

Long-term Health-Related Quality of Life of Patients Receiving Extended-Release Tolterodine for Overactive Bladder

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Abstract

Objective: To evaluate the long-term effects of tolterodine on the health-related quality of life (HRQoL) of patients diagnosed with overactive bladder with incontinence.

Methods: Patients who completed a 12-week randomized, double-blind, safety and efficacy trial comparing tolterodine with placebo were invited to enroll in a 12-month open-label continuation trial to assess the long-term safety and efficacy of tolterodine. This study reports the HRQoL results from the King's Health Questionnaire (KHQ) and the Short Form-36 (SF-36) that were administered at baseline, at the end of the 12-week trial, and 3 and 12 months following open-label treatment with tolterodine.

Results: One thousand seventy-seven patients were included in the intent-to-treat (ITT_B) population. KHQ translations were available for 838 patients (mean age, 61.1 years; 80.9% women) in the ITT_B population. HRQoL, as measured by the KHQ, significantly improved from baseline to months 3 and 12 on the following domains: incontinence impact, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep and energy, severity (coping) measures, and symptom severity. Improvements were generally consistent across all analyses for the 3- and 12-month measurements and for the ITT_B and completer (C_B) populations. Patients receiving tolterodine in the double-blind study showed additional improvement at the 3-month open-label assessment on all but the general health domain. At 12 months from treatment rollover, all improvements from rollover to 3 months were sustained with additional improvement seen on the incontinence impact and role limitations domains. The general health perceptions domain showed a slight decline from rollover that might be attributable to a natural decline in patients' health status at this life stage. These findings were consistent with other efficacy

results whereby efficacy was maintained over the 12-month open-label period. SF-36 results were consistent with previous experience of reduced sensitivity, as population groups were similar to the SF-36 Physical Component and Mental Component scores at various time points and with all populations.

Conclusion: Continued treatment with tolterodine provides additional benefits in HRQoL as measured by the KHQ. Of particular importance are improvements on the psychological aspects after longer-term treatment not detected after a short-term trial. Treatment effects on HRQoL are evident even after a 12-week placebo run-in supporting the true clinical effect of active treatment.

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Overactive bladder (OAB) is a common and distressing chronic bladder condition characterized by symptoms of urinary frequency, urgency, and, in many cases, urge incontinence. While not life threatening, OAB has significant health-related quality of life (HRQoL) implications. Discomfort, embarrassment, and loss of self-confidence in OAB sufferers may prompt withdrawal from social life. The condition may also affect multiple areas of functioning, including social, psychological, occupational, domestic, physical, and sexual domains.^{1,2} Sufferers often try to compensate for their abnormal urinary symptoms by adopting various coping behaviors. These habits are used

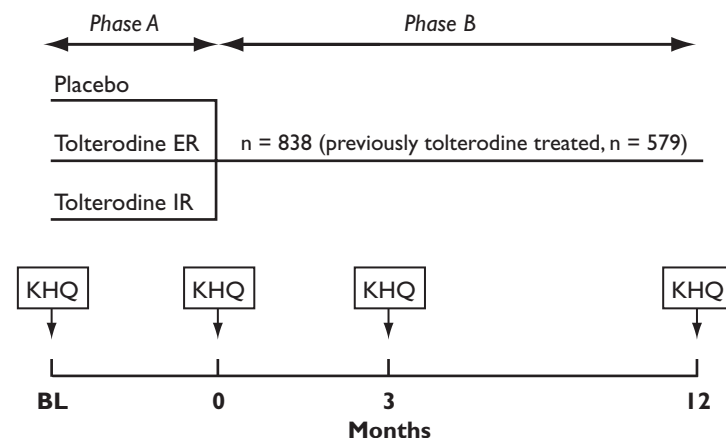
primarily to avoid the feeling of urinary urgency and the possibility of involuntary urinary leakage.

Additionally, patients with urinary incontinence and OAB have lower HRQoL compared with the healthy population or control patients,^{3,9} and often score lower on specific aspects of HRQoL than patients with other chronic diseases such as acquired immune deficiency syndrome, chronic obstructive pulmonary disease, and hyperlipidemia.¹⁰ Also, urge incontinence tends to diminish HRQoL more than stress incontinence or mixed incontinence.¹¹⁻¹⁶ While urge incontinence is typically thought to be the OAB symptom that has the greatest impact on patients, continent patients who experience symptoms of urinary urgency and frequency also experience significant reductions in HRQoL scores compared with controls.¹¹

The impact of treatments on HRQoL and other patient-reported outcomes should be assessed along with safety and efficacy evaluations. Such an approach was taken with tolterodine, a potent and competitive muscarinic receptor antagonist developed for the treatment of OAB.¹⁷ Details regarding the safety, efficacy, and tolerability of tolterodine have been reported elsewhere.^{18,19} Tolterodine has been shown to have short-term HRQoL benefits as measured by the King's Health Questionnaire (KHQ).²⁰ These HRQoL improvements were consistent with clinical efficacy results. Several KHQ domains showed significant improvement, including: incontinence impact, role limitations, physical limitations, sleep and energy, severity (coping) measures, and symptom severity. Tolterodine-treated patients were also found to have decreased severity of individual symptoms and improved ratings of bladder control compared with the placebo group.

A double-blind, randomized clinical trial demonstrated that tolterodine 4 mg administered once daily displayed a favorable tolerability and efficacy profile.²¹ In order to investigate the long-term tolerability, efficacy, and HRQoL impacts of tolterodine, an open-label, 12-month extension

Figure 1. Study Timelines



KHQ indicates King's Health Questionnaire.

of the 12-week study was performed. The objective of this paper is to report results assessing the impact of long-term tolterodine treatment on the HRQoL of patients with OAB and urge incontinence.

Methods

This 1-year, open-label, uncontrolled, nonrandomized extension study was conducted at 138 research centers and clinics in Australia, Austria, Belgium, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, Norway, the Russian Federation, Ukraine, the United Kingdom, and the United States. As **Figure 1** shows, patients with OAB completing 12 weeks of treatment in a multinational, randomized, double-blind, active- and placebo-controlled trial (Study 007A) were allowed to continue with 12 months of open-label treatment with tolterodine capsules 4 mg once daily (Study 007B). This treatment extension was not dependent on previous treatment assignment during the double-blind study (tolterodine 4 mg once daily, tolterodine 2 mg twice daily, or placebo). A washout period of 7 to 21 days occurred between the 2 studies. No dosage reduction was permitted in either the 12-week double-blind study or the 12-month open-label extension study. Participants in the extension study were kept blinded to

their original group assignment. The studies were conducted in accordance with the Declaration of Helsinki, local Independent Ethics Committee/Institutional Review Board requirements, and Good Clinical Practice Guidelines. Patients provided written informed consent prior to study entry.

Patients with an average of 8 or more micturitions per 24 hours over a 7-day period and at least 5 urge incontinence episodes per week prior to randomization as verified by a micturition diary were eligible for inclusion in the 007A study.^{19,22} Patients who had other types of bladder dysfunction, other diseases that may have affected urinary output, or who were pregnant were excluded. Patients with prior treatment, either successful or unsuccessful, could participate in this study. In order to be allowed to continue in the 007B study, patients had to fulfill the original inclusion/exclusion criteria of the double-blind study. Patients with an ongoing serious adverse event or who had poor compliance during the randomized double-blind trial (ie, missed more than 25% of the prescribed trial medication) were excluded from the open-label extension.

