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

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Abstract

Objective: To compare the health-related quality of life (HRQoL) of overactive bladder (OAB) patients following treatment with tolterodine extended-release (ER) 4 mg once daily versus placebo.

Study Design: Multinational, placebo-controlled, randomized, double-blind 12-week study.

Population: Patients with urinary frequency (≥8 micturitions/24 hours over a 7-day period), urge incontinence (≥5 episodes/week), and symptoms of OAB for at least 6 months were eligible for inclusion. Patients (81% female) received oral therapy with tolterodine ER (n = 507) or placebo (n = 508) for 12 weeks.

Outcomes Measured: HRQoL was assessed using the King's Health Questionnaire (KHQ) and Medical Outcomes Study Short Form 36-item questionnaire (SF-36). Patients also rated their bladder condition. Assessments were performed at baseline and at the end of treatment.

Results: At end of treatment, KHQ domains selected a priori as primary HRQoL end points (incontinence impact and role limitations) significantly improved ($P \leq .001$) with tolterodine ER. Domains selected a priori as secondary end points (physical limitations, sleep and energy, severity [coping] measures, and symptom severity) were also significantly improved ($P \leq .006$) following treatment with tolterodine ER. The tolterodine ER group had decreased symptom severity and statistically significant improvements in patient rating of bladder control compared with the placebo group at end of treatment. No treatment differences were detected using the SF-36.

Conclusion: Many aspects of HRQoL, as measured by the KHQ, showed statistically significant improvement following treatment with tolterodine ER. These HRQoL improvements were consistent with clinical efficacy benefits. Patients receiving tolterodine ER experienced overall improvement in their condition that was associated with an important impact on their HRQoL.

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Treatment outcome has historically been assessed using objective measures such as survival, frequencies of complications, and cure rates.[1] However, these clinical measures alone are no longer considered adequate, as it is widely accepted that health interventions should improve the quality of a patient's life in addition to providing therapeutic efficacy. This is particularly important as life expectancy increases and more people live for many years with chronic conditions that have little or no impact on mortality. Studies have shown that clinicians' and patients' judgements of quality of life differ considerably, leading to differing perceptions of the effects of clinical interventions.[2] The patient's opinion is therefore becoming recognized as central to the assessment of disease severity and the effects of treatment.

Several reliable and valid instruments have been developed to objectively measure subjective health-related quality of life (HRQoL), which may be defined as the individual's perceived level of physical, psychological, and social well-being.[2] Generic instruments, such as the Medical Outcomes Study Short Form 36-item questionnaire (SF-36),[3] provide a general

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profile of HRQoL and allow comparisons across populations and clinical conditions. Disease-specific instruments, such as the King's Health Questionnaire (KHQ) for overactive bladder (OAB),[4,5] evaluate specific conditions and assess symptoms and issues pertinent to that particular patient population. The 2 types of instruments are complementary and both are usually employed in quality-of-life research.[5]

Overactive bladder is a chronic condition affecting millions of people of both genders and all ages worldwide, with greater prevalence in the elderly.[5] It is characterized by urinary frequency and urgency, with or without urge incontinence.[6] Overactive bladder symptoms can cause great discomfort, embarrassment, and loss of confidence. Sufferers develop coping strategies to minimize their distress: daily activities are often restricted to within easy access of toilet facilities; fluid intake is reduced; physical and social activities are curtailed; and incontinence episodes are pre-empted by wearing protective garments, using pads, and carrying a change of clothing.[7]

Studies have shown that the symptoms and coping strategies associated with OAB reduce HRQoL.[5,8-11] Despite this, the majority of individuals with OAB do not seek treatment because they are either too embarrassed to discuss their problem, they assume that it is a natural result of aging, or they are unaware that effective treatment is available.[7,12]

Tolterodine is a potent and competitive muscarinic receptor antagonist for the treatment of OAB. An extended-release (ER) formulation (4-mg capsules) has recently been developed to allow for once-daily dosing. The objective of this article is to report the impact of tolterodine ER on the HRQoL of OAB patients with urge incontinence.

