladder: has mirabegron come of age? *Eur Urol.* 2020;77(2):221-222.
18. Kim YJ, Tae BS, Bae JH. Cognitive function and urologic medications for lower urinary tract symptoms. *Int Neurourol J.* 2020;24(3):231-240.
19. Srikrishna S, Robinson D, Cardozo L. Important drug–drug interactions for treatments that target overactive bladder syndrome. *Int Urogynecol J.* 2014;25(6):715-720.
20. PRNewswire. FDA approves overactive bladder treatment Myrbetriq™ (mirabegron) from Astellas. News release. June 28, 2012. Accessed March 1, 2021. https://www.prnewswire.com/news-releases/fda-approves-overactive-bladder-treatment-myrbetriq-mirabegron-from-astellas-160732575.html
21. Business Wire. Urovant Sciences announces U.S. FDA approval of GEMTESA® (vibegron) 75 mg tablets for the treatment of patients with overactive bladder (OAB). News release. December 23, 2020. Accessed March 1, 2021. https://apnews.com/press-release/business-wire/business-corporate-news-medication-products-and-services-health-care-industry-56ccded80096458a9cfe86d55884757e

22. Yamaguchi O. Beta3-adrenoceptors in human detrusor muscle. *Urology*. 2002;59(5)(suppl 1):25-29.
23. Schena G, Caplan MJ. Everything you always wanted to know about β_3-AR * (* but were afraid to ask). *Cells.* 2019;8(4):357.
24. Bhadada SV, Patel BM, Mehta AA, Goyal RK. β(3) receptors: role in cardiometabolic disorders. *Ther Adv Endocrinol Metab.* 2011;2(2):65-79.
25. Herschorn S, Barkin J, Castro-Diaz D, et al. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the β_3 adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. *Urology*. 2013;82(2):313-320.
26. US National Library of Medicine. Mirabegron package insert. Updated December 19, 2019. Accessed March 16, 2021. https://dailymed.nlm.nih.gov/dailymed/
27. 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.
28. Drake MJ, Chapple C, Esen AA, et al; BESIDE study investigators. 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;70(1):136-145.
29. Herschorn S, Chapple CR, Abrams P, et al. Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study). *BJU Int.* 2017;120(4):562-575.
30. Gratzke C, Chapple C, Mueller ER, et al. Efficacy and safety of combination pharmacotherapy for patients with overactive bladder: a rapid evidence assessment. *Eur Urol.* 2019;76(6):767-779.
31. Nitti VW, Khullar V, van Kerrebroeck P, et al. Mirabegron for the treatment of overactive bladder: a prespecified pooled efficacy analysis and pooled safety analysis of three randomised, double-blind, placebo-controlled, phase III studies. *Int J Clin Pract.* 2013;67(7):619-632.
32. Staskin D, Frankel J, Varano S, Shortino D, Jankowich R, Mudd PN Jr. International phase III, randomized, double-blind, placebo and active controlled study to evaluate the safety and efficacy of vibegron in patients with symptoms of overactive bladder: EMPOWUR. *J Urol.* 2020;204(2):316-324.
33. US National Library of Medicine. Vibegron package insert. Updated January 14, 2021. Accessed March 16, 2021. https://dailymed.nlm.nih.gov/dailymed/
34. Frankel J, Varano S, Staskin D, Shortino D, Jankowich R, Mudd PN Jr. Vibegron improves quality-of-life measures in patients with overactive bladder: patient-reported outcomes from the EMPOWUR study. *Int J Clin Pract.* 2020;e13937.
35. Staskin D, Frankel J, Varano S, Shortino D, Jankowich R, Mudd Jr PN. Once-daily vibegron 75 mg for overactive bladder: long-term safety and efficacy from a double-blind extension study of the international phase 3 trial (EMPOWUR). Accepted manuscript. Published online December 28, 2020. *J Urol.* doi:10.1097/JU.0000000000001574
36. Yoshida M, Kakizaki H, Takahashi S, Nagai S, Kurose T. Long-term safety and efficacy of the novel β_3-adrenoreceptor agonist vibegron in Japanese patients with overactive bladder: a phase III prospective study. *Int J Urol.* 2018;25(7):668-675.
37. Yoshida M, Takeda M, Gotoh M, et al. Efficacy of vibegron, a novel β_3-adrenoreceptor agonist, on severe urgency urinary incontinence related to overactive bladder: post hoc analysis of a randomized, placebo-controlled, double-blind, comparative phase 3 study. *BJU Int.* 2020;125(5):709-717.
38. Yoshida M, Takeda M, Gotoh M, et al. Efficacy of novel β_3-adrenoreceptor agonist vibegron on nocturia in patients with overactive bladder: a post-hoc analysis of a randomized, double-blind, placebo-controlled phase 3 study. *Int J Urol.* 2019;26(3):369-375.
39. Business Wire. Velicept Therapeutics announces positive top-line phase 2b results for solabegron in the treatment of overactive bladder (OAB). News release. March 28, 2019. Accessed March 1, 2021. https://www.businesswire.com/news/home/20190328005483/en/Velicept-Therapeutics-Announces-Positive-Top-Line-Phase-2b-Results-for-Solabegron-in-the-Treatment-of-Overactive-Bladder-OAB