King's Health Questionnaire

The KHQ is a disease-specific questionnaire designed to evaluate the impact of OAB on HRQoL, including areas of physical and emotional function shown to be important to patients.²³⁻²⁵ The questionnaire contains 32 items across 9 HRQoL domains and an 11-item symptom checklist. The 9 domains include: incontinence impact (1 item); general health perceptions (1 item); role limitations (2 items); physical limitations (2 items); social limitations (3 items); personal relationships (2 items); emotions (3 items); sleep and energy (2 items); and severity (coping) measures (5 items). The KHQ also includes a 10-symptom checklist, the Symptom Severity scale, where patients are asked to indicate each symptom that affects them. The KHQ has been widely used and its reliability and validity have been well established.²³⁻²⁵ The KHQ has been translated into a number of languages by Mapi

Research using the International Quality of Life Assessment approach established for the Short Form-36 (SF-36) translations, which takes the cultural aspects of health into consideration.²⁶ The KHQ version 7 was self-administered to patients (n = 1312) at baseline of the double-blind study, at the end of the double-blind study, and after 3 and 12 months of open-label treatment, in countries where translations were available (Figure 1).

Short Form-36

The SF-36 is a 36-item general HRQoL questionnaire measuring 8 generic health concepts that can be summarized into Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.^{27,28} Although the SF-36 and its many translations have been found to be reliable and valid in general and ambulatory patients, as well as in populations with chronic diseases,²⁷⁻³² it appears to be less sensitive than disease-specific measures to the treatment changes seen among urinary incontinence patients.^{25,33} The SF-36 was included in this study for use in reliability and validity comparisons with the KHQ and not to detect treatment differences over time. The SF-36 was self-administered to patients at baseline for the double-blind study, at the end of the double-blind study, and after 3 and 12 months of open-label treatment.

Scoring

Data from each questionnaire were scored according to the developers' instructions.^{34,35} The score for any patient at any time point was calculated if at least one half of the questions included in that domain were answered. Missing responses for a question were imputed by using the mean value of responses to other items within the same domain. If fewer than half of the questions in any domain at any time point were answered, the score for that domain and time point was set to missing. The KHQ domains were scored on a 0 (best) to 100 (worst) scale. Symptom severity scores are additive (0-30) and were transformed to a 0 to 100 scale (best to worst) for consistency in contrast to

previously reported data. The SF-36 summary scores were scored on a 0 (worst) to 100 (best) scale. Because of the unique scoring of the KHQ, HRQoL improvements are represented by negative change scores.

Populations

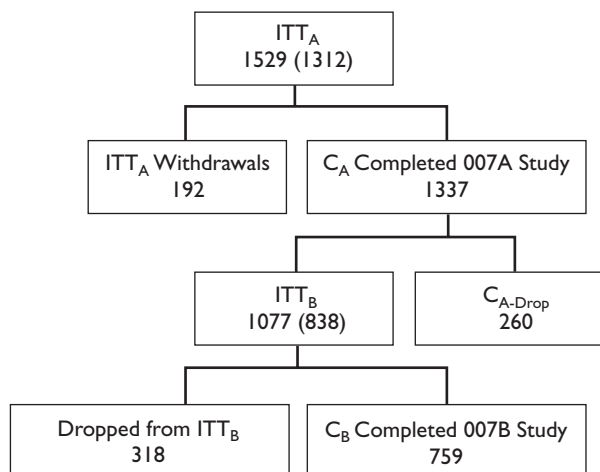
Multiple study populations were used in these analyses (Figure 2). All populations included patients for whom translations of the KHQ or SF-36 were available. For purposes of this study, the following populations were identified:

- The intent-to-treat (ITT_A) population was defined as all patients randomized to treatment in the double-blind study (007A) and receiving treatment.
- The completer (C_A) population was defined as all patients completing the double-blind (007A) study. This population was eligible to participate in the open-label (007B) study.
- The C_{A-Drop} population was defined as those patients in the C_A population eligible to continue but who chose not to continue into the open-label study (007B).
- The intent-to-treat (ITT_B) population was defined as all patients enrolled in the open-label extension study (007B) and receiving treatment with tolterodine.
- The completer (C_B) population was defined as all patients completing the open-label study (007B).
- The PT group was defined as ITT_B patients receiving placebo in the double-blind study (007A).
- The TT group was defined as ITT_B patients receiving tolterodine in the double-blind study (007A).

Statistical Analyses

The analyses were conducted using least square mean (LS mean) changes that were calculated using a split-plot analysis of covariance with repeated measures, with visits and treatment group as factors and age, gender, and country as covariates. Unavailable follow-up KHQ or SF-36 scores were estimated using the last observation carried forward (LOCF) approach

Figure 2. Study Populations*



*Number of patients, n, KHQ translations available (n) in each study population.

for the ITT analyses.³⁶ Multiple comparisons were controlled using the Hochberg procedure with α set at 0.05 for each hypothesis-wide test.³⁷ All analyses were performed using SAS for Windows® Version 6.12 (Microsoft Corporation).

Change scores were calculated in 2 ways. The primary analysis assessed the change in KHQ and SF-36 scores from baseline (visit 2) in the double-blind study to 3 months (visit 7) and 12 months (visit 10) following open-label treatment with tolterodine. A second analysis evaluated the change in KHQ and SF-36 scores from rollover (visit 4) to the open-label study to 3 months (visit 7) and 12 months (visit 10) following open-label treatment with tolterodine. Evaluations were also made to determine if the treatment effects for the TT groups in the ITT_A and ITT_B populations were different in order to establish the long-term HRQoL impacts of tolterodine.

Additionally, the extent and nature of selection bias for the rollover of patients from the double-blind study to open-label study was assessed. Three approaches were used:

- 1) The baseline characteristics and scores of the PT and TT groups were compared.

Table 1. Demographic Characteristics at Rollover

Demographic	KHQ	SF-36
Number of translations available*	838	961
Gender (n [%])		
Men	160 (19.1)	168 (17.5)
Women	678 (80.9)	793 (82.5)
Race (n [%])		
White	800 (95.5)	927 (96.5)
Black	28 (3.3)	24 (2.5)
Asian or Pacific Islander	6 (0.7)	6 (0.6)
Mixed	4 (0.5)	4 (0.4)
Age (years)		
Mean (SD)	61.1 (13.5)	60.2 (13.7)
Range	19 to 94	19 to 90

*KHQ translations were not available for Belgium (Flemish), The Netherlands, Norway, or Russia. SF-36 translations were available for all countries. KHQ indicates King's Health Questionnaire; SD, standard deviation.

These comparisons included demographics, micturitions per 24 hours, incontinence episodes, perceived bladder condition, and KHQ domains and SF-36 summary scores measured at baseline.

