

Medical Costs After Initiation of Drug Treatment for Overactive Bladder: Effects of Selection Bias on Cost Estimates

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Abstract

Objectives: To compare posttreatment medical costs for patients with overactive bladder (OAB) initiating treatment with oxybutynin chloride immediate release (oxybutynin IR), oxybutynin chloride extended release (oxybutynin ER), or tolterodine extended-release tartrate capsules (tolterodine ER).

Methods: Data were drawn from administrative claims of enrollees aged 18 years and older of a large US health plan. OAB patients were identified if at least 1 claim with an *International Statistical Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* code for OAB appeared in medical claims from January 1, 2001, to December 31, 2002. The index prescription was assigned as the first filled prescription of oxybutynin IR (n = 3052), oxybutynin ER (n = 4503), or tolterodine ER (n = 7027) during the subject identification period. Medical costs over the year after initiation were calculated as a function of the health plan and member liability. Independent variables were treatment cohort, sex, age group, geographic region, baseline costs, specific OAB diagnosis codes, and comorbid illnesses. To compare medical costs across treatment cohorts, multivariate regressions correcting for potential selection bias were used.

Results: Multivariate analysis results revealed that costs for patients taking oxybutynin IR were 48% higher than costs for patients taking tolterodine ER ($P = .026$), and costs for patients taking oxybutynin ER were 191% higher than costs for patients taking tolterodine ER ($P < .0001$). Adjusted medical costs were \$7486 for patients taking oxybutynin IR and \$14 766 for patients taking oxybutynin ER compared with \$5074 for patients taking tolterodine ER.

Conclusion: Differences in medical costs that remained after adjusting for patient characteristics suggest that treatment with tolterodine ER may be associated with lower medical care utilization after initiation of therapy for OAB.

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Despite recognition of the prevalence of overactive bladder (OAB) and its costly consequences in terms of patient outcomes, there is a dearth of evidence on the cost effectiveness of the most common pharmacological therapies for this condition.

The overall prevalence of OAB in the United States has been estimated at 16.9% for women (9.3% with frequency, urgency, and urgency incontinence) and 16% for men (2.6% with frequency, urgency, and urgency incontinence).¹ These figures translate to approximately 33.3 million adults in the United States with OAB and 12.2 million adults with urgency incontinence.

The cost of OAB in the United States is estimated to be greater than \$12 billion annually, a burden that is comparable with other chronic conditions, such as osteoporosis (\$13.8 billion).^{2,3} In contrast to many long-term diseases, a large portion of the cost of OAB (\$3.9 billion) is related to indirect costs beyond the costs of the condition itself.^{2,4} This is caused, in part, by the higher risk faced by patients with OAB for experiencing related comorbidities.^{4,6} A recent analysis of the prevalence of falls and fractures, urinary tract infections, skin infections, vulvovaginitis, and depression among 23 112 OAB patients and matched controls, found that patients with OAB were significantly more likely than controls to have each of the studied comorbidities.⁷ Compared with the general population, patients with OAB may also incur greater costs in managing these conditions.⁷

Although management of OAB may involve nonpharmacologic methods, antimuscarinic agents are the primary treatment for OAB.⁸⁻¹²

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These agents appear to improve both clinical outcomes and patients' quality of life,¹³⁻²¹ and there is some indication that use of pharmacotherapy as initial treatment is associated with decreased utilization of healthcare resources.²² Further, better treatment of OAB is expected to decrease the incidence of healthcare resource utilization associated with OAB-related comorbidities. Unfortunately, treatment rates are low because of a number of factors, including a reluctance to discuss OAB symptoms with a physician²³; possible physician undertreatment of OAB²³; and low rates of adherence and persistence with OAB therapy.²⁴⁻²⁷ The extent to which increasing treatment rates may reduce healthcare costs for patients with OAB depends on the impact of the specific therapies used on costs.

Few studies have directly examined the impact of specific pharmaceutical treatments for OAB on expenditures for medical care in a "real-world" population. Specifically, with the introduction of extended-release formulations of both oxybutynin and tolterodine, there are little data quantifying the extent to which these newer formulations may reduce medical costs for patients with OAB, or comparing the relative effects of the extended-release formulations on costs. Hall and colleagues found that although average per-patient-per-month total healthcare costs increased after the first indication of OAB, patients filling prescriptions for tolterodine immediate release (tolterodine IR) or oxybutynin immediate release (oxybutynin IR) did not have a statistically significant difference compared with untreated patients in the percentage change in total healthcare costs.²⁵ However, a lengthier follow-up time than was available in that study may be necessary to fully evaluate the impact of OAB therapies on costs.

