

SUPPLEMENT TO  
**Pharmacy and Therapeutics**

**P&T**<sup>®</sup>

A Peer-Reviewed Journal for Managed Care  
and Hospital Formulary Management

# Raising Expectations in the Management Of Overactive Bladder with Urge Urinary Incontinence: Clinical and Economic Implications for Health Care Providers

**A CME/CE–Certified Supplement**

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Supported by an educational grant from  
Astellas Pharma US, Inc. and GlaxoSmithKline

*Volume 30, No. 11  
November 2005*

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P&T<sup>®</sup> is a peer-reviewed journal for managed care and hospital formulary management (ISSN 1052-1372) (GST #128741063) (IPM #0608025) and is published monthly by MediMedia USA Inc., with business offices at 780 Township Line Road, Yardley, PA 19067; telephone: (267) 685-2788; fax: (267) 685-2966. This is Volume 30, Number 11.

Subscriptions: Individuals and institutions, U.S., \$80; U.S. Students/Residents/Nurses, \$30; Outside U.S.: \$120. Single copies: \$12 per copy U.S.; \$22 per copy outside U.S. Circulation records are maintained at 780 Township Line Road, Yardley, PA 19067.

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November 2005

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This supplement is supported by an educational grant from Astellas Pharma US, Inc. and GlaxoSmithKline. The material in this supplement has been independently peer reviewed. The grantors played no role in reviewer selection.

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### Raising Expectations in the Management of Overactive Bladder with Urge Urinary Incontinence: Clinical and Economic Implications for Health Care Providers

**Activity Release Date:** November 2005

**Activity Expiration Date:** November 30, 2006

#### Activity Description

Overactive bladder (OAB) is a common condition associated with numerous medical complications and comorbidities. Patients with OAB and OAB-associated medical conditions experience debilitating decrements in health-related quality of life (HRQoL) and generate substantial increases in medical expenditures.

This supplement reviews current research on OAB, with an emphasis on those OAB patients with urge urinary incontinence. The striking prevalence of OAB and the profound medical, HRQoL, and economic impact, as well as patients' reluctance to seek help for this condition, are explored. Pharmacological management is reviewed and focuses on treatment efficacy, tolerability, and the historical problem of patient persistence. The impact of treatment on the important clinical endpoint of complete resolution of incontinence is presented along with new data on the pharmacoeconomic implications of effective therapy.

#### Educational Objectives

Upon completion of this activity, participants should be able to do the following:

- define overactive bladder with urge urinary incontinence and describe the epidemiology of the condition.
- discuss the medical, health-related quality-of-life, and cost implications of overactive bladder and its associated complications and comorbidities.
- assess barriers to help-seeking among patients with overactive bladder.
- describe the efficacy, tolerability, and health-related quality-of-life impact of pharmacotherapy for overactive bladder.
- explain potential pharmacoeconomic implications of persistence and effective treatments for overactive bladder.

#### Target Audience

This activity will be of value to medical directors, chairpersons and members of P&T committees, physicians, pharmacists, nurse directors, and other health care professionals in the field.

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# Raising Expectations in the Management of Overactive Bladder with Urge Urinary Incontinence: Clinical and Economic Implications for Health Care Providers

## INTRODUCTION

Overactive bladder (OAB) is a common condition associated with numerous medical complications and comorbidities. Patients with OAB and OAB-associated medical conditions experience debilitating decrements in health-related quality of life (HRQoL) and generate substantial increases in medical expenditures.

The International Continence Society recently defined OAB syndrome as a symptom complex that includes urinary urgency, with or without urge urinary incontinence (UI), usually accompanied by urinary frequency and nocturia.<sup>1</sup> These symptoms occur in the absence of infection or other readily identifiable pathology.<sup>1</sup> OAB symptoms not associated with urge UI have been referred to as “OAB-dry,” and OAB symptoms with urge UI have been referred to as “OAB-wet.”

This supplement reviews current research on OAB, with an emphasis on those patients who have OAB with urge UI (i.e., OAB-wet). It also explores the striking prevalence of OAB and the profound medical, HRQoL, and economic impact of this condition, as well as the surprising reluctance of patients with OAB to seek help. Pharmacological management is reviewed in depth and focuses on treatment efficacy, tolerability, and the historical problem of patient persistence. The impact of treatment on the important clinical endpoint of complete resolution of incontinence is presented along with new data on the pharmacoeconomic implications of effective therapy.

## EPIDEMIOLOGY

Estimates of the prevalence of OAB in the U.S. population suggest that approximately 34 million adults are affected by this condition.<sup>2</sup> This makes OAB more prevalent than other important and common chronic conditions (e.g., hypertension, allergic rhinitis, and heart disease).<sup>3</sup>

The prevalence of OAB varies with age and sex. In the U.S., the prevalence of OAB in men (16.0%)

is similar to women (16.9%) and increases with age. However, the prevalence of urge UI is higher in women than men of all ages and escalates markedly in women who are older than 44 years of age and in men who are older than 64 years of age.<sup>4</sup> Although the prevalence of OAB in men and women is similar, the prevalence of urge UI among women with OAB is approximately 55%; for men, the prevalence is approximately 16%.<sup>4</sup> In Europe, the overall population prevalence of OAB is similar to that of the U.S., with a combined frequency in men and women of 16.6% for individuals 40 years of age or older. The combined prevalence of OAB with urge UI is 36%.<sup>5</sup>

A recent study of patients residing in 378 skilled nursing facilities reported the prevalence of UI among these patients.<sup>6</sup> Before exclusion of patients with bowel incontinence, the overall UI rate was 58%. After the exclusion of these patients, the prevalence of UI was 30%.<sup>6</sup>

The specific prevalence of OAB with urge UI in the overall population varies by age and sex; from just under one third to more than half of patients with OAB have urge UI.

## COMPLICATIONS AND CONSEQUENCES

### Medical

Overactive bladder and urge UI are associated with numerous complications and medical comorbidities, including falls and fractures, urinary tract infections (UTIs), skin infections, sleep disturbances, and depression.<sup>7</sup> In a study of urge UI in community-dwelling women (mean age, 78.5 years), during an average follow-up of three years, approximately 55% of women reported falling and 8.5% reported nonspinal fractures.<sup>8</sup> Urge UI was found to be an independent risk factor associated with these falls and fractures. Stress incontinence, when it occurred, was not associated with falls or fractures. The authors postulated that urinary frequency, nocturia, and rushing to bathrooms increased the risk of injury.<sup>8</sup>

In another study, the association between UI and hospital or nursing-home admission and mortality was explored.<sup>9</sup> After adjusting for age, cohort, and comorbid conditions, the risk of hospitalization was 30% higher in women and 50% higher in men with incontinence. The risk of nursing home admission was 2.0 times greater for women and 3.2 times greater in men with incontinence. The adjusted risk of mortality also was slightly greater for women and men with incontinence.<sup>9</sup> However, the increased risk of mortality among patients with UI was not confirmed in a second study,<sup>10</sup> which associated the overall increased mortality in these patients with increased frailty.