- 2) The baseline KHQ domain scores and response to therapy measures of patients who completed the double-blind study but chose to drop (C_{A-Drop}) were compared with those who completed the double-blind study and chose to participate in the open-label study (ITT_B). Response to therapy was measured as the percentage of patients who reported a treatment benefit following 12 weeks of treatment with tolterodine.
- 3) An analysis of change from baseline scores using the ITT_A and LOCF method for those who dropped or were missing scores was also conducted.

Table 2. Summary of Mean Changes in King's Health Questionnaire Scores from Baseline (Visit 2) to Month 3 (Visit 7) for the ITT_B Population

Domain	Change from Baseline to Month 3 (Visit 7)				
	Total (n = 838)		PT (n = 259)	TT (n = 579)	PT vs TT
	LS Mean [*] (SE)	<i>P</i> ^{†‡}	LS Mean [*] (SE)	LS Mean [*] (SE)	<i>P</i> ^{†§}
Incontinence impact	-24.0 (1.1)	.001	-22.2 (1.8)	-25.9 (1.2)	.652
Role limitations	-23.6 (1.1)	.001	-22.4 (1.8)	-24.9 (1.2)	.888
Physical limitations	-19.0 (1.1)	.001	-17.3 (1.7)	-20.7 (1.2)	.652
Social limitation	-11.8 (0.8)	.001	-11.9 (1.4)	-11.6 (0.9)	.888
Personal relationships	-8.9 (1.2)	.001	-7.2 (1.9)	-10.6 (1.3)	.737
Emotions	-14.9 (0.9)	.001	-14.5 (1.5)	-15.3 (1.0)	.888
Sleep and energy	-12.2 (0.8)	.001	-10.6 (1.4)	-13.8 (0.9)	.580
Severity (coping) measures	-13.7 (0.8)	.001	-11.9 (1.3)	-15.6 (0.9)	.244
General health perception	-0.4 (0.6)	0.540	-0.5 (1.1)	-0.3 (0.7)	.888
Symptom severity	-12.3 (0.5)	.001	-11.4 (0.9)	-13.3 (0.6)	.631

*Split plot analysis of covariance (ANCOVA) with repeated measures; visits and treatment start group (placebo or tolterodine) are factors with age, gender, and country as covariates.

[†]*P* values are adjusted for multiple testing using the Hochberg procedure.

[‡]*P* value for change from baseline using the ITT_B population.

[§]*P* value for change difference between PT and TT groups.

ITT_B indicates all patients enrolled in the open-label extension study (007B) and receiving treatment with tolterodine; LS mean, least square mean; PT, ITT_B patients receiving placebo in the double-blind study (007A); TT, ITT_B patients receiving tolterodine in the double-blind study (007A).

Results

A total of 1077 patients were included in the ITT_B population (Figure 2). KHQ translations were available for 838 patients in the ITT_B population. KHQ translations were not available for Belgium (Flemish), the Netherlands, Norway, or Russia. SF-36 translations were available for all patients and were collected for 961 patients in the ITT_B population.

Demographic characteristics (gender, race, and age distribution) for the KHQ and SF-36 populations at rollover are shown in Table 1. The majority of patients completing the KHQ were white women. The mean age of these patients was 61.1 years (range = 19-94 years). Results were similar for those completing the SF-36.

King's Health Questionnaire

Change from Baseline. The first analysis examined all patients in the ITT_B population to determine a change from baseline in KHQ scores. At the end of month 3 (visit 7) of open-label treatment, the cohort of all patients experienced statistically significant improvements from baseline in incontinence impact, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep and energy, severity (coping) measures, and symptom severity domains ($P \leq .001$) (Table 2). These improvements were maintained at the end of month 12 ($P \leq .001$) (Table 3). However, statistically significant differences in the general health perception domain scores were not

Table 3. Summary of Mean Changes in King's Health Questionnaire Scores from Baseline (Visit 2) to Month 12 (Visit 10) for the ITT_B Population

Domain	Placebo Effect [†]	Change from Baseline to Month 12 (Visit 10)					
		Total (n = 838)			PT (n = 259)	TT (n = 579)	PT vs TT
		Change from LS Mean [‡] (SE)	Baseline P [§]	P vs Placebo Effect [¶]			
Incontinence impact	-8.9	-23.1 (1.1)	.0002	.0000	-21.8 (1.8)	-24.4 (1.2)	.9179
Role limitations	-10.3	-23.8 (1.1)	.0002	.0000	-23.7 (1.8)	-23.9 (1.2)	.9179
Physical limitations	-8.7	-19.9 (1.1)	.0002	.0000	-20.1 (1.7)	-19.7 (1.2)	.9179
Social limitation	-6.3	-11.5 (0.8)	.0002	.0000	-12.9 (1.4)	-10.1 (0.9)	.8530
Personal relationships	-4.1	-8.4 (1.2)	.0002	.0006	-8.6 (2.0)	-8.1 (1.3)	.9179
Emotions	-6.5	-13.8 (0.9)	.0002	.0000	-13.4 (1.5)	-14.2 (1.0)	.9179
Sleep and energy	-5.1	-11.7 (0.8)	.0002	.0000	-11.5 (1.4)	-11.9 (0.9)	.9179
Severity (coping) measures	-6.1	-13.8 (0.8)	.0002	.0000	-12.8 (1.3)	-14.8 (0.9)	.9179
General health perception	-0.1	-0.1 (0.6)	.8302	.9753	-1.0 (1.1)	-0.7 (0.7)	.9179
Symptom severity	-5.0	-11.7 (0.5)	.0002	.0000	-11.4 (0.9)	-12.0 (0.6)	.9179

*The placebo effect is a constant value that was determined from the ITT_A population by calculating the amount of improvement or decline during the first 12 weeks of placebo use. The 2 groups (PT and TT) were combined as there was no significant difference between the 2 groups at the end of 12 months despite different lengths of time on active treatment.

[†]Split plot analysis of covariance (ANCOVA) with repeated measures; visits and treatment start group (placebo or tolterodine) are factors with age, gender, and country as covariates.

[‡]P values are adjusted for multiple testing using the Hochberg procedure.

[§]P value for change from baseline using the ITT_B population.

^{||}P value for change difference between PT and TT groups.

[¶]The 12-week placebo effect constant was subtracted from the change from baseline to visit 7 or visit 10, respectively, to remove the placebo effect observed in the first 12 weeks of treatment. The remaining value was tested using a t test comparison with zero in order to determine if an additional treatment benefit observed at visit 7 or visit 10 was statistically significant from the placebo effect that was achieved during the first 12 weeks. P values are adjusted for multiple testing using the Hochberg procedure.

ITT_A indicates all patients randomized to treatment in the double-blind study (007A) and receiving treatment; ITT_B, all patients enrolled in the open-label extension study (007B) and receiving treatment with tolterodine; LS mean, least square mean; PT, ITT_B patients receiving placebo in the double-blind study (007A); TT, ITT_B patients receiving tolterodine in the double-blind study (007A).