This study assessed medical cost outcomes for patients with OAB who initiated treatment with tolterodine tartrate capsules extended release (tolterodine ER) compared with patients initiating treatment with oxybutynin chloride extended release (oxybutynin ER) or oxybutynin IR.

Methods

Study Design, Data Source, and Study Population. This retrospective study used

eligibility, medical, and pharmacy claims of a large national US health plan affiliated with Ingenix. The research database includes discounted, fee-for-service, independent, practice-associated model plans covering all regions of the United States. During the study period, approximately 5.7 million patients older than the age of 18 years had claims in the database.

Patients were included in the study if they had commercial or Medicare insurance with a prescription drug benefit. For each subject, an index date was identified as the first filled prescription for tolterodine ER, oxybutynin ER, or oxybutynin IR during January 1, 2001, to December 31, 2002. The study period consisted of a 6-month baseline period before and a 12-month follow-up period after the index prescription. Subjects who filled prescriptions for these drugs during the 6-month baseline period were excluded, as were subjects who filled prescriptions for more than 1 of the 3 drugs on their index date. In addition, subjects with *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis codes for Alzheimer's disease, spinal cord injuries, or spina bifida were excluded (see **Appendix**). Subjects were required to be continuously covered by the health plan for 6 months before and 12 months after their index date. Claims with OAB-related diagnosis codes were identified during the subject identification period (**Table 1**).

Statistical Analyses. Drug cohorts were compared on medical costs over 12 months of follow-up. Medical costs were calculated as a function of health plan and member liability for nonpharmacy costs, including hospital, emergency room, physician, outpatient, laboratory, and other nonpharmacy costs. Differences between cohorts in proportions were tested using chi-square tests. Kruskal-Wallis chi-squares were used to test for differences in distribution of costs, and Bonferonni-adjusted *t*-tests were used to compare pairs of drug cohorts. Multivariate analyses assessed medical costs adjusted for drug cohort and covariates. Other covariates included in multivariate models were sex, age group, geographic region, logged total

Table 1. ICD-9-CM Codes Used to Define Overactive Bladder

ICD-9-CM code	ICD-9-CM code description
595.3	Trigonitis
596.51	Hypertonicity of bladder (hyperactivity, overactive bladder)*
597.81	Urethral syndrome NOS
788.30	Unspecified urinary incontinence
788.31	Urge incontinence
788.33	Mixed incontinence, urge and stress
788.34	Incontinence without sensory awareness
788.36	Nocturnal enuresis
788.39	Other urinary incontinence
788.4	Frequency of urination, unspecified
788.41	Urinary frequency
788.43	Nocturia

*The “overactive bladder” description was added in October 2001. ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification*; OAB, overactive bladder; NOS, not otherwise specified.

healthcare costs in the 6-month baseline period, OAB-related diagnosis code, and diagnoses of comorbid conditions. Comorbid illnesses were identified during the baseline period using the Washington method of clustering illnesses.²⁸ Specific interactions were tested to examine whether the effect of treatment cohorts on medical costs differed by sex, age group, baseline total healthcare costs, or specific OAB-related diagnosis code.

A major concern in estimating the cost models was the potential for selection bias as a result of unobserved differences between the treatment cohorts (ie, whether an unobserved factor was correlated with both the selection of a specific treatment and with medical cost in the follow-up period). To examine this issue, we estimated the cost equation using several methods. Ordinary least squares (OLS) regression did not include an adjustment for any potential selection bias. Treatment effects regressions estimated a pair of equations, with one equation to predict the selection of treatment and another equation to estimate cost. This technique estimates the correlation between the equation predicting treatment and the equation predicting cost, giving an estimate

of the direction and size of the bias produced by the OLS estimation. A positive correlation indicates OLS estimates are biased upwards and a negative correlation indicates OLS estimates are biased downward. Chow tests assessed whether the coefficients for other covariates included in the cost model differed between the treatment cohorts. Treatment regression models were estimated separately for the comparisons of oxybutynin IR with tolterodine ER, and of oxybutynin ER with tolterodine ER.