After the researchers controlled for confounding variables, people with OAB identified during a telephone survey were found to visit physicians 20% more often and had 138% more UTIs during the preceding year than people without OAB. In addition, they had 2.27 times the risk of experiencing injury from falls and 1.53 times the risk of experiencing a bone fracture than controls (although the risk was not statistically significant because of the small sample size).<sup>11</sup>

Two studies assessed depression in patients with incontinence.<sup>12,13</sup> In the first trial,<sup>12</sup> consecutive patients presenting to an incontinence clinic and matched continent controls were compared for pre-existing or current depression. Approximately 30% of all incontinent patients were either depressed or had a history of depression compared with 17% of controls. However, 60% of patients with urge UI were either depressed or had a history of depression.<sup>12</sup> In the second trial,<sup>13</sup> 44% of women with urge UI and 18% of patients with stress UI had a history of depression.

In a recent, large retrospective analysis of a managed care claims database, Darkow and colleagues evaluated the clinical and economic implications of OAB on the management of associated comorbidities.<sup>14</sup> During the one-year study, they assessed the prevalence and cost of falls, fractures, depression, UTIs, skin infections, and vulvovaginitis in patients with OAB (N = 11,556) and in matched controls (N = 11,556).

Patients with OAB were significantly more likely than controls to have each of the studied comorbidities.

UTIs were most common in patients with OAB, followed by falls and fractures, depression, vulvovaginitis, and skin infections. After adjustments were made for various confounders, these conditions were 2.8 times more likely to occur in patients with OAB than in control patients (95% confidence interval [CI], 2.6–2.9) (Table 1).<sup>14</sup>

### Health-Related Quality of Life

Approximately two thirds of patients with OAB report a deleterious effect on their activities of daily living (ADL).<sup>5</sup> For many patients, the symptom that is most bothersome and detrimental to quality of life is UI.<sup>15</sup> In studies, UI has been shown to reduce the social and psychological well-being of affected individuals.<sup>16</sup>

Patients with OAB, with or without urge UI, have lower QoL scores, higher depression scores, and poorer quality of sleep than matched controls.<sup>4</sup> However, OAB-wet patients have significantly reduced HRQoL scores across all domains compared with OAB-dry patients and matched controls.<sup>17</sup> Health perception and role functioning scores among OAB-wet patients were most affected, although all HRQoL domains were significantly reduced in OAB-wet patients.<sup>17</sup>

In a study of younger, community-dwelling women 20 to 45 years of age, urge UI was common (15%) and resulted in a significant decrement in HRQoL among affected individuals.<sup>18</sup> Most significantly affected were the HRQoL domains of social function, physical function, mobility, emotional, and embarrassment. Stress UI also was common (39%) but did not significantly reduce HRQoL. Although many women were bothered by their symptoms, few consulted health care providers.<sup>18</sup>

**TABLE 1** Overactive bladder (OAB)-related comorbidities: prevalence

Morbidity	Adjusted Prevalence		P Value
	OAB (%)	Controls (%)	
Any comorbidity	52.1	27.9	<0.0001
Urinary tract infections	28.0	8.4	<0.0001
Falls and fractures	25.3	16.1	<0.0001
Depression	10.5	4.9	<0.0001
Vulvovaginitis	4.7	1.8	<0.0001
Skin infections	3.9	2.3	<0.0001

Data from *Pharmacotherapy* 2005;25:511–519.<sup>14</sup>

In a case–control study conducted in Italy,<sup>19</sup> patients with OAB without incontinence had significantly higher physical scores than women with urge UI or mixed (urge and stress) UI. Decrement in physical function in these patients appears related to the involuntary and unpredictable loss of urine.

In a recent study by Ko and colleagues,<sup>20</sup> information obtained from the Medicare Health Outcomes Survey was used to assess the impact of UI on depression and HRQoL in patients enrolled in a Medicare managed care plan. The analysis applied to beneficiaries more than 65 years of age (N = 141,815), where 90% were white, 58% were women, and 59% were married. One third were high school graduates, and one third had some college education.

The prevalence of UI overall was 24.7%, with rates of 20.9% reported for men and 27.5% reported for women.<sup>20</sup> Patients with UI reported poorer overall health and higher rates of declining health than patients without UI. Approximately twice as many patients with UI reported short-term and long-term depression than patients without UI.<sup>20</sup>

With respect to HRQoL, patients with UI scored significantly lower on all eight subscales and the two summary domains of the 36-item Short Form Health Survey (SF-36) ( $P < 0.001$ ). The greatest mean

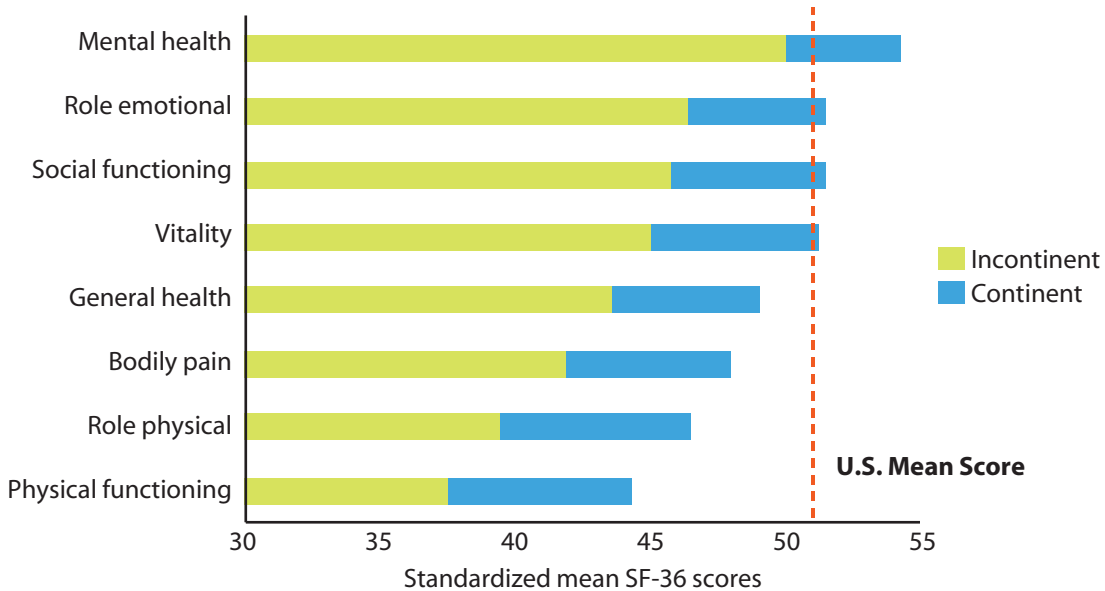
differences among the subscales were seen for role physical, physical functioning, and vitality. After adjustments were made for comorbidities and demographic differences, all subscale and summary scores remained significantly different ( $P < 0.05$ ). In addition, UI had a greater impact on vitality, social functioning, role emotional, and mental health than any of the other studied major medical comorbidities (i.e., hypertension, congestive heart failure, stroke, myocardial infarction, and diabetes) (Figure 1).<sup>20</sup>