Table 4. Summary of Mean Changes in King's Health Questionnaire Scores from Rollover (Visit 4) to Month 3 (Visit 7) and Month 12 (Visit 10) for the ITT_B Population

Domain	Change from Rollover to Month 3 (Visit 7)					Change from Rollover to Month 12 (Visit 10)				
	PT (n = 259)		TT (n = 579)		PT vs TT <i>P</i> [§]	PT (n = 259)		TT (n = 579)		PT vs TT <i>P</i> [§]
	LS Mean* (SE)	<i>P</i> ^{††}	LS Mean* (SE)	<i>P</i> ^{††}		LS Mean* (SE)	<i>P</i> ^{††}	LS Mean* (SE)	<i>P</i> ^{††}	
Incontinence impact	-13.0 (1.8)	.0005	-7.4 (1.2)	.001	.0954	-12.7 (1.8)	.0005	-5.9 (1.2)	.0010	.0132
Role Limitations	-10.3 (1.8)	.0005	-5.0 (1.2)	.001	.1088	-11.6 (1.8)	.0005	-4.1 (1.2)	.0063	.0036
Physical limitations	-7.3 (1.7)	.0005	-3.9 (1.2)	.005	.5505	-10.1 (1.7)	.0005	-2.9 (1.2)	.0822	.0048
Social limitations	-3.1 (1.4)	.0645	-2.1 (0.9)	.044	.7525	-4.1 (1.4)	.0069	-0.5 (0.9)	.6443	.0800
Personal relationships	-3.8 (2.0)	.1052	-3.1 (1.3)	.044	.7525	-5.2 (2.0)	.0190	-0.6 (1.3)	.6443	.0800
Emotions	-6.8 (1.5)	.0005	-3.6 (1.0)	.002	.4578	-5.6 (1.5)	.0008	-2.5 (1.0)	.0822	.0800
Sleep and energy	-5.4 (1.4)	.0005	-2.4 (0.9)	.044	.4578	-6.2 (1.4)	.0005	-0.5 (0.9)	.6443	.0049
Severity (coping) measures	-4.2 (1.3)	.0072	-2.9 (0.9)	.006	.7525	-5.1 (1.3)	.0005	-2.1 (0.9)	.0920	.0800
General health perception	0.3 (1.1)	.7854	1.1 (0.7)	.115	.7525	-0.2 (1.1)	.8560	2.1 (0.7)	.0240	.0800
Symptom severity	-6.6 (0.9)	.0005	-2.1 (0.6)	.004	.0010	-6.6 (0.9)	.0005	-0.8 (0.6)	.6443	.0010

*Split plot analysis of covariance (ANCOVA) with repeated measures; visits and treatment start group (placebo or tolterodine) are factors with age, gender, and country as covariates.

[†]*P* values are adjusted for multiple testing using the Hochberg procedure.

^{††}*P* value for change from rollover within the respective population.

[§]*P* value for change difference between PT and TT populations.

ITT_B indicates all patients enrolled in the open-label extension study (007B) and receiving treatment with tolterodine; LS mean, least square mean; PT, ITT_B patients receiving placebo in the double-blind study (007A); TT, ITT_B patients receiving tolterodine in the double-blind study (007A).

observed at either time period. No statistically significant differences between treatment groups (PT vs TT) were found at either time period (Tables 2 and 3); however, most domains had a numeric difference in favor of the TT group at 3 months, but there was no discernible trend at 12 months.

Change from Rollover. A second analysis evaluated the change from rollover (visit 4) to 3 months (visit 7) and 12 months (visit 10). At the end of month 3 (visit 7), the PT group experienced a within-group improvement that was significant from rollover for incontinence impact, role limitations, physical limitations, emotions, sleep and energy, severity

(coping) measures, and symptom severity ($P \leq .007$) (Table 4). The TT group experienced a within-group improvement that was significant from rollover for incontinence impact, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep and energy, severity (coping) measures, and symptom severity ($P \leq .044$). Statistically significant differences between treatment groups (PT vs TT) were observed on symptom severity indicating that the PT group experienced more improvement in symptom severity than the TT group.

At the end of month 12 (visit 10), the within-PT group improvement was significant from rollover for incontinence impact, role limitations, physical limita-

Table 5. Change in King’s Health Questionnaire Scores from Baseline – TT Group from ITT_A and ITT_B Populations

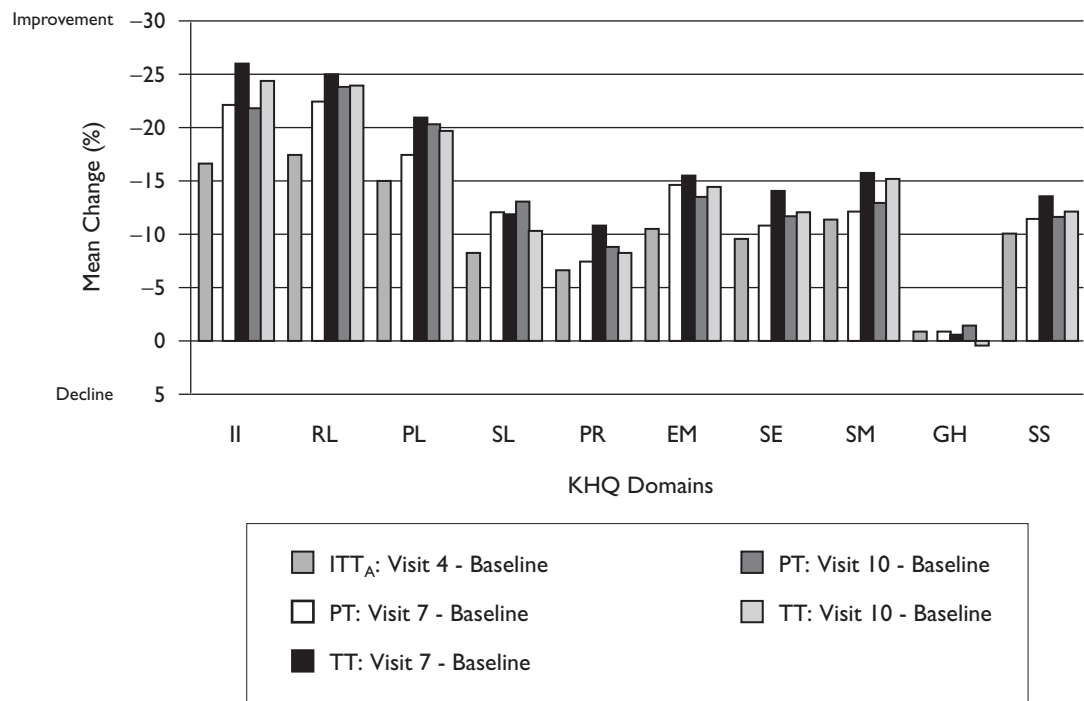
Domain	n	12-Week Treatment Effect*	Change from baseline to 6 Months’ Active Treatment (Visit 7-Visit 2)			Change from Baseline to 15 Months’ Active Treatment (Visit 10-Visit 2)		
			LS Mean [†] (SE)	95% CI	P ^{‡§}	LS Mean [†] (SE)	95% CI	P ^{‡§}
Incontinence impact	576	-16.6	-25.9 (1.2)	(-28.3, -23.5)	.0000	-24.4 (1.2)	(-26.8, -22.0)	.0000
Role limitations	576	-17.4	-24.9 (1.2)	(-27.2, -22.6)	.0000	-23.9 (1.2)	(-26.2, -21.6)	.0000
Physical limitations	576	-14.8	-20.7 (1.2)	(-23.0, -18.4)	.0000	-19.7 (1.2)	(-22.0, -17.4)	.0003
Social limitations	572	-8.1	-11.6 (0.9)	(-13.4, -9.9)	.0004	-10.1 (0.9)	(-11.9, -8.3)	.0095
Personal relationships	227	-6.4	-10.6 (1.3)	(-13.1, -8.0)	.0036	-8.1 (1.3)	(-10.6, -5.6)	.1936
Emotions	570	-10.3	-15.3 (1.0)	(-17.2, -13.3)	.0000	-14.2 (1.0)	(-16.2, -12.3)	.0005
Sleep and energy	573	-9.4	-13.8 (0.9)	(-15.6, -11.9)	.0000	-11.9 (0.9)	(-13.7, -10.1)	.0283
Severity (coping) measures	571	-11.2	-15.6 (0.9)	(-17.3, -13.8)	.0000	-14.8 (0.9)	(-16.5, -13.0)	.0005
General health perception	579	-0.6	-0.3 (0.7)	(-1.7, 1.1)	.6328	0.7 (0.7)	(-0.7, 2.1)	.1228
Symptom severity	519	-10.1	-4.0 (0.2)	(-4.4, -3.7)	.0000	-12.0 (0.6)	(-13.1, -10.8)	.0116