Log-transformed medical costs were used as the dependent variable in all multivariate estimations to account for the non-normal distribution of the cost data. To interpret the coefficients in dollar terms (instead of log dollars), coefficients and predicted means were obtained by retransformation. Kennedy’s correction was used to generate retransformed coefficients that represent the magnitude of the effect of the independent variables on cost in real dollar values.²⁹ After retransformation, the coefficients represent the percent change in costs associated with the treatment cohort compared with the reference treatment cohort. Robust estimates of standard errors (SEs) using White’s correction were obtained for models violating the assumption of homoscedasticity in the error term.^{30,31}

We estimated the dollar value of the impact of treatment drug on medical cost by multiplying the Kennedy-corrected exponentiated coefficients for the oxybutynin IR and oxybutynin ER cohorts by the mean cost for the tolterodine ER cohort (reference group). To calculate 95% confidence intervals (CIs) for the adjusted means, the upper and lower limits for Kennedy-corrected log-scale coefficients were exponentiated.

Results

Descriptive Statistics. A total of 14 582 subjects met all inclusion criteria. Of those subjects, 3052 initiated oxybutynin IR, 4503 initiated oxybutynin ER, and 7027 initiated tolterodine ER. Cohorts differed in baseline characteristics. The tolterodine ER cohort had the lowest proportion of men compared with the oxybutynin IR and oxybutynin ER cohorts (17% vs 32% and 23% respectively; *P* <.0001). Cohorts also differed slightly in

Table 2. Characteristics of Study Sample: Means and Percentages

Independent variable	Oxybutynin IR	Oxybutynin ER	Tolterodine ER	Test/P value
	n = 3052 %/Mean	n = 4503 %/Mean	n = 7027 %/Mean	
Men	31.98	23.10	17.39	χ^2 , 2 df = 265.16, P < .0001
Region				χ^2 , 12 df = 162.70, P < .0001
East North Central	30.31	27.96	24.39	
East South Central	6.62	7.79	8.72	
Mid Atlantic/New England	7.11	8.75	7.33	
Mountain/Pacific	7.31	4.86	4.65	
South Atlantic	21.92	26.78	26.58	
West North Central	18.61	13.88	16.32	
West South Central	8.13	9.97	12.00	
Age group, yrs				MH χ^2 , 1 df = 16.25, P < .0001
18-34	9.34	8.04	7.57	
35-44	17.73	16.43	17.11	
45-54	22.71	27.16	23.39	
55-64	19.66	23.81	23.25	
65-74	15.69	13.48	12.32	
75+	14.88	11.08	10.36	
Age mean (SD)	55.40 (16.02)	54.61 (14.69)	54.23 (14.28)	Bonferonni t-test P < .05 for oxybutynin IR vs tolterodine ER; NS for other comparisons
Baseline total cost mean (SD)	\$4956 (14 396)	\$4146 (8695)	\$3349 (6715)	Bonferonni t-tests P < .05 for all comparisons
OAB-related diagnosis code (%)*				
595.3 Trigonitis	0.29	0.78	0.77	χ^2 , 2 df = 8.23, P = .0163
596.51 Hypertonicity of bladder (hyperactivity, OAB)	3.18	6.53	6.45	χ^2 , 2 df = 48.24, P < .0001
596.59 Other functional disorder of bladder	2.33	4.17	3.09	χ^2 , 2 df = 21.02, P < .0001
597.81 Urethral syndrome NOS	0.66	1.11	1.01	χ^2 , 2 df = 4.20, P = .1224
788.30 Unspecified UI	16.12	20.03	17.46	χ^2 , 2 df = 21.29, P < .0001
788.31 Urge incontinence	9.31	13.64	13.29	χ^2 , 2 df = 37.59, P < .0001
788.33 Mixed incontinence, urge and stress	4.55	7.77	7.63	χ^2 , 2 df = 36.26, P < .0001
788.34 Incontinence without sensory awareness	0.39	0.53	0.48	χ^2 , 2 df = 0.75, P = .6879
788.35 Postvoid dribbling	0.13	0.18	0.21	χ^2 , 2 df = 0.80, P = .6698
788.36 Nocturnal enuresis	0.33	0.44	0.30	χ^2 , 2 df = 1.72, P = .4239
788.39 Other UI	1.05	1.35	1.02	χ^2 , 2 df = 2.91, P = .2334
788.4 Frequency of urination, unspecified	0.59	0.73	0.80	χ^2 , 2 df = 1.25, P < .5343
788.41 Urinary frequency	19.82	26.27	25.47	χ^2 , 2 df = 47.27, P < .0001
788.42 Polyuria	1.57	1.95	2.31	χ^2 , 2 df = 5.97, P = .0507
788.43 Nocturia	5.60	6.80	5.96	χ^2 , 2 df = 5.26, P = .0719

*Patients may have had more than 1 OAB-related *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis code.