40. Ohlstein EH, von Keitz A, Michel MC. A multicenter, double-blind, randomized, placebo-controlled trial of the β_3-adrenoceptor agonist solabegron for overactive bladder. *Eur Urol.* 2012;62(5):834-840.
41. Rovner E, Chai TC, Jacobs S, et al. Evaluating the safety and potential activity of URO-902 (hMaxi-K) gene transfer by intravesical instillation or direct injection into the bladder wall in female participants with idiopathic (non-neurogenic) overactive bladder syndrome and detrusor overactivity from two double-blind, imbalanced, placeco-controlled randomized phase 1 trials. *Neurourol Urodyn.* 2020;39(2):744-753.
42. URO-902 in female subjects with overactive bladder and urge urinary incontinence. ClinicalTrials.gov. December 26, 2019. Updated August 17, 2020. Accessed March 17, 2020. https://clinicaltrials.gov/ct2/show/NCT04211831
43. Kim TH, Choo M-S, Kim Y-J, Koh H, Lee K-S. Drug persistence and compliance affect patient-reported outcomes in overactive bladder syndrome. *Qual Life Res.* 2016;25(8):2021-2029.
44. Balkrishnan R, Bhosle MJ, Camacho FT, Anderson RT. Predictors of medication adherence and associated health care costs in an older population with overactive bladder syndrome: a longitudinal cohort study. *J Urol.* 2006;175(3 Pt 1):1067-1071.
45. Veenboer PW, Bosch JLHR. Long-term adherence to antimuscarinic therapy in everyday practice: a systematic review. *J Urol.* 2014;191(4):1003-1008.
46. Vouri SM, Schootman M, Strope SA, Xian H, Olsen MA. Antimuscarinic use and discontinuation in an older adult population. *Arch Gerontol Geriatr.* 2019;80:1-11.
47. Wagg A, Franks B, Ramos B, Berner T. Persistence and adherence with the new beta-3 receptor agonist, mirabegron, versus antimuscarinics in overactive bladder: early experience in Canada. *Can Urol Assoc J.* 2015;9(9-10):343-350.
48. Nitti VW, Rovner ES, Franks B, et al. Persistence with mirabegron versus tolterodine in patients with overactive bladder. *Am J Pharm Benefits.* 2016;8(2):e25-e33.
49. Wagg AS, Foley S, Peters J, Nazir J, Kool-Houweling L, Scrine L. Persistence and adherence with mirabegron vs antimuscarinics in overactive bladder: retrospective analysis of a UK General Practice prescription database. *Int J Clin Pract.* 2017;71(10).
50. Soda T, Tashiro Y, Koike S, Ikeuchi R, Okada T. Overactive bladder medication: persistence, drug switching, and reinitiation. *Neurourol Urodyn.* 2020;39(8):2527-2534.
51. Chapple CR, Nazir J, Hakimi Z, et al. Persistence and adherence with mirabegron versus antimuscarinic agents in patients with overactive bladder: a retrospective observational study in UK clinical practice. *Eur Urol.* 2017;72(3):389-399.
52. Yeowell G, Smith P, Nazir J, Hakimi Z, Siddiqui E, Fatoye F. Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB): a systematic literature review. *BMJ Open.* 2018;8(11):e021889.
53. Benner JS, Nichol MB, Rovner ES, et al. Patient-reported reasons for discontinuing overactive bladder medication. *BJU Int.* 2010;105(9):1276-1282.
54. Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction. Overactive bladder CCP. Accessed March 1, 2021. https://sufuorg.com/resources/overactive-bladder-ccp.aspx
55. 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2019;67(4):674-694.
56. Green AR, Segal J, Boyd CM, Huang J, Roth DL. Patterns of potentially inappropriate bladder antimuscarinic use in people with dementia: a retrospective cohort study. *Drugs Real World Outcomes.* 2020;7(2):151-159.
57. Griebling TL, Campbell NL, Mangel J, et al. Effect of mirabegron on cognitive function in elderly patients with overactive bladder: MoCA results from a phase 4 randomized, placebo-controlled study (PILLAR). *BMC Geriatr.* 2020;20(1):109.
58. Welk B, McArthur E. Increased risk of dementia among patients with overactive bladder treated with an anticholinergic medication compared to a beta-3 agonist: a population-based cohort study. *BJU Int.* 2020;126(1):183-190.
59. Ancelin ML, Artero S, Portet F, Dupuy A-M, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ.* 2006;332(7539):455-459.
60. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med.* 2015;175(3):401-407.
61. Dmochowski RR, Thai S, Iglay K, et al. Increased risk of incident dementia following use of anticholinergic agents: a systematic literature review and meta-analysis. *Neurourol Urodyn.* 2021;40(1):28-37.
62. Hong C-T, Chan L, Wu D, Chen W-T, Chien L-N. Antiparkinsonism anticholinergics increase dementia risk in patients with Parkinson's disease. *Parkinsonism Relat Disord.* 2019;65:224-229.
63. Park H-Y, Park J-W, Song HJ, Sohn HS, Kwon J-W. The association between polypharmacy and dementia: a nested case-control study based on a 12-year longitudinal cohort database in South Korea. *PLoS One.* 2017;12(1):e0169463.
64. Richardson K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case-control study. *BMJ.* 2018;361:k1315.