**Cost**

The total cost of OAB (in year 2000 dollars) is \$12.6 billion, with \$9.1 billion and \$3.5 billion incurred by community and institutional residents, respectively. The annual costs associated with community residents include \$2.9 billion for diagnosis and treatment, \$1.6 billion for routine care, \$3.9 billion for treatment of health-related consequences, and \$0.8 billion in lost productivity. The average cost per community resident with OAB is estimated at \$267. The overall costs of OAB are comparable to those associated with osteoporosis and gynecological and breast cancer.<sup>2,21,22</sup>

The relative cost of UTIs, falls, and fractures associated with OAB have been estimated. UTIs account for approximately \$1.37 billion, falls with-

**FIGURE 1** Impact of urinary incontinence on health-related quality-of-life Short Form (SF-36) subscale domains



Data from *Am J Manag Care* 2005;11(4 Suppl):S103–S111.<sup>20</sup>

out fractures account for \$55 million, and falls with fractures account for \$386 million (all in year 2000 dollars).<sup>11</sup>

OAB-wet patients incur additional expenses, including the cost of incontinence pads. These patients report more physician visits and a greater utilization of health care services. In a survey of HRQoL by Liberman and colleagues,<sup>17</sup>

38.3% of OAB-wet patients, 30.9% of OAB-dry patients, and 13.1% of control patients reported more than four physician visits during the previous year.

In the study of a managed care population by Darkow and colleagues<sup>14</sup> (discussed earlier), patients with OAB were significantly more likely than controls to experience higher medical charges for each of the studied conditions. Mean adjusted medical charges in patients with OAB during the one-year study period were highest for falls and fractures, followed by UTIs, depression, skin infections, and vulvovaginitis (Table 2).<sup>14</sup> Overall mean adjusted medical charges for these conditions and total charges were \$1,689 and \$16,238, respectively, for patients with OAB and \$829 and \$10,415, respectively, for control patients. In addition, medical charges for depression and skin infections were significantly higher in patients with these conditions when they occurred in patients with OAB (\$1,154 for depression and \$1,866 for skin infections) than when they occurred in control patients (\$592 and \$507, respectively).<sup>14</sup>

In another study,<sup>23</sup> Shih and colleagues evaluated the use of resources and the impact of the cost of caring for patients with UI in 51 long-term care facilities in North Carolina. Patients were classified as either “occasionally incontinent” if they experienced leakage of a few drops of urine each month or as “frequently incontinent” if they leaked a few drops every day and larger amounts at least weekly.

The group with UI tended to be older, included more women, had more Medicare coverage, and more often resided in skilled or intermediate-care units. Approximately 89% of patients with UI also reported bowel incontinence. For patients with UI, the three activities requiring the most time spent by

**TABLE 2** Overactive bladder (OAB)-related comorbidities: medical costs

Morbidity	Adjusted Medical Charges		
	OAB	Controls	P Value
Any comorbidity	\$1,689	\$829	<0.0001
Falls and fractures	\$934	\$598	<0.0001
Urinary tract infections	\$603	\$176	<0.0001
Depression*	\$93	\$23	<0.0001
Skin infections	\$67	\$10	<0.0001
Vulvovaginitis*	\$11	\$3	0.002

\* Unadjusted.

Data from *Pharmacotherapy* 2005;25:511-519.<sup>14</sup>

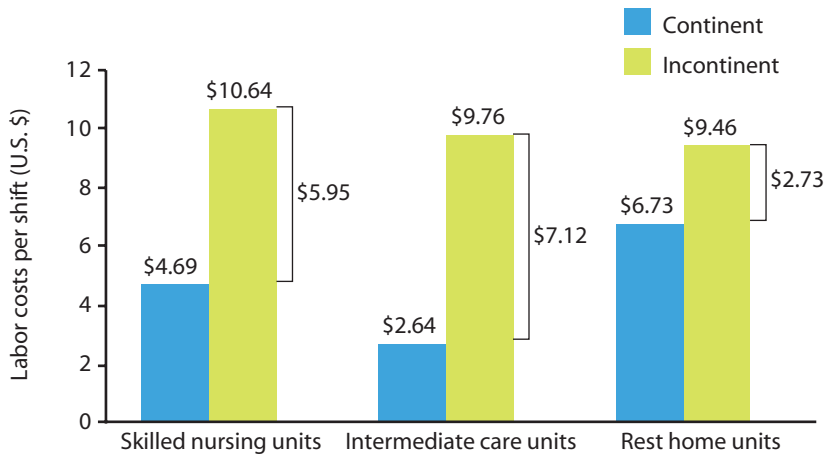
health care providers were feeding (22 minutes), bathing (19 minutes), and providing bowel and bladder training (11.8 minutes). Overall, the staff spent an average of 191 minutes per day caring for patients with UI and 60 minutes per day for patients who were continent.<sup>23</sup>

The overall annual incremental increase in labor costs to care for patients with UI in these long-term care facilities was \$4,957. Patients with occasional incontinence incurred fewer incremental shift costs (\$3.31) compared with patients with frequent incontinence (\$5.16). The greatest overall increase in shift costs occurred during the daytime shifts. When facility types were compared, the greatest overall incremental increase in costs occurred in intermediate-care units (\$7.12), followed by skilled nursing units (\$5.95) and rest-home units (\$2.73). These relationships held after a multivariate analysis controlled for demographic variables, although costs were slightly lower after the multivariate analysis (Figure 2).<sup>23</sup>

### HELP-SEEKING AND PHYSICIAN RESPONSIVENESS AMONG AFFECTED PATIENTS

Barriers to help-seeking in patients affected by OAB and urge UI are significant and contribute to low help-seeking rates. Interviews with patients were conducted regarding their help-seeking behavior in a study of those who had either agreed to receive treatment or who were already receiving treatment for urinary problems.<sup>24</sup> The most common reasons for not seeking help were lack of knowledge of the condition and available treatments. Patients considered urinary symptoms to be a normal part of aging, a consequence of childbirth, or a personal problem not warranting medical

**FIGURE 2 Urinary incontinence labor costs: long-term care facilities**



Data from *Urology* 2003;62:442–446.<sup>23</sup>

attention. Older patients were more likely to accept urinary symptoms and were less likely to seek medical assistance than younger patients. Even when patients had concerns about their symptoms, they did not always report them to their physicians.<sup>24</sup>

Patients often attempt nonmedical coping strategies before or instead of visiting their health care providers. In a cross-sectional household telephone survey,<sup>25</sup> 70% of patients with OAB reported attempting at least one nonmedical coping strategy, and OAB-wet patients were significantly more likely to use these strategies than OAB-dry patients or continent control patients. Fewer than 50% of patients with OAB had spoken to a health care provider during the preceding 12 months. Of note, when discussions with health care providers occurred, patients initiated 90% of the discussions.<sup>25</sup>