IR indicates immediate release; ER, extended release; df, degrees of freedom; MH χ^2 , Mantel-Haenszel chi-square; SD, standard deviation; NS, nonsignificant; NOS, not otherwise specified; OAB, overactive bladder; UI, urinary incontinence.

geographic distribution. Mean age for oxybutynin IR was 55 years (standard deviation [SD] = 16.02), similar to the oxybutynin ER cohort (55 years, SD = 14.69) and slightly older than the tolterodine ER (54 years, SD = 14.28) cohort ($P < .05$). Cohorts also differed on the proportion of patients with specific OAB-related ICD-9-CM codes. Mean total costs during the 6-month baseline period were highest for the oxybutynin IR cohort (\$4956), followed by the oxybutynin ER cohort (\$4146) and the tolterodine ER cohort (\$3349) (Table 2).

Total unadjusted medical costs over the follow-up period differed between cohorts. The majority of subjects in each cohort incurred some level of medical costs over the 12 months after initiation of therapy. Among the oxybutynin IR cohort, 3% of subjects did not incur medical costs compared with 2% in the oxybutynin ER and tolterodine ER cohorts, a difference which was statistically significant. With a mean of \$7083, subjects in the oxybutynin IR cohort had the highest unadjusted medical costs during follow-up, followed by \$5980 for the oxybutynin ER cohort and \$5074 for the tolterodine ER cohort. The \$2010 difference in mean cost (rounded to the nearest dollar) between the oxybutynin IR and tolterodine ER cohorts was statistically significant (95% CI, \$924-\$3096). However, differences in unadjusted mean cost were not statistically significant for comparisons of the oxybutynin IR and oxybutynin ER cohorts (\$1103; 95% CI, \$-72-\$2278) and the oxybutynin ER

and tolterodine ER cohorts (\$906; 95% CI, \$-50-\$1863) (Table 3).

Multivariate Results. Tables present statistically significant covariates only; although adjusted for the analyses, coefficients for comorbid illnesses are not presented because of the number of these covariates. The treatment regression estimation indicated that oxybutynin IR was associated with 48% higher medical costs during the follow-up period compared with tolterodine ER (Table 4). The statistically significant negative correlation between the treatment selection and cost equations for this model ($\rho = -.1340$, $P = .0405$) suggested that OLS estimates may be biased downward (ie, the OLS coefficient for oxybutynin IR was too small), and the selectivity-corrected results were likely better estimates. Other factors that were associated with medical cost ($P < .05$) included age group, baseline total costs, specific OAB-related diagnosis code, and specific comorbid illnesses. For each \$1000 increase in baseline total costs, subjects' follow-up medical costs were approximately 2% higher. Specific OAB-related diagnosis codes were associated with varying levels of higher costs compared with subjects without those specific diagnosis codes. The largest effect was for subjects with "Urethral syndrome NOS [not otherwise specified]," who had 65% higher costs compared with subjects without that code.

Results adjusted for covariates and for selection suggest that the oxybutynin ER

Table 3. Medical Costs in 12-month Follow-up Period, Unadjusted for Covariates

Cohort	% Subjects with cost	Mean (\$)	SD	Minimum	Median	Maximum
Oxybutynin IR (n = 3052)	96.85	7083	39 420	0	2352	1 753 290
Oxybutynin ER (n = 4503)	97.98	5980	13 263	0	2253	348 203
Tolterodine ER (n = 7027)	97.91	5074	11 007	0	1902	252 588
χ^2 (1 df)/Bonferonni-adjusted t-test/Kruskall Wallis χ^2 (2 df), P value	12.67 $P = .0018$	Oxybutynin IR vs Tolterodine ER $P < .05$ Oxybutynin IR vs Oxybutynin ER, Oxybutynin IR vs Tolterodine ER, NS			39.69 $P < .00021$	

SD indicates standard deviation; IR, immediate release; ER, extended release; df, degree of freedom; NS, not statistically significant at $P < .05$.