Instant CME/CE Certificate Available With Online Testing and Course Evaluation at

https://tinyurl.com/OABOutcomes

CME/CE POSTTEST QUESTIONS

To obtain CME/CE credit for this activity, complete the posttest and course evaluation online at **https://tinyurl.com/OABOutcomes.** Upon successful completion of the posttest and evaluation, you will be able to generate an instant certificate of credit.

See detailed instructions at Instructions for Obtaining Credit on page 2.

1. A 75-year-old widow who has homecare assistance complains about urinary frequency, urgency, and nocturia. Current medications include donepezil, losartan, and alendronate. What would you prescribe in addition to behavioral therapy?
   a. Oxybutynin extended release
   b. Oxybutynin immediate release
   c. Tolterodine
   d. Mirabegron

2. According to the results of a recent meta-analysis, long-term use of anticholinergics for ≥ 3 months has which of the following effects on the risk of dementia?
   a. Decreases
   b. Increases
   c. Has no effect on
   d. It depends on the anticholinergic agent

3. According to data from several studies, which OAB medication is least likely to be associated with adverse cognitive effects?
   a. Darifenacin
   b. Mirabegron
   c. Oxybutynin extended release
   d. Tolterodine

4. In a meta-analysis of 6 studies, use of anticholinergics for ≥ 3 months increased the risk of dementia by ___ compared with nonuse.
   a. 26%
   b. 36%
   c. 46%
   d. 56%

5. At which follow-up visit in the phase 3 EMPOWUR study did vibegron first show statistical superiority to placebo for reducing daily micturitions and daily urge urinary incontinence episodes?
   a. Week 2
   b. Week 4
   c. Week 8
   d. Week 12

6. URO-902 is an investigational therapy for OAB designed to deliver a gene to induce expression of _____ in urinary bladder smooth muscle cells.
   a. BK channel
   b. M_2 receptors
   c. A muscarinic antagonist
   d. β_3-adrenergic receptors

7. Vibegron is distinguished from mirabegron according to lack of inhibition of the _____ hepatic enzyme.
   a. CYP1A2
   b. CYP2D6
   c. CYP2C9
   d. CYP3A4

8. In a study that surveyed patients who discontinued antimuscarinic OAB medications, the most common reason for stopping was:
   a. Cost
   b. Lack of expected efficacy
   c. Dry mouth
   d. Constipation

9. Which test does the AUA/SUFU guideline on non-neurogenic OAB recommend performing to assess for cognitive impairment?
   a. Mini-Cog
   b. Mini-Mental State Examination
   c. Montreal Cognitive Assessment
   d. General Practitioner Assessment of Cognition

10. In initial counseling on OAB treatment, patients should be advised on all the following, EXCEPT:
    a. Medications can improve symptoms but are not a cure
    b. OAB is a chronic condition that requires ongoing treatment for symptom control
    c. A follow-up visit should be scheduled to review their response to recommended treatment and the need for modifications
    d. Because of their potential adverse effects, medications are considered only after behavioral treatments fail to provide sufficient benefit

11. The antimuscarinics used for OAB differ in receptor selectivity and pharmacokinetic profile. These differences translate clinically into:
    a. Variable efficacy for reducing urinary urgency
    b. Variable efficacy for reducing urge urinary incontinence
    c. Variable adverse event risk
    d. No differences with respect to efficacy or safety outcomes