*The 12-week treatment effect is a constant value that was determined by combining the active treatment groups from the ITT_A population and calculating the amount of improvement or decline during the first 12 weeks of treatment.
[†]Split plot analysis of covariance (ANCOVA) with repeated measures; visits and treatment start group (placebo or tolterodine) are factors with age, gender, and country as covariates. Visits are restricted to the 2 visits of interest for each treatment start group.
[‡]The 12-week treatment effect constant was subtracted from the change from baseline to visit 7 or visit 10, respectively, to remove the active treatment effect observed in the first 12 weeks of treatment. The remaining value was tested using a *t* test comparison to zero in order to determine if an additional treatment benefit observed at visit 7 or visit 10 was statistically significant from that achieved during the first 12 weeks. *P* values are adjusted for multiple testing using the Hochberg procedure.
[§]Comparisons were made to the change from baseline (visit 2) to rollover (visit 4) in patients receiving tolterodine ER or IR treatment in 007A.
 CI indicates confidence interval; ER, extended-release; IR, immediate-release; ITT_A, all patients randomized to treatment in the double-blind study (007A) and receiving treatment; ITT_B, all patients enrolled in the open-label extension study (007B) and receiving treatment with tolterodine; LS mean, least square mean; TT, ITT_B patients receiving tolterodine in the double-blind study (007A).

tions, social limitations, personal relationships, emotions, sleep and energy, severity (coping) measures, and symptom severity ($P \leq .019$) (Table 4). At the end of month 12, the within-TT group improvement was significant from rollover for incontinence impact and role limitations and significantly worse from rollover on the general health perception. Statistically significant differences between treatment groups (PT vs TT) were observed with the PT group showing more improvement than the TT group on the incontinence impact, role limitations, physical limitations, sleep and energy, and symptom severity.

Comparison with ITT_A. To establish the long-term HRQoL impacts of tolterodine, comparisons were made between the change from baseline (visit 2) to rollover (visit 4) of blinded, active treatment with the change from baseline (visit 2) to month 3 (visit 7) and month 12 (visit 10) of open-label treatment for the TT group. This resulted in 6 and 15 months of active treatment in the TT groups. It was found that continued treatment with tolterodine resulted in continued improvement in almost all domains of the KHQ (Table 5; Figure 3). After 6 months of active treatment (3 months in the blinded study and 3 months in the open-label study), the TT

Figure 3. Short-term and Long-term Treatment Effects



II indicates incontinence impact; RL, role limitations; PL, physical limitations; SL, social limitations; PR, personal relationships; EM, emotions; SE, sleep and energy; SM, severity (coping) measures; GH, general health perception; SS, symptom severity.

Note: A negative score indicates improvement in health-related quality of life (HRQoL) and a positive score indicates decline in HRQoL.

group showed significant improvements over those achieved during the initial 3 months of treatment in all domains except general health perception. After 15 months of active treatment (3 months in the blinded study and 12 months in the open-label study), the TT group maintained improvements that were significantly better than those achieved in the initial 3 months of treatment on all domains except general health perception, social limitations, and personal relationships.

Selection Bias. Several approaches were used to assess whether or not these results might be attributed to a selection bias resulting from the patient's decision to continue into the open-label (007B) study. Baseline comparisons of the PT and TT groups found them to be similar in age,

gender, race, micturitions per 24 hours, incontinence episodes, and perceived bladder condition. Furthermore, there were no differences between the groups in KHQ scores at baseline.

The second approach compared patients who continued to the open-label study with those who dropped out after completing the double-blind study. These 2 populations were found to be similar at baseline on the following comparisons: age, gender, micturitions per 24 hours, and perceived bladder condition (Table 6). The continuing population had a significantly higher proportion of white patients (96% vs 91%; $P = .012$) and a higher median number of incontinence episodes (16.9 vs 14.0; $P = .049$) compared with the population that dropped out. These differences between populations appear to be due to

Table 6. Mean Patient Clinical Characteristics by Treatment Group and Population at Baseline (Visit 2) and Response to Treatment

Variable	Total (n = 1065)		Placebo* (n = 346)		Treated† (n = 719)	
	C _{A-Drop} (n = 227)	ITT _B (n = 838)	C _{A-Drop} (n = 87)	ITT _B (n = 259)	C _{A-Drop} (n = 140)	ITT _B (n = 579)
Micturitions/24 hours						
Median	10.3	10.3	10.6	10.4	10.1	10.1
<i>P</i> [‡]		.941		.621		.591
Incontinence episodes						
Median	14.0	16.9	14.0	19.0	14.0	16.0
<i>P</i> [‡]		.049		.049		.281
Perceived bladder conditions (n [%])						
No problems at all	0 (0.0)	3 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.2)
Some very minor problems	12 (5.3)	25 (3.0)	6 (6.9)	10 (3.9)	6 (4.3)	15 (2.6)
Some minor problems	29 (12.8)	102 (12.2)	13 (14.9)	29 (11.2)	16 (11.4)	73 (12.6)
Some moderate problems	97 (42.7)	387 (46.2)	34 (39.1)	108 (41.7)	63 (45.0)	279 (48.2)
Severe problems	66 (29.1)	251 (30.0)	28 (32.2)	89 (34.4)	38 (27.1)	162 (28.0)
Many severe problems	23 (10.1)	70 (8.4)	6 (6.9)	21 (8.1)	17 (12.1)	49 (8.5)
Missing	0 (0.0)	0 (0.0)				
<i>P</i> value [‡]		.921		.331		.545
Response to treatment [§] (n [%])	143 (63.6)	604 (72.3) [¶]	44 (50.6)	143 (55.2)	99 (71.7)	461 (79.9) [¶]
<i>P</i> value [‡]		.011		.453		.037

* Placebo in 007A study.