Table 4. Selectivity-corrected Model of Effect of Oxybutynin IR vs Tolterodine ER on Medical Cost

	Coefficient on medical cost (\$)	Robust SE	% Change in medical costs (\$)	Z score	P value
Tolterodine ER	(Reference group)				
Oxybutynin IR	0.405	0.182	47.53	2.23	.0260
Age group, yrs					
18-34	0.298	0.100	34.11	2.99	.0030
35-44	0.312	0.086	36.16	3.62	<.0001
45-54	0.508	0.077	65.71	6.59	<.0001
55-64	0.578	0.074	77.73	7.82	<.0001
65-74	0.037	0.074	3.47	0.50	.6180
75+	(Reference group)				
Baseline total cost (per \$1000)	0.016	0.002	1.66	7.64	<.0001
OAB-related diagnosis code					
595.3 Trigonitis	0.335	0.145	38.27	2.30	.0210
597.81 Urethral syndrome NOS	0.511	0.130	65.33	3.92	<.0001
788.31 Urge incontinence	0.097	0.046	10.02	2.11	.0350
788.33 Mixed incontinence, urge and stress	0.381	0.058	46.18	6.63	<.0001
788.34 Incontinence without sensory awareness	0.414	0.215	47.77	1.92	.0550
788.41 Urinary frequency	0.187	0.037	20.51	5.03	<.0001
788.30 Unspecified urinary incontinence	0.203	0.040	22.40	5.08	<.0001
Constant	5.547	0.113		48.92	<.0001
<i>Rho = -0.1320, Wald test of independence of equations, $\chi^2 = 4.20, 1 \text{ df}, P = .0405.$</i>					

Table includes results for statistically significant independent variables only.

Analysis controlled for comorbid diagnosis clusters, but the coefficients are not included in the table.

IR indicates immediate release; ER, extended release; SE, standard error; OAB, overactive bladder; NOS, not otherwise specified; df, degree of freedom.

cohort had medical costs over the follow-up period that were 191% higher than for the tolterodine ER cohort (Table 5). The negative correlation ($\rho = -0.3843, P = .0003$) between the treatment selection equation and the cost equation suggested that the OLS estimated coefficient for oxybutynin ER was biased downward and underestimated follow-up medical costs for the oxybutynin ER. Other statistically significant coefficients included age group, baseline total healthcare costs, specific OAB-related diagnosis code, and comorbid illnesses. Baseline total healthcare costs were associated with an increase of follow-up medical costs of approximately 2% per \$1000 of baseline costs. Subgroups with specific ICD-9-CM OAB-related diagnosis codes had higher

follow-up costs compared with subjects without those codes, with the largest effect for the diagnosis of "Urethral syndrome NOS."

Mean medical costs after adjusting for covariates and selection effects were significantly higher for the oxybutynin IR and oxybutynin ER cohorts compared with the tolterodine ER cohort (Table 6). Results indicated that subjects initiating oxybutynin IR had an adjusted medical cost of \$7486 (95% CI, \$5242-\$10 690); this cost was \$2412 higher than costs for subjects initiating tolterodine ER. Subjects initiating oxybutynin ER had an adjusted mean medical cost of \$14 766 (95% CI, \$8501-\$25 649), which is \$9692 higher than the medical costs for subjects initiating tolterodine ER.

Table 5. Selectivity-corrected Model of Effect of Oxybutynin ER vs Tolterodine ER on Medical Cost

Independent variable	Coefficient on medical costs (\$)	Robust SE	% Change in medical costs (\$)	Z score	P value
Tolterodine ER	(Reference Group)				
Oxybutynin ER	1.108	0.282	191.02	3.93	<.0001
Age group, yrs					
18-34	0.140	0.091	14.51	1.53	.1250
35-44	0.159	0.076	16.92	2.08	.0370
45-54	0.338	0.069	39.87	4.90	<.0001
55-64	0.388	0.067	47.04	5.79	<.0001
65-74	0.001	0.068	-0.16	0.01	.9910
75+	(Reference group)				
Baseline total cost (per \$1000)	0.019	0.005	1.88	3.67	<.0001
OAB-related diagnosis code					
595.3 Trigonitis	0.306	0.140	34.53	2.19	.0280
788.31 Urge incontinence	0.127	0.041	13.42	3.07	.0020
788.33 Mixed incontinence, urge and stress	0.310	0.053	36.20	5.82	<.0001
788.41 Urinary frequency	0.170	0.034	18.41	4.92	<.0001
788.43 Nocturia	0.128	0.057	13.50	2.23	.0260
788.30 Unspecified urinary incontinence	0.152	0.040	16.36	3.80	<.0001
788.4 Frequency of urination, unspecified	0.310	0.143	34.95	2.16	.0310
Constant	5.570	0.129		43.21	<.0001

Rho = -0.3843, Wald test of independence of equations, $\chi^2 = 13.08, 1 df, P = .0003.$

Table includes results for statistically significant independent variables only. Analysis controlled for comorbid diagnosis clusters, but the coefficients are not included in the table. ER indicates extended release; SE, standard error; OAB, overactive bladder; df, degree of freedom.