Methods

This placebo-controlled, randomized, double-blind, parallel-group study was conducted at 167 centers in Europe (n = 81), North America (n = 74), Australia/New Zealand (n = 7), and the Russian Federation/Ukraine (n = 5). It was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The study protocol was approved by the local Ethics Committees and all patients provided written informed consent.

Patients. Male and female patients aged 18 years or older with urinary frequency (average of ≥8 micturitions/24 hours over a 7-day period), urge incontinence (≥5 episodes/week), and symptoms of OAB for at least 6 months were eligible for randomization to the study. Patients with other types of bladder dysfunction, with 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. Full details of the inclusion and exclusion criteria are reported elsewhere.[13,14]

Study Design. Eligible patients entered a prestudy 1- to 2-week washout/run-in period during which the number of incontinence episodes and frequency of micturition were verified by means of a micturition diary. Subsequently, patients were randomized to oral therapy with tolterodine ER once daily (n = 507), tolterodine immediate-release (IR) 2 mg twice daily (n = 514), or placebo (n = 508) for 12 weeks. Efficacy and safety data[13,14] and HRQoL data pertaining to tolterodine IR 2-mg tablets are reported elsewhere.[15]

HRQoL Assessment. HRQoL was measured by the disease-specific KHQ and the generic SF-36, and patients also rated their bladder condition. The KHQ and SF-36 were self-administered and the rating of bladder condition was investigator-administered at baseline (following the washout/run-in period) and at the end of treatment (after 12 weeks or at withdrawal).

King's Health Questionnaire. The KHQ consists of 8 multi-item domains: role limitations, physical limitations, social limitations, personal relationships, emotions, sleep and energy, and severity (coping) measures.[4] Two single-item domains

address incontinence impact and general health perception. In addition, a multi-item Symptom Severity scale measures the severity of urinary symptoms (frequency, urgency, urge incontinence, stress incontinence, intercourse incontinence, nocturia, nocturnal enuresis, frequent urinary tract infections, bladder pain, and difficulty passing urine). The KHQ has been translated into numerous languages by Mapi. Research using the International Quality of Life Assessment approach established for the SF-36 translations which takes the cultural aspects of health into consideration.[16]

Short Form-36. The SF-36 includes 36 items grouped into 8 domains that may be scored as 8 domains or summarized in Physical and Mental Component Scales.[3,17] Linguistically validated translations for the SF-36 were available for all participating countries.[18]

Scoring of HRQoL Instruments. Questionnaires were scored according to the developers' instructions.[3,19] A domain score for any patient at any time point was calculated if at least one half of the questions included in that domain were answered. A missing response to a question was substituted with 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. In the KHQ, the severity of each of 10 urinary symptoms was measured on a scale ranging from "1" for "a little" to "3" for "a lot" with a score of "0" assigned if a response was omitted. The overall symptom severity was therefore scored on a 0 (best) to 30 (worst) scale. All other KHQ domains were scored on a 0 (best) to 100 (worst) scale. In contrast, the SF-36 physical and mental summaries were scored on a 0 (worst) to 100 (best) scale.

Patient Rating of Bladder Condition. To obtain patients' assessments of their disease severity and as a way of evaluating treatment effectiveness, patients rated the severity of problems caused by their bladder symptoms using a global 6-point rating scale (1 = no problems; 6 = many severe problems).

Statistical Analyses. Missing follow-up scores were substituted with the last (baseline) value carried forward. Between-group differences in KHQ and SF-36 scores were assessed using analysis of covariance. Baseline response, age, and gender were included as covariates and the analysis was performed on the intent-to-treat (ITT) population. The incontinence impact and role limitations domains of the KHQ have been shown in previous work to be responsive to changes over time and were selected a priori as primary HRQoL end points.[5] Other KHQ domains and SF-36 summary scores were considered secondary HRQoL end points. Multiple comparisons were controlled using the Hochberg procedure, with the initial α set at 0.05 for each of the HRQoL instruments.[20]

Between-group comparisons of bladder condition were made using the Kruskal-Wallis test. If statistically significant differences were found, data for each level of bladder control rating were assessed using the Mann-Whitney U test. An α level of 0.05 was used for both tests.