† Treated in 007A study with tolterodine (IR or ER).

‡ *P* value is for difference compared with the ITT_B population; Mann-Whitney test.

§ Response to therapy is defined as patients who reported a treatment benefit after 12 weeks.

|| Two patients in the C_{A-Drop} population did not answer the treatment benefit question.

¶ Two patients in the ITT_B population did not answer the treatment benefit question.

‡ *P* value is for difference with the ITT_B population; chi-square test.

C_{A-Drop} indicates those patients in the C_A population eligible to continue but who chose not to continue into the open-label study (007B); ER, extended-release; IR, immediate-release; ITT_B, all patients enrolled in the open-label extension study (007B) and receiving treatment with tolterodine.

continuation differences within the placebo group. Patients in the placebo group who continued were more likely to be white (95.8% vs 89.70%), experienced more incontinence episodes (19.0 vs 14.0), and tended to be women (81.9% vs 72.4%) compared with those who dropped out. There were no significant differences between the patients who continued in the open-label study compared with those who dropped out after completing the randomized trial in their response to treatment at the end of the double-blind study. Also, there were no differences between patients who continued and those who dropped out in KHQ scores at baseline.

The third approach repeated the analysis using the population originally randomized to the double-blind study and LOCF method for those who dropped out or had missing scores for any reason. At the end of months 3 and 12, all domains except general health perception showed statistically significant within-group improvement from baseline ($P \leq .001$). The TT group had significantly more improvement compared with the PT group in the incontinence impact and symptom severity domains ($P \leq .042$) at month 3 and in the severity (coping) measures at both month 3 ($P = .001$) and month 12 ($P = .031$).

Short Form-36

The population groups were similar for the SF-36 PCS and MCS scores. Consistent with other research, the SF-36 scores were not responsive to treatment group changes.^{38,39} Additional analyses showed that there were no statistically significant between-group differences in change from rollover using the ITT_B population, nor were there differences between groups at baseline, which might suggest a selection bias (data not shown).

Discussion

There is a substantial humanistic burden associated with patients suffering from OAB. These patients demonstrate symptoms of urinary frequency, urgency, and often urge incontinence. Urge incontinence is particularly bothersome with considerable consequences for daily functioning. Daily activities such as hobbies, household chores, and physical recreation are often organized around the location of toilets to avoid potentially embarrassing situations. The need for such coping behavior may significantly reduce patients' HRQoL. Given the significant impact on multiple dimensions of daily functioning, assessing the HRQoL of OAB patients is an important aspect of OAB research.^{40,41}

Currently, there is no "gold standard" for measuring HRQoL among OAB patients. Among the instruments that have been used to measure HRQoL in OAB patients are the KHQ, the Incontinence Impact Questionnaire, Incontinence Quality of Life Questionnaire, and the Overactive Bladder Questionnaire (OAB-q).⁴² The KHQ was chosen as the primary HRQoL assessment tool in this study because early work has shown it to have good reliability and validity in patients (most often women) with urge incontinence. The KHQ also covers the range of dimensions important to OAB patients, particularly urgency and frequency, which were not included in the other instruments available at the time of the study. The KHQ is also available in translations that considered cultural aspects of health.

Patients receiving tolterodine have shown significant HRQoL improvements on a number of physical and role functioning domains after 12 weeks of treatment.^{43,44} However, little is known about whether improvements in HRQoL seen after 12 weeks of tolterodine therapy are sustained in the long term, or if the psychological aspects of HRQoL not impacted in the short term would show improvement after prolonged treatment. The open-label study shows that patients on tolterodine treatment improved on the incontinence impact and role limitations domains at the end of 3 months. At the end of the treatment period (12 months), in addition to these 2 domains, improvements were also achieved on the social limitations and personal relationships domains. These results also show that patients being treated with tolterodine had fewer limitations on physical activities, such as walking, running, or the ability to travel. Based on items measured in the KHQ, it appeared that these patients also felt less depressed, anxious, and bad about themselves than prior to treatment. Problems with sleep or feeling worn-out or tired were also reduced with tolterodine treatment, as was the need for coping measures such as wearing pads, monitoring fluid intake, changing underclothes, worrying about odor, and embarrassment about bladder problems. Long-term treatment with tolterodine also enabled patients to perform social activities and decreased the impact on their personal relationships. No improvements were seen on the general health perceptions domain at either time point. However, given the age of the patients and the length of the study, this finding could be caused by the effects of comorbidities.

The results from this study show that long-term treatment with tolterodine has a positive and sustained effect on patient-reported HRQoL. In the original 12-week analysis, patients reported immediate and significant improvements in HRQoL on domains generally considered to be symptom and function related, such as role limitations and physical limitations. These short-term benefits are maintained or show

continued improvement over the course of the long-term study. Additionally, we see that the PT and the TT groups converge during the study period.

At 12 weeks, improvements in the more psychosocial-oriented domains (emotions, personal relationships, and social limitations) did not achieve statistical significance. After an additional 3 months of treatment, however, improvements were detected and these improvements were sustained after 12 months. At the time of the short-term study, we hypothesized that these changes would be measurable after longer treatment because patients require additional time to learn to “trust” the medication effects before placing themselves at risk for embarrassment. These results support this hypothesis of a lagged response for these domains.

The results of both the blinded and open-label studies show that OAB patients, both responders and nonresponders to previous treatment, should be considered for treatment with tolterodine. The inclusion criteria for these studies allowed patients with previous treatment failure to participate in these studies and approximately a quarter of the patients in this study had failed to respond to previous treatments for their condition. There are many potential reasons for treatment failure. The chronic nature of OAB necessitates long-term treatment, yet adverse effects associated with antimuscarinic agents can cause early discontinuation.^{45,46} However, these study results suggest that patients who have previously failed treatment may achieve short- and long-term gains in HRQoL, although additional research in this area is warranted.

The effect of placebo treatment on HRQoL was also examined in this study. Generally, when active treatments are compared with placebo in patients with OAB, there is usually a strong placebo effect, but this effect typically decreases over time.⁴⁷⁻⁴⁹ In this study we noted a placebo effect within the first 12 weeks of treatment. Although the study design did not include a placebo group in the open-label phase, the researchers think it is unlikely that a placebo effect accounts for

the changes that were observed with long-term treatment. First, it seems unlikely that patients would maintain a placebo effect over a long period of time and therefore it is unlikely for a placebo effect to exist at the end of the 12 months of treatment. Additionally, patients were blinded to the treatment they received during the first phase of the study, although it is possible that they might have been able to tell if symptoms of dry mouth occurred. Furthermore, patients achieved gains compared with their rollover into the open-label phase. This is evident at 3- and 12-months postrollover, indicating that patients experience significant improvement in HRQoL beyond the placebo effect on all domains of the KHQ except the general health perceptions domain. Therefore, the researchers are reasonably confident that improvements in patients' HRQoL can be attributed to the long-term treatment effect of tolterodine.