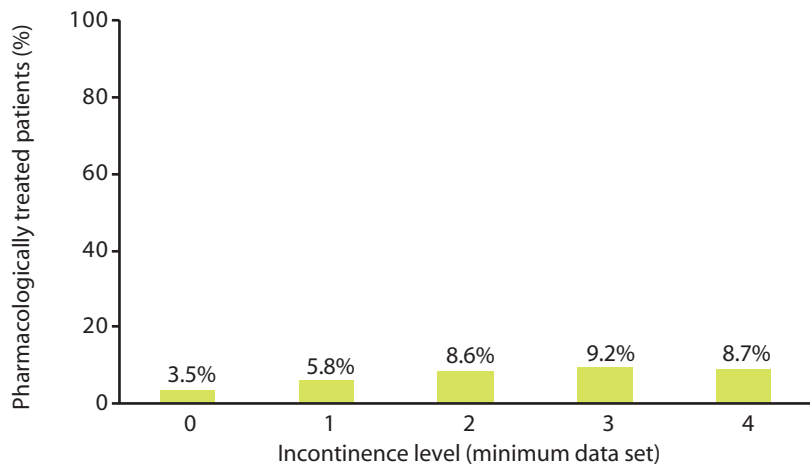
In a study of physician decision-making regarding OAB management,<sup>26</sup> OAB-wet patients were significantly more likely to be treated pharmacologically than were continent patients with nocturia or urinary frequency. Patients also were more likely to be treated

pharmacologically if they were white or black, had moderate or severe OAB (based on physicians' assessments), had used medications previously, or had incontinence more frequently. A physician's assessment of urinary severity included patient distress because of OAB, incontinence episodes during the previous 24 hours, and prior pharmacological treatment.<sup>26</sup>

In the study of patients in skilled nursing facilities described previously,<sup>6</sup> only 4.9% of incontinent

patients were receiving drug treatment ( $P < 0.001$ ). Overall, incontinent patients tended to have poor ADL and cognitive performance scores, more frequent hospitalizations, and more UI-associated comorbidities (e.g., UTIs, pressure ulcers, and depression) (Figure 3). Patients treated pharmacologically had a lower adjusted prevalence of hospitalization (15.1%) than those not treated in this manner (22.7%); ( $P < 0.001$ ). The authors suggest that some possible reasons for the underuse of pharmacological agents may include lack of safety and

**FIGURE 3 Urinary incontinence in patients in skilled nursing facilities: current pharmacological treatment rates**



Data from *Am J Manag Care* 2005;11(4 Suppl):S112–S120.<sup>6</sup>

tolerability data in this population, uncertainty among clinicians regarding the risk–benefit ratio of treatment, and the myth that UI is to be expected in the elderly.<sup>6</sup>

## TREATMENT

### Nonpharmacological Therapy

Although OAB is most commonly treated pharmacologically, nonpharmacological strategies can be used alone or in combination with pharmacotherapy. Bladder training, pelvic floor muscle exercises, and urge-suppression strategies have been used to help patients manage OAB symptoms. Rigorous studies comparing the relative efficacy among these methodologies and with pharmacotherapy have not been reported.

### Antimuscarinic Therapy

Antimuscarinic medications have long been considered first-line pharmacological agents for treating OAB. There are five known forms of muscarinic receptors,  $M_1$  through  $M_5$ . All five receptor types have been identified in the human bladder, although  $M_2$  and  $M_3$  are predominant.  $M_3$  is considered the most important for detrusor contraction. These receptors mediate normal bladder contraction and the abnormal contraction associated with OAB.<sup>27</sup> The pharmacological efficacy of the various antimuscarinic agents is believed to be mediated by M-receptor binding. The most common pharmacological adverse events (e.g., dry mouth, constipation, and blurred vision) also are believed to be mediated by antimuscarinic binding to M receptors located on other target organs (e.g., salivary glands), which also have  $M_3$  receptors.

Although traditional antimuscarinic agents, such as immediate-release (IR) formulations of oxybutynin (Ditropan®, Ditropan XL®, Oxytrol™, Ortho-McNeil Pharmaceutical, Inc.) and tolterodine (Detrol®, Detrol LA®, Pharmacia & Upjohn) have been shown to be efficacious, they have not been effective in all patients. In addition, adverse events have limited their clinical use.<sup>28,29</sup>

Extended-release (ER) formulations of oxybutynin and tolterodine have been developed. These agents are reported to have efficacy similar to their IR formulations with reduced adverse events. Although persistence rates during clinical trials for these medications are higher than rates seen in the community, as will be discussed later, persistence rates in the community are low and have been

reported to range from 5% to 21% at one year.<sup>30–32</sup>

Solifenacin (VESIcare®, Astellas Pharma US, Inc., GlaxoSmithKline), darifenacin (Enablex®, Novartis Pharmaceuticals Corporation), and trospium (Sanctura™, Odyssey Pharmaceuticals, Inc., Indevus Pharmaceuticals, Inc.) are newly available antimuscarinic agents. Trospium, an IR anticholinergic medication long used in Europe, was recently approved for use in the U.S. Darifenacin and solifenacin are new antimuscarinic agents that have also been recently approved for use in the U.S. Darifenacin is an  $M_3$ -selective muscarinic receptor antagonist, and solifenacin is a bladder-selective M-receptor antagonist. The bladder selectivity of solifenacin may be responsible for the lower incidence of adverse events (e.g., dry mouth).<sup>33</sup>

### Efficacy and Tolerability

Clinical studies addressing the efficacy and tolerability of oxybutynin, tolterodine, trospium, and the two new antimuscarinic agents, darifenacin and solifenacin, are presented here. Primary and secondary efficacy endpoints are reviewed, as are study completion rates or persistence and incidence of the most common adverse effect—dry mouth. Because urge UI, when it occurs, is often considered the most distressing symptom of OAB, restoration of continence should be a primary goal of therapy.<sup>34</sup> Therefore, when available, specific data on the complete resolution of incontinence are reported.

In an early study by Drutz and colleagues comparing the efficacy and safety of IR formulations of oxybutynin (5 mg three times daily) and tolterodine (2 mg twice daily),<sup>35</sup> both medications were equally efficacious. However, tolterodine IR was significantly better tolerated than oxybutynin IR as assessed by frequency and intensity of dry mouth, dose reductions, and patient withdrawals. Overall, 147 (53%) of 277 patients completed the 12-week study.<sup>35</sup>

A subsequent study by Appell and colleagues compared the efficacy and tolerability of oxybutynin ER 10 mg once daily and tolterodine IR 2 mg twice daily.<sup>36</sup> Although both drugs were efficacious, oxybutynin ER was significantly more effective in reducing weekly urge UI ( $P = 0.03$ ), total incontinence ( $P = 0.02$ ), and urinary frequency ( $P = 0.02$ ) episodes compared with tolterodine IR. Adverse events were similar for both medications; dry mouth was reported by 28.1% and 33.2% of patients treated with oxybutynin ER and tolterodine IR, respectively ( $P = 0.32$ ).<sup>36</sup>

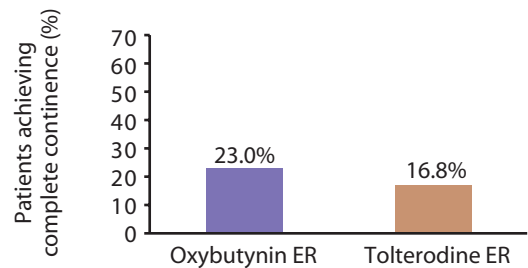
A third study by Diokno and colleagues<sup>37</sup> compared the efficacy and tolerability of oxybutynin ER 10 mg once daily and tolterodine ER 4 mg once daily. Again, both medications were found to be efficacious, although oxybutynin ER was significantly more effective at reducing urinary frequency than was tolterodine ER. In addition, urge UI was eliminated in 23.0% of women taking oxybutynin ER and 16.8% of women taking tolterodine ER ( $P = 0.03$ ) (Figure 4). Dry mouth was more common with oxybutynin ER (29.7%) than with tolterodine ER (22.3%) ( $P = 0.02$ ).<sup>37</sup>