Individual items within the symptom severity domain were explored retrospectively using a chi-square analysis. Treatment groups were compared on the number of patients with and without each symptom at baseline and the number of patients with and without symptom improvement at the end of treatment. An α level of 0.05 was used for both analyses with no adjustment for multiple comparisons.

Results

A total of 1015 patients (827 women; 188 men) aged 20 to 93 years (tolterodine ER group mean age = 60.3 ± 14.4 years; placebo group mean age = 61.1 ± 13.9 years) were randomized to receive tolterodine ER or placebo and included in the ITT analysis. The study population represented treatment-seeking OAB patients with

Table 1. Mean Changes in KHQ Domain Scores from Baseline to End of Treatment*

	Summary of Mean Changes		Difference in Mean Changes	
	Placebo (n = 488)†	Tolterodine ER (n = 487)†	Tolterodine ER vs Placebo	
KHQ Domains	Mean (SD)	Mean (SD)	Mean Change	*P*‡
Incontinence impact	–8.86 (26.65)	–15.68 (29.36)	–6.75	.001
Role limitations	–10.26 (29.20)	–17.93 (30.58)	–7.36	.001
Physical limitations	–8.73 (27.90)	–15.60 (29.98)	–6.43	.001
Social limitations	–6.25 (22.76)	–8.49 (23.24)	–2.50	.062
Personal relationships	–3.44 (23.15)	–5.66 (26.74)	–1.38	.446
Emotions	–6.52 (23.98)	–9.31 (24.85)	–2.40	.106
Sleep and energy	–5.08 (21.06)	–9.82 (24.45)	–3.85	.006
Severity (coping) measures	–6.12 (20.39)	–11.98 (22.04)	–5.58	.001
General health perception	–0.12 (17.49)	–0.41 (17.55)	–0.13	.900
Symptom severity	–1.42 (3.99)	–2.90 (4.10)	–1.46	.001

*Analyses conducted on available data for each domain.
†Number of translations available.
‡Multiple comparisons were controlled using the Hochberg procedure, with the initial α set at 0.05.
ER indicates extended-release; KHQ, King's Health Questionnaire; SD, standard deviation.

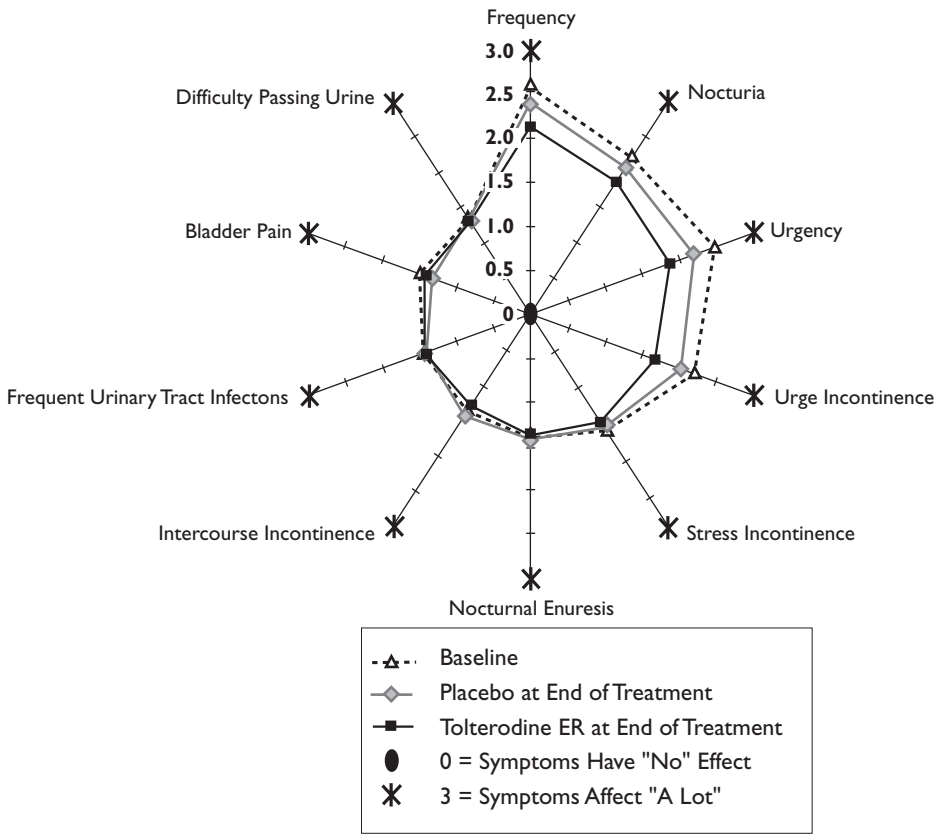
incontinence. The treatment groups were well matched with regard to demographic and baseline disease characteristics. Just over 50% of patients in each treatment group had received previous treatment for OAB, of whom approximately 40% had experienced poor results. Acceptable compliance with study medication (≥75%) was achieved by 95% of patients in each treatment group. Fewer patients were prematurely withdrawn from the tolterodine ER group (57; 11.2%) than the placebo group (68; 13.4%); reasons for early discontinuations were similar in both groups, with most withdrawals occurring because of adverse events.