The KHQ findings were consistent with the clinical efficacy measures in the open-label study.²¹ Patients treated with tolterodine had an 83% reduction in the number of incontinence episodes per week and a 21% reduction in the number of micturitions per 24 hours between baseline and month 12.²¹ There was also a 20% increase in volume voided compared with baseline. Of the 71% of patients who completed 12 months' treatment with tolterodine, 75% reported an improvement in perception of bladder condition, and 51% reported an improvement in sense of urgency. The consistency of these findings provides increased confidence that efficacy was maintained in tolterodine-treated patients that in turn resulted in important impacts on their HRQoL.

Additionally, demonstrating and communicating that HRQoL is improved by treatment may facilitate patient care-seeking behavior. Increased awareness of OAB and its symptoms by physicians, including primary care physicians, internists, urologists, and gynecologists, will ensure that more patients are screened and treated for this condition.⁵⁰ Educational efforts may also encourage patients to discuss these symptoms with

their physicians, but careful questioning by physicians will also assist in the identification of OAB sufferers who can benefit from treatment. Consideration should also be given to encouraging patients to continue treatment for at least several months in order to evaluate the impact of treatment on all aspects of HRQoL.

Limitations

The inclusion and exclusion criteria of this study limit its generalizability to patients with characteristics similar to those enrolled in the randomized trial. Specifically, the results support HRQoL benefits of treatment in a population that is predominantly affected by OAB with urge incontinence. As with many OAB studies, the majority of participants were women. The limited number of men enrolled in the trial precluded the separate analysis of this subgroup.

Several potential sources of bias in this study were also evaluated. Patients completing the randomized trial could elect to enroll in the open-label extension trial. Of the 1529 patients who began the blinded study, 70.4% continued into the open-label study, of which 31.5% were in the PT group and 68.5% in the TT group (as expected since the original enrollment had a 2:1 bias favoring treatment). Although there was no baseline difference between the 2 open-label study groups (PT vs TT), it is likely that patients who perceived a treatment benefit during the blinded study elected to continue to the open-label study to form the ITT_B population. This situation could have introduced a self-selection bias in the composition of the ITT_B population. However, the choice to continue in the extension study is much like the choice of whether or not to continue on a therapeutic treatment in the everyday clinical setting. The ITT_B population was used as the primary analysis population because of this similarity to the “real world.”

Other patient populations were also analyzed to determine if conclusions from the study were somehow biased by population-dependent factors. Since patients

with ongoing serious adverse events and those demonstrating poor compliance were excluded from the ITT_B population, the safety and efficacy of tolterodine extended release could be overstated in this study. However, results were similar for the ITT_A and ITT_B populations, making this bias less likely. Long-term maintenance and improvement in HRQoL domains was also detected in the C_B population, with the exception that a statistically significant ($P = .047$) decline in general health perception was noted at the end of the open-label study; however, given the age of the patients and the length of the study, this finding could be caused by effects of comorbidities. By its design, the open-label study does not have a comparison group with which to better evaluate this finding. Several additional assessments of potential selection bias were made. It appears that selection bias was minimal and did not materially affect the results of this study.

Future Studies

It should be noted that in studies with large sample sizes, minor and even trivial differences are often statistically significant. The questions become: Are the statistically significant findings in this study clinically significant? Are the differences in HRQoL demonstrated in this study clinically meaningful? The minimal important difference or meaningful clinically important difference for the KHQ have been suggested but not confirmed.^{51,52} The long-term change from baseline scores appear to have reached, and in most cases exceeded, the minimally important differences of the 5 to 15 points estimated as clinically meaningful depending on domain. Additional work on this aspect of the KHQ is warranted.

Conclusion

This study found that HRQoL among OAB patients, as measured by the KHQ, improved with tolterodine treatment. These HRQoL improvements were sustained over a 12- to 15-month time period. Continued treatment also improved complex social and psychological aspects,

measured by emotions, social limitations, and personal relationships domains. Persistent treatment with tolterodine results in improvements in those domains that likely require “unlearning” of coping strategies often used to adapt to distressing OAB symptoms. Placebo response in the treatment of OAB is considerable though these study results support that tolterodine provides real benefits beyond placebo even after a lengthy placebo washout. Finally, these results support that the long-term use of tolterodine in the treatment of OAB patients experiencing urinary urge incontinence can lead to additional HRQoL benefits.

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...REFERENCES...

1. **Abrams P, Kelleher CJ, Kerr LA, Rogers RG.** Overactive bladder significantly affects quality of life. *Am J Manag Care.* 2000;6(suppl):S580-S590.
2. **Wein AJ, Rovner ES.** The overactive bladder: an overview for primary care health providers. *Int J Fertil.* 1999;44:56-66.
3. **Johannesson M, O'Connor RM, Kobelt-Nguyen G, Mattiasson A.** Willingness to pay for reduced incontinence symptoms. *Br J Urol.* 1997;80:557-562.
4. **O'Connor RM, Johannesson M, Hass SL, Kobelt-Nguyen G.** Urge incontinence: quality of life and patient's valuation of symptom reduction. *Pharmacoeconomics.* 1998;14:531-539.
5. **Kobelt G.** Economic considerations and outcomes measurement in urge incontinence. *Urology.* 1997;50 (suppl 6A):100-107.
6. **Grimby A, Svanborg A.** Morbidity and health related quality of life among ambulant elderly citizens. *Aging Clin Exp Res.* 1997;9:356-364.
7. **Samuelsson E, Victor A, Tibblin G.** A population study of urinary incontinence and nocturia among women aged 20-59 years. *Acta Obstet Gynecol Scand.* 1997;76:74-80.
8. **Wyman JF, Fantl JA, McClish DK, et al.** Quality of life following bladder training in older women with urinary incontinence. *Int Urogynecol J.* 1997;8: 223-229.
9. **Norton PA, MacDonald LD, Sedgwick PM, Stanton SL.** Distress and delay associated with urinary incontinence, frequency and urgency in women. *Br Med J.* 1988;297:1187-1189.
10. **Schlenk EA, Erlen JA, Dunbar-Jacob J, et al.** Health-related quality of life in chronic disorders: a comparison across studies using the MOS SF-36. *Qual Life Res.* 1998;7:57-65.
11. **Coyne L, Schmier J, Hunt T, et al.** Developing a specific HRQL instrument for overactive bladder [abstract]. *Value Health.* 2000;3:141.
12. **Grimby A, Milsom I, Molander U, Wiklund I, Ekelund P.** The influence of urinary incontinence on the quality of life of elderly women. *Age Ageing.* 1993;22:82-89.
13. **Hunnskaar S, Visnes A.** The quality of life in women with urinary incontinence as measured by the Sickness Impact Profile: Erratum. *J Am Geriatr Soc.* 1992;40:976-977.
14. **Kelleher CJ, Cardozo LD, Toozs-Hobson PM.** Quality of life and urinary incontinence. *Curr Opin Obstet Gynecol.* 1995;7:404-408.
15. **Kelleher CJ, Cardozo LD, Khullar V, Salvatore S.** A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol.* 1997;104:1374-1379.
16. **Lenderking WR, Nackley JF, Anderson RB, Testa MA.** A review of the quality-of-life aspects of urinary urge incontinence. *Pharmacoeconomics.* 1996;9: 11-23.
17. **Abrams P, Freeman R, Anderstrom C, Mattiasson A.** Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder. *Br J Urol.* 1998;81:801-810.
18. **Chancellor M, Freedman S, Mitcheson HD, et al.** Tolterodine, an effective and well tolerated treatment for urge incontinence and other overactive bladder symptoms. *Clin Drug Invest.* 2000;19:83-91.
19. **Van Kerrebroeck P, Kreder K, Jonas U, Zinner N, Wein A.** Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology.* 2001;57:414-421.
20. **Pleil AM, Reese PR, Kelleher CJ, Okano GJ.** Health-related quality of life of patients with overactive bladder receiving immediate-release tolterodine. *HEPAC.* 2001;2:69-75.
21. **Kreder K, Mayne C, Jonas U.** Long-term tolerability and efficacy of extended-release tolterodine in the treatment of overactive bladder. *Eur Urol.* 2002;41: 588-595.
22. **Chancellor M, Freedman S, Mitcheson HD, et al.** Tolterodine, an effective and well tolerated treatment for urge incontinence and other overactive bladder symptoms. *Clin Drug Invest.* 2000;19:83-91.
23. **Kelleher CJ, Cardozo LD, Toozs-Hobson PM.** Quality of life and urinary incontinence. *Curr Opin Obstet Gynecol.* 1995;7:404-408.
24. **Kelleher CJ, Cardozo LD, Khullar V, Salvatore S.** A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol.* 1997;104:1374-1379.
25. **Kobelt G, Kirchberger I, Malone-Lee J.** Review. Quality-of-life aspects of the overactive bladder and the effect of treatment with tolterodine. *BJU Int.* 1999;83:583-590.
26. **Conway K, Uzun V, Marrel A, et al.** Linguistic validation of the King's Health Questionnaire (KHQ) in eight languages [abstract]. *Value Health.* 1999;2:204.
27. **Ware JE, Snow KK, Kosinski M, Gandek B.** SF-36