Chow tests and interaction terms tested between treatment cohort and covariates were not statistically significant in either estimation.

Discussion

Subjects initiating oxybutynin IR, oxybutynin ER, and tolterodine ER differed in their adjusted medical costs over a 1-year follow-up period. Results of these analyses are particularly intriguing, because the presence of a selection effect suggests that analyses of costs that fail to account for this effect may underestimate the extent to which tolterodine ER may be associated with reduced costs after treatment initiation. The size of the treatment effects were substantial, with adjusted mean medical

costs that were \$2412 higher for the oxybutynin IR cohort and \$9692 higher for the oxybutynin ER cohort compared with the tolterodine ER cohort.

This study addressed an important issue common to observational studies. Because data were collected retrospectively, there may be some concern that nonrandom assignment to treatment may result in comparisons of unbalanced populations with unobserved characteristics that may be associated with higher costs over the follow-up period.³² This study used econometric techniques to identify the bias in the uncorrected estimates and to generate estimates of the association between treatment and cost that account for this bias resulting from unobserved factors.

One argument against examining medical costs alone is that the differences in medical cost between the treatment cohorts may have been offset by higher prescription drug costs for the tolterodine ER cohort. To examine this, models were re-estimated on total costs that included both pharmacy and medical costs over the follow-up period. Results of these analyses were mixed. For the comparison of oxybutynin IR with tolterodine ER, the correlation between the treatment selection and the cost equation was no longer statistically significant (Wald chi-square = 2.52, $P = .112$), suggesting that the OLS estimate of the association between oxybutynin IR and total cost was not biased by treatment selection. The coefficient from the OLS estimation (beta = $-.0803259$, robust SE = 0.0246, $T = -3.26$, $P < .001$) indicated that oxybutynin IR was associated with a 7.75% decrease in total costs compared with the tolterodine ER cohort (95% CI, -12.09% - 3.19%). These results suggest that although oxybutynin IR may be associated with higher medical costs, these may be offset by lower pharmacy costs for this group. The opposite result was found in comparing total costs for oxybutynin ER with tolterodine ER. In the model estimated to compare total healthcare costs for the oxybutynin ER cohort with the tolterodine ER cohort, the correlation between treatment selection equation and total cost equation was statistically significant ($\rho = -0.664$, Wald chi-square = 261.55, $P < .0001$), indicating that there was a substantial selection bias. The coefficient of 1.2596 (robust SE = 0.069, $T = 18.23$, $P < .0001$) from this estimation suggested that after adjusting for covariates, subjects initiating oxybutynin ER had total healthcare costs in the year after treatment initiation that were 251.58% higher compared with total costs for subjects initiating tolterodine ER (95% CI, 207.05%-302.57%).

The selection of specific therapies for OAB may represent a significant driver of medical costs in treating patients with OAB. For the 7027 subjects included in this study who had initiated tolterodine ER, the 48% higher cost associated with oxybutynin IR suggests that if this group had initiated oxybutynin IR in lieu of tolterodine ER, they

Table 6. Mean Medical Cost Adjusted for Covariates and Treatment Selection

Treatment cohort	% Increase in cost vs tolterodine ER	95% CI for % increase	Mean cost (\$)	95% CI for cost (\$)
Oxybutynin IR	47.53	(3.31-110.69)	7486	5242-10 690
Oxybutynin ER	191.02	(67.55-405.49)	14 766	8501-25 649
Tolterodine ER	—		5074	—

IR indicates immediate release; ER, extended release; CI, confidence interval.

would have accrued \$16 949 124 in extra medical costs over the year after treatment initiation. If subjects had initiated oxybutynin ER in lieu of tolterodine ER, results suggest that an extra \$68 105 684 in medical costs would have accrued for this group. At the low end, the 95% lower confidence limit of a 3.31% increase in medical costs attributable to oxybutynin IR translates to a total of \$1 180 536 in extra medical costs if the 7027 tolterodine ER initiators had initiated oxybutynin IR instead.