KHQ

KHQ translations were available for 975 patients. KHQ data are presented in **Table 1**. The tolterodine ER group experienced significant improvements in the majority (6 of 10) of the KHQ domains compared with the placebo group. The tolterodine ER group had significantly more improvement in scores for the 2 domains specified a priori as the primary HRQoL end points: incontinence impact (P = .001) and role limitations (P = .001). In addition, the tolterodine ER group experienced statistically significant improvements on other KHQ domains selected as secondary HRQoL or symptom end points: physical limitations (P = .001), sleep and energy (P = .006), severity (coping) measures (P = .001), and symptom severity (P = .001), compared with the placebo group. Statistically significant differences between tolterodine and placebo were not found for the social limitations, personal relationships, emotions, and general health perception domains.

Results of the multi-item symptom severity measure are presented in the **Figure**. The rating for each of the symptom components is shown on a radar or "spider" graph. This technique allows evaluation of the magnitude of changes

Figure. Mean KHQ Symptom Severity Scores at Baseline and End of Treatment



Symptoms
Frequency: going to the toilet very often; urgency: a strong and difficult-to-control desire to pass urine; urge incontinence: urinary leakage associated with strong desire to pass urine; stress incontinence: urinary leakage with physical activity (eg, coughing, sneezing, running); intercourse incontinence: urinary leakage with sexual intercourse; nocturia: getting up at night to pass urine; nocturnal enuresis: wetting the bed at night; frequent urinary tract infections; bladder pain; difficulty passing urine.

across all symptoms. For all patients at baseline, values ranged from 1.35 for difficulty passing urine, indicating that few patients experienced this symptom, to 2.59 for frequency, indicating that many patients experienced considerable difficulties. The symptoms affecting patients most were frequency, urgency, urge incontinence, and nocturia. There were no differences between treatment groups at baseline. Results at the end of treatment are also shown in the Figure, with improvements indicated by rings that are closer to the center of the graph. Little change was observed for symptoms of nocturnal enuresis, difficulty passing urine, and frequent urinary tract infections, and only a small improvement in bladder pain was noted. Overall symptom severity decreased for both treatment groups by the end of the 12-week period. Apart from bladder pain for which the placebo group showed a slightly lower mean score, improvements were consistently greater for the tolterodine ER group, particularly for frequency, urgency, urge incontinence, intercourse incontinence, and nocturia. In addition, a significantly greater proportion of patients improved in the tolterodine ER group compared with the

Table 2. Mean Changes in SF-36 Scores from Baseline to End of Treatment*

	Summary of Mean Changes		Differences in Mean Changes	
	Placebo (n = 508)	Tolterodine ER (n = 507)	Tolterodine ER vs Placebo	
Dimension	Mean (SD)	Mean (SD)	Mean change	*P*
Physical summary	0.72 (6.57)	0.97 (7.34)	0.32	.451
Mental summary	0.10 (8.43)	0.67 (8.63)	0.21	.684

*Analyses conducted on available data for each domain.
ER indicates extended release; SD, standard deviation; SF-36, Short Form-36.

placebo group for frequency, urgency, and urge incontinence symptoms.