In a study by Zinner and colleagues,<sup>38</sup> who compared the efficacy of trospium 20 mg twice daily with that of placebo, trospium significantly decreased average frequency of toilet voids ( $P \leq 0.05$ ) and urge UI episodes ( $P \leq 0.001$ ). Trospium also reduced urge severity, daytime frequency, and nocturnal frequency and increased the average volume voided and QoL scores. Resolution of urge UI occurred in 11% of controls and in 21% of trospium-treated patients (Figure 5). Dry mouth was reported in 21.8% of trospium-treated patients (6.5% for controls), and the adverse event–associated discontinuation rates were 8.8% (5.7% for controls).<sup>38</sup>

Darifenacin, at three different dosages (3.75 mg, 7.5 mg, and 15 mg), was compared with placebo in a multicenter, double-blind, parallel-group study.<sup>39</sup> At the 7.5- and 15-mg dosages, it was significantly more effective than placebo in improving micturition frequency, bladder capacity, episodes and severity of urgency, and the number of incontinence episodes. Nocturnal awakenings were unchanged. Resolution rates for urge UI were not reported. Dry mouth occurred in 18.8% and 31.3% of patients treated with darifenacin 7.5 and 15 mg, respectively (8.5% for placebo). Fewer than 3% of patients discontinued the study because of adverse events.<sup>39</sup>

The efficacy, safety, and tolerability of solifenacin 5 mg and 10 mg daily in patients with symptoms of OAB were investigated by Cardozo and colleagues.<sup>40</sup> Results indicated that solifenacin 5 mg and 10 mg produced statistically significant decreases in urinary frequency, incontinence episodes, urge UI, urgency, and nocturia (in the solifenacin 10-mg group) compared with placebo. The volume voided was significantly increased ( $P = 0.0001$ ) in both the solifenacin 5-mg and 10-mg groups. For those patients reporting incontinence at baseline, 50.3% and 49.7% of the patients treated with solifenacin 5 mg and 10 mg, respectively, reported complete

**FIGURE 4 Complete continence rates: oxybutynin ER versus tolterodine ER at 12 weeks**



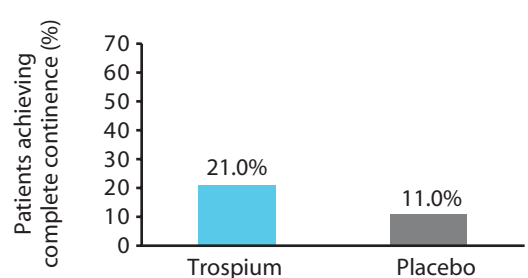
Data from *Mayo Clin Proc* 2003;78:687–695.<sup>37</sup>

continence at the end of the study (Figure 6). The overall rates of dry mouth were 7.7% for patients treated with solifenacin 5 mg and 23.1% for patients treated with solifenacin 10 mg (2.3% for controls).<sup>40</sup>

A subsequent flexible dosing trial of patients with OAB by Chapple and colleagues compared the efficacy and safety of solifenacin 5 mg or two 5-mg solifenacin tablets (10 mg is the maximum recommended dose) to tolterodine ER 4 mg or tolterodine 4 mg plus a placebo tablet (4 mg is the maximum recommended dose).<sup>41</sup> For the primary endpoint of reduction of micturition, solifenacin was at least as effective as tolterodine ( $P = 0.004$ , noninferiority). Solifenacin-treated patients also improved significantly in urge UI ( $P = 0.001$ ), overall incontinence ( $P = 0.006$ ), and urgency ( $P = 0.035$ ) compared with tolterodine ER–treated patients.

For patients who were incontinent at baseline, 59% of those treated with solifenacin were continent at the conclusion of the study compared with 49%

**FIGURE 5 Complete continence rates: trospium versus placebo at 12 weeks**



Data from *J Urol* 2004;171(6 Part 1):2311–2315.<sup>38</sup>

of patients treated with tolterodine ER ( $P = 0.006$ ) (Figure 7). In addition, the mean volume voided increased ( $P = 0.01$ ), the use of incontinence pads decreased ( $P = 0.0023$ ), and patients' perception of bladder condition improved ( $P = 0.006$ ) at significantly higher rates with solifenacin than with tolterodine ER. Overall discontinuation rates were 5.9% for solifenacin and 7.3% for tolterodine ER.<sup>41</sup>

A final study by Haab and colleagues evaluated persistence among solifenacin-treated patients entering a 40-week extension of two 12-week clinical trials.<sup>42</sup> A total of 91% of patients completing the 12-week trials chose to enter the extension trial, and 81% of those patients completed the 40 weeks of treatment. The discontinuation rate attributable to adverse events was 4.7%. Patients reported high rates of satisfaction with solifenacin tolerability (85%) and efficacy (74%).<sup>42</sup>

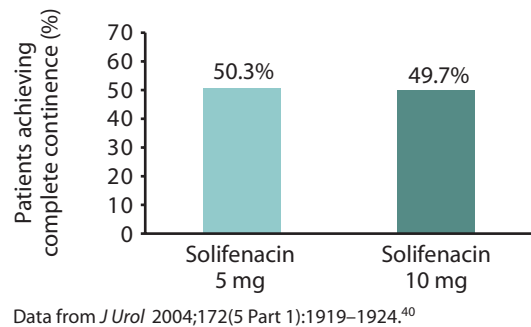
### Health-Related Quality of Life

The data evaluating the impact of OAB treatments on HRQoL are limited. An HRQoL assessment was performed in a trial by Diokno and colleagues<sup>43</sup> that examined the long-term efficacy of oxybutynin IR and oxybutynin ER but was limited because of low rates of persistence. In this study, 25.5% of patients discontinued treatment at three months, and 62% of those remaining continued oxybutynin ER therapy for one year (46% overall). The most common reason for discontinuation was the occurrence of adverse events. The General Health and Bother Scale results of those remaining on treatment were significantly improved over their baseline values, as were reports of "urine leakage and bladder problems" and nighttime awakenings.<sup>43</sup>

The King's Health Questionnaire (KHQ) is a validated study instrument designed to assess patient-reported outcomes used to measure the effect of treatment on HRQoL.<sup>44</sup> It includes nine general domains and one domain related to bladder problems.<sup>45</sup> In a study of tolterodine ER by Kelleher and colleagues,<sup>45</sup> patients reported significant ( $P \leq 0.001$ ) improvement at three and 12 months for each of the KHQ study domains except general health perception.