Limitations. These findings should be interpreted in light of the limitations of the data and study design. The pattern of the association of age group with costs suggests that these data may underestimate costs for the Medicare-eligible population, particularly because there was little difference in cost among subjects older than the age of 65 years. Although these data may capture the costs paid by patients and by the Ingenix-affiliated health plan as the secondary payer, the data may not entirely capture costs that are paid by Medicare. However, this underestimation is not expected to differ between the different drug cohorts, and it is unlikely to have affected the estimates of the association between drug cohort and cost.

Claims data may more accurately capture patients' interactions with the healthcare system rather than patients' actual medical history, and are subject to possible coding errors and coding for the purpose of ruling out rather than actual disease. With OAB in particular, the difference between OAB rates

seen in administrative claims data compared with the rates in the literature based on surveys may, in part, be a result of underreporting of OAB. The analysis used an intent-to-treat approach, with patients assigned to cohorts based on their first prescription of the period, without adjusting for discontinuation of medications. In addition, patients may have received drugs without the presence of a prescription claim through samples provided by their physicians. Both discontinuation and presence of samples would tend to reduce the estimated difference in effect of treatment on costs towards zero if patients had low adherence to their prescribed medication, or if patients in one treatment cohort were also taking the other treatment. Medical claims also will not capture provider-prescribed therapies, such as Kegel exercises, habit training, or biofeedback, that are not covered by the health plan. Since clinical efficacy measures were not tested in this analysis, results do not imply superiority in clinical measures or outcomes for any of the treatments.

The results are primarily applicable to the treatment of OAB in managed care settings similar to the data source. However, as the plans included were discounted fee-for-service plans and not capitated or gatekeeper

models, the results may be more broadly applicable to populations covered under similar plans. In addition, the wide geographic distribution provides for generalization to managed care populations on a national level for the United States.

Despite these limitations, this examination of outcomes associated with medication use in a “real-world” setting, away from the highly controlled environment of the clinical trial, establishes a benchmark for the impact that OAB therapies may have on medical costs in a large, insured population.

Conclusion

This study found that patients who initiated either oxybutynin IR or oxybutynin ER had higher medical costs over 1 year of follow-up compared with patients initiating treatment with tolterodine ER. The extent to which the healthcare system can reduce costs and improve outcomes for patients with OAB may depend in part on the selection of specific treatments as well as increasing overall diagnosis and treatment rates.

Possible reasons behind the cost differences between the therapies were not explored in this study and remain to be investigated. However, there is some suggestion in the literature of lower rates of illnesses, such as fractures and urinary tract infections for treated compared to untreated OAB patients.⁶ The assessment of whether a similar relationship may partially explain the cost differential between therapies presents an interesting subject for future research.

Appendix. Identification of ICD-9-CM Codes for OAB

A preliminary study was performed to identify the appropriate ICD-9-CM codes for defining OAB in administrative claims. Although the ICD-9-CM added a description of OAB in October 2000, because the subject identification period was immediately after this, a larger list of codes was developed for this study because of concern over lag-time in implementing use of the code and uncertainty over the practice patterns surrounding coding of OAB. This preliminary study encompassed a literature search for retrospective studies that listed ICD-9-CM codes used to define OAB (and not simply urinary incontinence), an examination of the frequency of the codes in the research database, and clinician review. The literature review identified 2 published articles that used administrative claims data and listed the specific ICD-9-CM codes used to define OAB.^{4,25} This preliminary study determined that 5 of the codes overlapped between the articles, and those 5 codes accounted for 86% of the potential OAB subjects in the population, suggesting that changes in the code list beyond those 5 codes would likely have a small impact on outcomes analyses.³³ The codes identified for defining OAB are listed in Table 1, and include the 5 codes that overlap as well as codes that had face validity as identifiers for OAB.

REFERENCES

1. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol.* 2003;20:327-336.
2. Hu TW, Wagner TH, Bentkover JD, LeBlanc K, Zhou SZ, Hunt T. Estimated economic costs of overactive bladder in the United States. *Urology.* 2003;61:1123-1128.
3. Hu TW, Wagner TH, Bentkover JD, et al. Costs of urinary incontinence and overactive bladder in the United States: a comparative study. *Urology.* 2004;63:461-465.
4. Zhou Z, Jensen G. Insurance claim costs for overactive bladder disorder. *Drug Benefit Trends.* 2001;13:45-48.
5. Wagner TH, Hu TW, Bentkover J, et al. Health-related consequences of overactive bladder. *Am J Manag Care.* 2002;8(19 suppl):S598-S607.