- Health Survey: Manual and Interpretation Guide.* Boston, Mass: Health Assessment Lab, New England Medical Center Health Institute; 1993.
- 28. Ware JE, Kosinski M, Keller SD.** *SF-36 Physical & Mental Health Summary Scales: A User's Manual.* Boston, Mass: Health Assessment Lab, New England Medical Center Health Institute; 1994.
- 29. McHorney CA, Ware JE, Lu RJF, Sherbourne CD.** The MOS 36-item short-form health survey (SF-36) III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care.* 1994;32:40-66.
- 30. Stewart AL, Hays RD, Ware JE, Jr.** The MOS short-form general health survey. Reliability and validity in a patient population. *Med Care.* 1988;26:724-735.
- 31. Stewart AL, Greenfield S, Hays RD, et al.** Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study [published erratum appears in *JAMA* 1989;262:2542]. *JAMA.* 1989;262:907-913.
- 32. Aaronson NK, Acquadro C, Alonso J, et al.** International Quality of Life Assessment (IQOLA) Project. *Qual Life Res.* 1992;1:349-351.
- 33. Fantl JA, Bump RC, Robinson D, McClish DK, Wyman JF.** Efficacy of estrogen supplementation in the treatment of urinary incontinence. *Obstet Gynecol.* 1996;88:745-749.
- 34. Kelleher CJ.** Quality of life. In: Cardozo L, editor. *Urogynecology: The King's Approach.* Edinburgh: Churchill Livingstone; 1997:673-688.
- 35. Ware JE, Snow KK, Kosinski M, Gandek B.** *SF-36 Health Survey: Manual and Interpretation Guide.* Boston, Mass: Health Assessment Lab, New England Medical Center Health Institute; 1993.
- 36. Siddiqui O, Ali MW.** A comparison of the random-effects pattern mixture model with last-observation-carried-forward (LOCF) analysis in longitudinal clinical trials with dropouts. *J Biopharm Stat.* 1998;8:545-563.
- 37. Sankoh AJ, Huque MF, Dubey SD.** Some comments on frequently used multiple endpoint adjustment methods in clinical trials. *Stat Med.* 1997;16:2529-2542.
- 38. Pleil AM, Reese PR, Okano GJ, Kelleher CJ.** Validation of King's Health Questionnaire in patients with symptoms of overactive bladder. *Qual Life Res.* 2000;9:347.
- 39. Reese PR, Pleil AM, Okano GJ, Kelleher CJ.** Psychometric evaluation of the King's Health Questionnaire and the Short Form 36 in patients with overactive bladder receiving tolterodine. *Qual Life Res.* In press.
- 40. Wein AJ, Rovner ES.** The overactive bladder: an overview for primary care health providers. *Int J Fertil Womens Med.* 1999;44:56-66.
- 41. Abrams P, Kelleher CJ, Kerr LA, Rogers RG.** Overactive bladder significantly affects quality of life. *Am J Manag Care.* 2000;6:S580-S590.
- 42. Coyne K, Revicki D, Hunt T, et al.** Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. *Qual Life Res.* 2002;11:563-574.
- 43. Pleil AM, Reese PR, Okano GJ, Kelleher CJ.** Validation of King's Health Questionnaire in patients with symptoms of overactive bladder [abstract]. *Qual Life Res.* 2000;9:347.
- 44. Kelleher CJ, Pleil AM, Reese PR.** Health related QoL of patients with overactive bladder receiving tolterodine once daily. *Neurourology Urodynamics.* 2000;19:519-520.
- 45. Kelleher C, Cardozo L, Khullar V, Salvatore S.** A medium-term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. *Br J Obstet Gynaecol.* 1997;104:988-993.
- 46. Yarker YE, Goa KL, Fitton A.** Oxybutynin. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. *Drugs Aging.* 1995;6:243-262.
- 47. Meyhoff HH, Gerstenberg TC, Nordling J.** Placebo - the drug of choice in female motor urge incontinence? *Br J Urol.* 1983;55:34-37.
- 48. Abrams P, Larsson G, Chapple C, Wein AJ.** Factors involved in the success of antimuscarinic treatment. *BJU Int.* 1999;83(suppl 2):42-47.
- 49. Chancellor M, Freedman S, Mitcheson HD, et al.** Tolterodine, an effective and well tolerated treatment for urge incontinence and other overactive bladder symptoms. *Clin Drug Invest.* 2000;19:83-91.
- 50. Roberts RG.** Current management strategies of overactive bladder. *Patient Care.* 2000;(winter suppl):22-30.
- 51. Pleil AM, Reese PR, Slaton TL, Okano GJ, Kelleher CJ.** Minimally perceived differences of the King's Health Questionnaire: a comparison of results from two studies. Abstract presented at: Drug Information Association Quality of Life Conference; March, 2001.
- 52. Reese PR, Okano GJ, Pleil AM, Kelleher CJ.** Minimally perceived difference of the King's Health Questionnaire in patients with symptoms of overactive bladder: a comparison of results from two studies. Abstract presented at: International Society for Quality of Life Research Annual Conference; October 29-31, 2000.