In a recently published paper, Kelleher and colleagues pooled data from two 12-week trials and a long-term extension of these studies to assess the HRQoL impact of solifenacin.<sup>46</sup> In the pooled analysis, patients treated with either solifenacin 5 mg or 10 mg showed significant improvement at three and

**FIGURE 6 Complete continence rates: solifenacin 5 mg and 10 mg at 12 weeks**

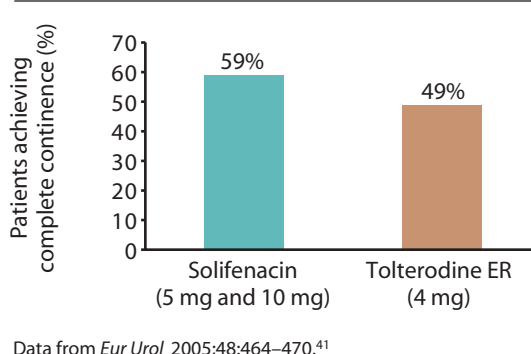


12 months in all KHQ study domains, except for personal relationships. Approximately two thirds of the improvement occurred during the first three months, with the remainder of the improvement occurring during the extension study.<sup>46</sup>

### Pharmacoeconomics and Patients' Persistence of Use

As discussed previously, the annual costs associated with OAB are high. Effective and well-tolerated therapies can be expected to reduce overall OAB-associated health care costs. Unfortunately, limited clinical efficacy and frequent adverse events have affected patients' willingness to continue traditional antimuscarinic therapies. Low persistence rates among antimuscarinic-treated patients have occurred both in drug trials and in retrospective reviews of patients who were prescribed antimuscarinic medications. The next series of studies

**FIGURE 7 Complete continence rates: solifenacin versus tolterodine ER ( $P = 0.006$ )**



reviews medication persistence rates and the pharmaco-economic implications of antimuscarinic therapy.

In a retrospective study of Medicaid managed care patients, Shaya and colleagues evaluated antimuscarinic medication persistence, possession time, and switching among patients prescribed either tolterodine ER, oxybutynin ER, or oxybutynin IR.<sup>30</sup> Patients were eligible if they were enrolled in one of eight prepaid, mid-Atlantic state-contracted managed care organizations and if they were new users of the study medications.

The 30-day persistence rates, with a 30-day refill allowance, were 49% for tolterodine ER, 48% for oxybutynin ER, and 39% for oxybutynin IR ( $P = 0.004$ ). The corresponding one-year persistence rates were 12%, 5%, and 8%, respectively ( $P = 0.038$ ). For more than 80% of patients, possession time was 30 days longer than persistence. At the end of a year, possession rates were 22% for tolterodine ER, 15% for oxybutynin ER, and 16% for oxybutynin IR. There was no significant difference between groups. Switching occurred in 6% of patients without significant difference among the study drugs.<sup>30</sup>

Older patients (40–64 years of age) were significantly less likely than younger patients (18–39 years of age) to discontinue therapy (hazard ratio [HR], 1.56; 95% CI, 1.33–1.82). White patients were significantly less likely to discontinue than were non-white patients (HR, 1.22; 95% CI, 1.09–1.36). A similar relationship between age and race and possession time also was observed. In addition, during the first 30 days, men who were going to discontinue did so at a higher rate than women, but men who persisted were less likely to discontinue than women after 30 days (HR, 1.16; 95% CI, 1.01–1.34) (Figure 8).<sup>30</sup>

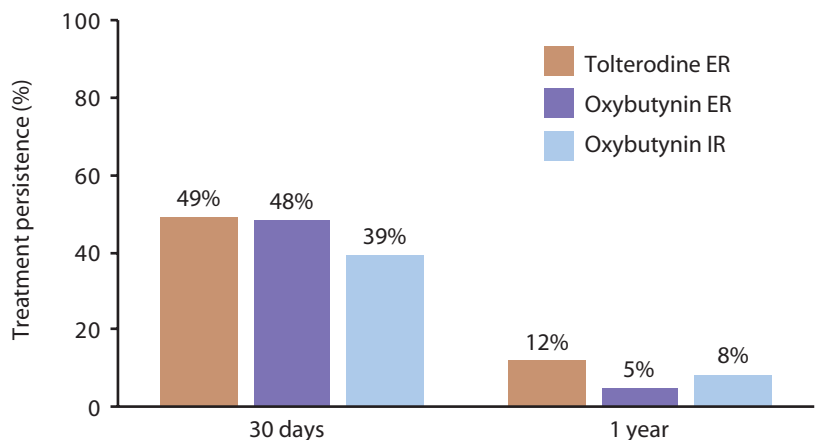
In a second study, Perfetto and colleagues abstracted data on patients with OAB from a large managed care database and reviewed them retrospectively.<sup>31</sup> A decision-analysis model was developed to compare one-year total health care costs for

patients initiating therapy with either tolterodine ER or oxybutynin ER. The model incorporated costs for OAB pharmacotherapy and for medical management. Patients enrolled in the plan for the 12 months prior to either an initial diagnosis of OAB or the initial filling of the study drug index prescription and for the ensuing 12 months were included in the study ( $N = 23,328$ ).

At the conclusion of the study,<sup>31</sup> 21% of tolterodine ER-treated patients and 15% of oxybutynin ER-treated patients remained with therapy (Figure 9). Most patients who eventually discontinued therapy did so within three months of initiating therapy. The average adjusted monthly medical cost (excluding costs of pharmacotherapy) for each treatment group and for those patients with OAB managed without pharmacotherapy was \$662 for tolterodine ER, \$712 for oxybutynin ER, and \$723 for non-pharmacotherapy-treated patients. The one-year average total health care costs were \$8,876 for patients started on tolterodine ER and \$9,080 for patients started on oxybutynin ER. This represented an annual difference of \$204 per patient. Cost differences remained after the investigators controlled for medication costs and discontinuation rates. The authors suggest that the advantage conferred to tolterodine ER was a result of its lower cost, the lower cost of medical management for tolterodine ER-treated patients, and greater persistence for tolterodine ER-treated patients (Figure 10).<sup>31</sup>

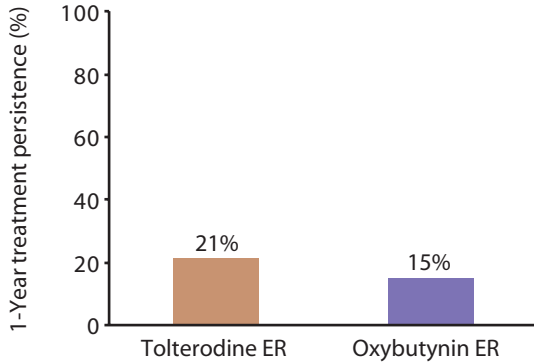
In the third retrospective study,<sup>32</sup> Varadharajan and colleagues evaluated the persistence, compli-

**FIGURE 8 Overactive bladder drug treatment persistence: measured at 30 days ( $P = 0.004$ ) and at one year ( $P = 0.038$ )**



Data from *Am J Manag Care* 2005;11(4 Suppl):S121–S129.<sup>30</sup>

**FIGURE 9** Overactive bladder drug treatment persistence: tolterodine ER versus oxybutynin ER at one year



Data from *Am J Manag Care* 2005;11(4 Suppl):S150-S157.<sup>31</sup>

ance, and medical costs among a large cohort of patients with OAB who were enrolled in commercial managed care plans and were treated with tolterodine ER, oxybutynin ER, or oxybutynin IR. Patients were eligible if they had been enrolled in the plan during the 12 months prior to the index prescription, had not been treated previously with the study medications, and remained enrolled for the ensuing 12 months. Persistence was based on the number of days from initiation of therapy until the first discontinuation. *Compliance* was defined as the ratio of therapy days supplied divided by persistence.