- 6. Brown JS, McGhan WF, Chokroverty S.** Comorbidities associated with overactive bladder. *Am J Manag Care.* 2000;6(11 suppl):574-579.
- 7. Darkow T, Fontes CL, Williamson TE.** Costs associated with the management of overactive bladder and related comorbidities. *Pharmacotherapy.* 2005;25:511-519.
- 8. Holroyd-Leduc JM, Straus SE.** Management of urinary incontinence in women: clinical applications. *JAMA.* 2004;291:996-999.
- 9. Holroyd-Leduc JM, Straus SE.** Management of urinary incontinence in women: scientific review. *JAMA.* 2004;291:986-995.
- 10. Elliott DS, Lightner DJ, Blute ML.** Medical management of overactive bladder. *Mayo Clin Proc.* 2001;76:353-355.
- 11.** Assessment and treatment of urinary incontinence. Scientific Committee of the First International Consultation on Incontinence. *Lancet.* 2000;355:2153-2158.
- 12. Sarkar PK, Ritch AE.** Management of urinary incontinence. *J Clin Pharm Ther.* 2000;25:251-263.
- 13. Homma Y, Kawabe K.** Health-related quality of life of Japanese patients with overactive bladder treated with extended-release tolterodine or immediate-release oxybutynin: a randomized, placebo-controlled trial. *World J Urol.* 2004;22:251-256.
- 14. Andersson KE.** Antimuscarinics for the treatment of overactive bladder. *Lancet Neurol.* 2004;3:46-53.
- 15. Herbison P, Hay-Smith J, Ellis G, Moore K.** Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review. *BMJ.* 2003;326:841-844.
- 16. Diokno AC, Appell RA, Sand PK, et al.** Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc.* 2003;78:687-695.
- 17. Zinner NR, Mattiasson A, Stanton SL.** Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients. *J Am Geriatr Soc.* 2002;50:799-807.
- 18. Sussman D, Garely A.** Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the Antimuscarinic Clinical Effectiveness Trial (ACET). *Curr Med Res Opin.* 2002;18:177-184.
- 19. Appell RA, Sand P, Dmochowski R, et al.** Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. *Mayo Clin Proc.* 2001;76:358-363.
- 20. Drutz HP, Appell RA, Gleason D, Klimberg I, Radomski S.** Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. *Int Urogynecol J Pelvic Floor Dysfunct.* 1999;10:283-289.
- 21. Appell RA.** Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. *Urology.* 1997;50:90-96.
- 22. Boone TB, Kusek JW, Nyberg LM, et al.** Treatment patterns and associated symptom improvement during six months of care for overactive bladder: a prospective, observational study. *Clin Ther.* 2002;24:397-408.
- 23. Milsom I, Abrams P, Cardozo L, et al.** How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int.* 2001;87:760-766.
- 24. Noe L, Becker R, Williamson T, Chen D.** A pharmacoeconomic model comparing two long-acting treatments for overactive bladder. *J Manag Care Pharm.* 2002;8:343-352.
- 25. Hall JA, Nelson MA, Meyer JW, Williamson T, Wagner S.** Costs and resources associated with the treatment of overactive bladder using retrospective medical care claims data. *Manag Care Interface.* 2001;14:69-75.
- 26. Lawrence M, Guay DR, Benson SR, Anderson MJ.** Immediate-release oxybutynin versus tolterodine in detrusor overactivity: a population analysis. *Pharmacotherapy.* 2000;20:470-475.
- 27. Malone DC, Okano GJ.** Treatment of urge incontinence in Veterans Affairs medical centers. *Clin Ther.* 1999;21:867-877.
- 28. Schneeweiss R, Rosenblatt RA, Cherkin DC, Kirkwood CR, Hart G.** Diagnosis clusters: a new tool for analyzing the content of ambulatory medical care. *Med Care.* 1983;21:105-122.
- 29. Kennedy PE.** Estimation with correctly interpreted dummy variables in semilogarithmic equations. *Am Econ Rev.* 1981;71:801.
- 30. White H.** A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. *Econometrica.* 1980;48:817-830.
- 31. White H.** Maximum likelihood estimation of misspecified models. *Econometrica.* 1982;50:1-25.
- 32. Laupacis A, Mamdani M.** Observational studies of treatment effectiveness: some cautions. *Ann Intern Med.* 2004;140:923-924.
- 33. Nitz N, Jumadilova Z, Meyer J, Bavendam T.** Implications of overactive bladder ICD-9-CM code changes and use of codes in a managed care population. Presented at: International Society of Pharmacoeconomics and Outcomes Research; October 24-26, 2004; Hamburg, Germany.