Short Form-36. No statistically significant differences in SF-36 physical or mental summary scores were observed after 12 weeks' treatment with tolterodine ER or placebo (**Table 2**).

Patient Rating of Bladder Condition. After 12 weeks' treatment with tolterodine ER, the proportion of patients reporting an improvement in their bladder conditions was significantly higher than that observed with placebo (58% vs 43%; $P = .001$). Fewer patients in the tolterodine ER group reported deterioration in their bladder condition compared with the placebo group (7% vs 13%; $P = .004$).

Discussion

It is reasonable to expect that the symptoms of OAB would result in impairment in HRQoL; however, many factors are likely to affect patients' perceptions of their problems with OAB. These include age; race; culture; social class; marital status; sexual problems; duration of symptoms; and the severity of frequency, urgency, and urinary leakage. This multinational study, using linguistically valid translations of the SF-36 and KHQ, which take cultural aspects of health into consideration,[16,18] provided an opportunity to evaluate HRQoL in OAB across a broad range of populations. The KHQ was initially designed and validated for use in women with urinary incontinence,[4] but has now been shown to be valid and reliable for use in men[5] and for patients with OAB.[21]

In this study, the tolterodine ER group showed statistically significant improvements in the majority of the KHQ domains compared with the placebo group. These improvements were consistent with reductions in the severity of symptoms and improvement in bladder condition, and also with other clinical efficacy outcomes.[14] No treatment differences were detected using the SF-36. Similar observations using the SF-36 have been noted in other therapeutic studies in OAB.[5,8,10] Since the SF-36 is a generic HRQoL instrument, it is not expected to be as sensitive to differences in changes in symptoms of OAB as the disease-specific KHQ.[2,4]

It is difficult to measure HRQoL and assess treatment in patients with OAB. When active treatments are compared with placebo in OAB patients, there is usually a strong placebo effect that decreases over time.[13,22,23] In the present study, patients receiving placebo showed a decrease in episodes of incontinence (–6.9 episodes/week) and frequency of micturition (–1.2 voids/day) compared with baseline values.[14] These findings were consistent with improvements in HRQoL as assessed with the KHQ, reduced severity of symptoms, and a high proportion of patients in the placebo group reporting improved bladder

condition. Patients may also have reduced their daily fluid intake to control their symptoms. This latter possibility is supported in the present study by decreases in episodes of incontinence and frequency being paralleled by only minor increases in volume voided per micturition among patients receiving placebo.[13]

Study results are also consistent with other research that found statistically significant improvements in all domains of the KHQ except personal relationships and general health perception.[5,10] In this study, significant improvements were found for all domains except social limitations, emotions, personal relationships, and general health perception. The short-term nature of the trial (lasting only 12 weeks) may limit the responsiveness of the measure since coping behaviors may continue even with effective treatment until the patient becomes confident that treatment works. This is a possible explanation for the nonsignificant trend in the social limitations and emotions domains seen in this study. Effects on interpersonal relationships are also difficult to evaluate due to the limited number of questions and to the exclusion of patients who are not having interpersonal relationships at the start of the study. The general health perception domain is generally unresponsive to short-term treatment.

A limitation of the present study may be the short duration of treatment. Longer studies are needed to understand if the perceived benefits encourage patients to continue treatment, to determine if domains show improvement after longer treatment, and to evaluate the sustainability of the improvement over time. A recently concluded extension to this study may provide data to further explore this proposition.

In conclusion, HRQoL, as measured by the KHQ, improved with tolterodine ER therapy in patients with OAB. The positive impact on HRQoL paralleled improvements in clinical efficacy outcomes. These observations are important for a chronic condition like OAB that requires long-term therapy. If patients perceive an improvement in their HRQoL as a result of treatment, then they may be more likely to continue to maintain the treatment.

Conclusion

This study suggests that HRQoL in patients with moderate to severe incontinence associated with urinary urgency and frequency improves after treatment with tolterodine ER. Further, the HRQoL improvement is evident across most domains addressed by the KHQ for these patients. Finally, improvement in HRQoL in patients with moderate to severe incontinence associated with urinary urgency and frequency was consistent with clinical efficacy results.

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