In this study, patients tended to be compliant but not persistent. Three quarters of patients discontinued therapy by six months. Although the continuance rates for all groups were low, differences in persistence favored tolterodine ER at months 1, 2, 3, and 12 compared with oxybutynin ER and oxybutynin IR ( $P < 0.0001$ ).<sup>32</sup>

Overall utilization of pharmacy, inpatient, and outpatient resources was lower in patients receiving tolterodine ER than in those receiving oxybutynin ER or oxybutynin IR. Total overall health care costs were lower with tolterodine ER (\$8,303) than with oxybutynin ER (\$8,862) and with tolterodine ER (\$9,975) than with oxybutynin IR (\$10,521). A multivariate analysis of total overall costs indicated that tolterodine ER was signifi-

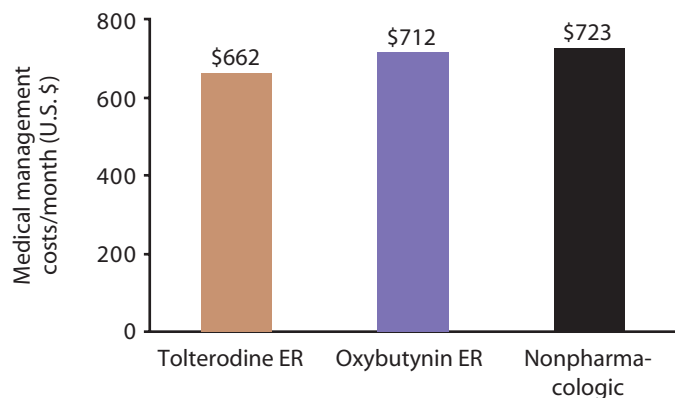
cantly less costly than oxybutynin ER ( $P = 0.0032$ ) and that tolterodine ER was significantly less costly than oxybutynin IR ( $P < 0.0001$ ) (Figure 11).<sup>32</sup>

In a final retrospective study,<sup>47</sup> Nitz and colleagues used eligibility, medical, and pharmacy claims data from a large U.S. health plan to assess the medical cost outcomes for patients (N = 14,582) who began therapy with tolterodine ER, oxybutynin ER, or oxybutynin IR. The study period was for one year and began after an index prescription was filled for one of the study drugs after a six-month drug-free period. Differences noted in baseline characteristics included sex, geographic region, age, specific OAB-related diagnosis, and costs.

A multivariate analysis revealed that medical costs for the oxybutynin ER and IR cohorts during the one-year follow-up period were 191% ( $P < 0.001$ ) and 48% ( $P = 0.026$ ) higher, respectively, than those for the tolterodine ER cohort. Mean adjusted medical costs were \$5,074 for tolterodine ER, \$14,766 for oxybutynin ER, and \$7,486 for oxybutynin IR. The adjusted mean medical costs were \$9,692 higher for oxybutynin ER and \$2,412 higher for oxybutynin IR compared with tolterodine ER.<sup>47</sup>

The reasons for differences between treatment arms were not evaluated in the study.<sup>47</sup> The authors noted the potential for treated OAB patients to incur lower medical costs than untreated OAB patients. However, they did not report treatment persistence or efficacy outcomes in this study (Figure 12).<sup>47</sup>

**FIGURE 10** Overactive bladder monthly medical management costs: tolterodine ER versus oxybutynin ER versus neither



Data from *Am J Manag Care* 2005;11(4 Suppl):S150-S157.<sup>31</sup>

**CONCLUSION**

Overactive bladder is a highly prevalent condition that affects millions of adults in the U.S. The disease and its associated complications and comorbidities take a tremendous toll on the individuals affected and on the health care systems serving them. Recent estimates suggest that OAB is more prevalent than hypertension and more costly than osteoporosis.

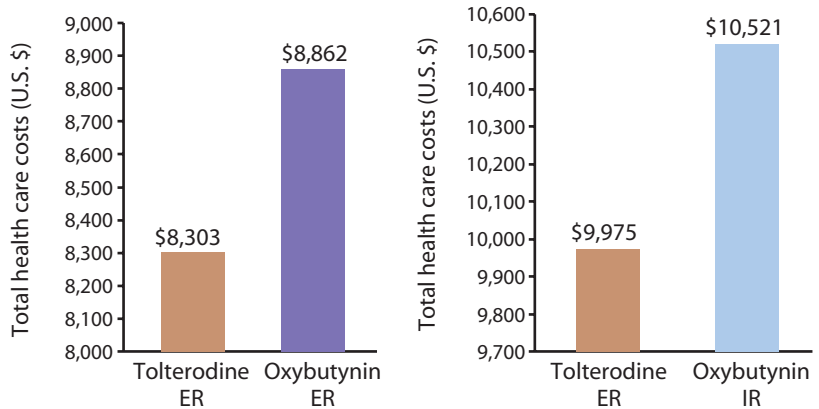
Although urgency is a defining symptom of OAB, as many as 50% of affected women have urge UI as well. OAB-wet patients tend to have more health problems and poorer HRQoL, and they are more costly to care for than OAB-dry patients.

Despite the profound impact of OAB on the lives of affected patients, many do not discuss their symptoms with their health care providers, and most health care providers do not initiate discussions about OAB symptoms with their patients. As a result, OAB often remains undiagnosed until one of the many medical or social consequences of the condition occurs.

Although nonpharmacological therapies are sometimes used in combination with pharmacotherapy, pharmacological management with antimuscarinic receptor antagonists is the most frequently used and effective form of therapy for patients with OAB and urge UI. Despite their common use, traditional antimuscarinic agents are associated with low persistence rates both in clinical trials and in clinical practice settings. Improving persistence is an important step to increasing efficacy and reducing the overall medical, social, and economic costs of OAB.

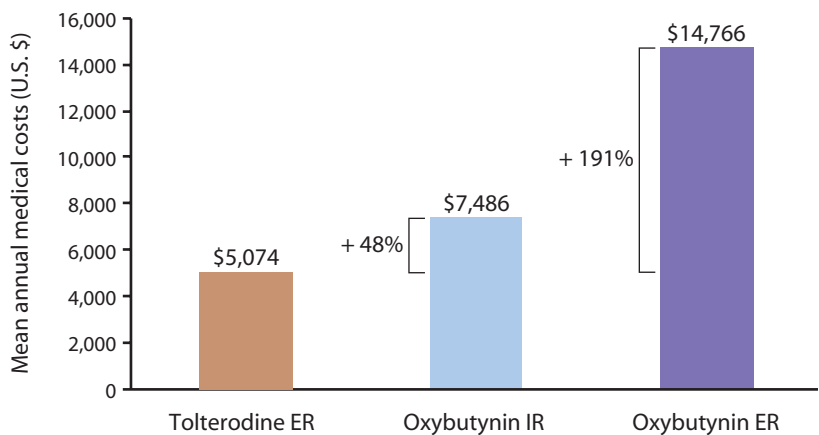
Limited efficacy in some patients and prominent adverse effects (e.g., dry mouth) in other patients have contributed to poor persistence with traditional agents. Although traditional and newly developed antimuscarinic agents are effective at managing many of the symptoms of OAB, they do not appear to be equally effective in reducing each symptom (e.g., in restoring continence to OAB-wet patients). In addition, adverse-effect profiles

**FIGURE 11** Comparative total health care costs: tolterodine ER versus oxybutynin ER ( $P = 0.0109$ ) and tolterodine ER versus oxybutynin IR ( $P = 0.3612$ )



Data from *Am J Manag Care* 2005;11(4 Suppl):S140–S149.<sup>32</sup>

**FIGURE 12** Comparative overactive bladder–related mean medical costs: absolute and percentage increases versus tolterodine



Data from *Am J Manag Care* 2005;11(4 Suppl):S130–S139.<sup>47</sup>

vary among agents. Therapies that optimize the management of the most bothersome symptoms of OAB and urge UI, while minimizing adverse effects, are likely to have the greatest long-term clinical utility.

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continued on page 17

## P&T SUPPLEMENT POST-TEST

Please enter your answers on the Post-test Answer Form on page 16.  
Select the single most appropriate answer for each question.

- 1. Overactive bladder (OAB) is a highly prevalent condition affecting millions of adults in the U.S. Which statement about OAB and urge urinary incontinence (UI) is true?**
  - a. Women are more likely to have OAB than men.
  - b. Men with OAB are more likely to have urge UI than women.
  - c. From one third to one half of patients with OAB have urge UI.
  - d. OAB is more common in younger people than in older people.
  - e. All of the above.
- 2. Which statement about the complications and consequences of OAB and urge UI is correct?**
  - a. Urge UI increases a patient's risk of falls, fractures, and urinary tract infections.
  - b. Urge UI increases the risk of both hospitalization and nursing-home admission.
  - c. Although the overall risk of depression is higher in incontinent patients, the risk is highest in patients with urge UI.
  - d. Approximately two thirds of patients with OAB report a deleterious effect on their activities of daily living.
  - e. All of the above.
- 3. Despite the profound impact of OAB and urge UI on the health and lives of affected individuals, many patients do not seek treatment. Which of the following statements about help-seeking and physician responsiveness among affected patients is true?**
  - a. Patients with OAB and urge UI are rarely bothered by their illness.
  - b. Health care providers initiate most of the discussions about OAB and urge UI.
  - c. Most patients with incontinence residing in skilled nursing facilities receive drug treatment.
  - d. Patients frequently resort to nonmedical coping strategies prior to or instead of seeking help from a health care provider.
  - e. None of the above.
- 4. Which statement about treatment efficacy in the following three head-to-head trials is correct?**
  - a. In a study comparing the efficacy of oxybutynin IR and tolterodine IR, tolterodine IR was found to be significantly more efficacious than oxybutynin IR.
  - b. In a study comparing the efficacy of oxybutynin ER and tolterodine ER, tolterodine ER was found to be significantly more efficacious than oxybutynin ER.
  - c. In a study comparing the efficacy of solifenacin and tolterodine ER, solifenacin was found to be significantly more efficacious than tolterodine ER.
  - d. All of the above.
  - e. None of the above.
- 5. Complete resolution of incontinence is an important clinical endpoint in the management of urge UI. Which of the following ranges approximates the rate of complete resolution of urge UI in solifenacin-treated patients in two recently reported studies?**
  - a. 10% to 20%
  - b. 21% to 30%
  - c. 31% to 40%
  - d. 41% to 50%
  - e. 51% to 60%
- 6. A series of studies reviewed medication persistence and economic considerations for patients with OAB and urge UI. Which of the following statements is correct?**
  - a. Persistence rates for medications at one month and at one year tended to be similar.
  - b. Persistence rates in the community at one year for tolterodine ER and oxybutynin ER ranged from 5% to 21%.
  - c. Overall medical costs tended to be higher in the tolterodine-treated patients than in the oxybutynin-treated patients.
  - d. Overall medical resource utilization tended to be higher in the tolterodine-treated patients than in the oxybutynin-treated patients.
  - e. None of the above.

## CME/CE POST-TEST ANSWER FORM AND ACTIVITY EVALUATION

**Instructions:** Circle the single most appropriate answer for each question.

- |    |   |   |   |   |   |
|----|---|---|---|---|---|
| 1. | A | B | C | D | E |
| 2. | A | B | C | D | E |
| 3. | A | B | C | D | E |
| 4. | A | B | C | D | E |
| 5. | A | B | C | D | E |
| 6. | A | B | C | D | E |

### STATEMENT OF PARTICIPATION APPLICATION

In order to receive a statement of credit, participants must successfully complete the CME/CE post-test after reviewing the supplement. Participants will have two opportunities to pass the post-test with a score of 65% or higher. Please follow one of the options below:

#### Online Option

Log on to <http://em.ahe.edu/?c231>, complete the user information form, and submit your post-test answer form and activity evaluation electronically by **November 30, 2006**. Tests will be graded and results displayed instantaneously. Participants will receive an electronic, printable statement of credit immediately after successfully completing the post-test.

#### Fax or Mail Option

Answer **all** post-test questions and complete the name and address section below. Fax the post-test answer form and activity evaluation by **November 30, 2006**, to 212-338-9829; or mail to: Academy for Healthcare Education, 330 Madison Avenue, 21st Floor, New York, NY 10017. A statement of credit will be mailed to you within six to eight weeks.

**IMPORTANT:** Please **print** all information below. Post-tests without a complete name and mailing address cannot be processed for CME/CE credit.

Name \_\_\_\_\_

Degree (circle): MD DO PharmD RN Other \_\_\_\_\_

Specialty \_\_\_\_\_

Street Address (home  office ):  
\_\_\_\_\_

City \_\_\_\_\_

State \_\_\_\_\_ Zip \_\_\_\_\_

E-mail (home  office ): \_\_\_\_\_

Telephone (home  office ): \_\_\_\_\_

Fax (home  office ): \_\_\_\_\_

**You may fax me information regarding educational activities:** Yes  No

Signature \_\_\_\_\_

Date \_\_\_\_\_

Length of time to complete this CME/CE activity:  
 45 min     1 hr     1.25 hrs

### ACTIVITY EVALUATION

#### 1. After completing this activity, I am able to do the following:

- define overactive bladder with urge urinary incontinence and describe the epidemiology of the condition.
- discuss the medical, health-related quality-of-life, and cost implications of overactive bladder and its associated complications and comorbidities.
- assess barriers to help-seeking among patients with overactive bladder.
- describe the efficacy, tolerability, and health-related quality-of-life impact of pharmacotherapy for overactive bladder.
- explain potential pharmacoeconomic implications of persistence and effective treatments for overactive bladder.

#### 2. The information was relevant to my practice.

#### 3. The activity provided new information.

#### 4. The information was communicated clearly.

#### 5. The overall content of the educational activity was satisfactory.

#### 6. The format of this activity was conducive to learning.

#### 7. Did you perceive inappropriate commercial influence for or against a specific commercial product in the program content?

Yes     No

If yes, please explain: \_\_\_\_\_

8. Additional comments: \_\_\_\_\_

N5-236

5 = Strongly agree                      1 = Strongly disagree

5    4    3    2    1

continued from page 14

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