J Incl Phenom Macrocycl Chem (2011) 71:517–522
DOI 10.1007/s10847-011-0013-8

ORIGINAL ARTICLE

Predictors of response to fesoterodine in patients with an overactive bladder

Hyeon Woo Kim · Jeong Zoo Lee · Dong Gil Shin

Received: 7 June 2011 / Accepted: 4 July 2011 / Published online: 5 August 2011

Abstract An analysis has been conducted of the predictors of the fesoterodine treatment response for female patients with overactive bladder (OAB) syndrome. Eighty-seven women diagnosed with OAB and who had undergone 12 weeks of treatment with fesoterodine (4 mg/day) were involved. Prior to treatment, the patients were evaluated through their medical history, physical examinations, urine analysis, urine cultures, voiding diaries and urodynamic studies. The voiding diaries and personal interviews concerning urinary symptoms were analyzed 12 weeks after treatment. Seventy-nine (82.3%) women experienced improvement of OAB symptoms (Improvement group), and for seventeen (17.7%) women the symptoms remained unchanged or worsened (Persistence group) after treatment. In the urodynamic studies, detrusor overactivity was noted in 37 (46.8%) patients of the improvement group and 3 (17.6%) of the persistence group. The number of patients who showed detrusor overactivity in urodynamic studies before the treatment was significantly larger in the improvement group. Maximum detrusor pressure and detrusor pressure at maximum flow were higher in the persistence group but not to statistically significant levels. In pre-treatment voiding diaries, the number of urgencies per day was significantly larger in the improvement group. The efficacy of fesoterodine treatment for female OAB problems was found to be be associated with the frequency of urgency and detrusor overactivity. Thus, both voiding diaries and urgency/detrusor symptom records may aid in predicting the efficacy of fesoterodine treatment.

Keywords Fesoterodine · Overactive bladder · Women

Introduction

Accurate terminology for the description of voiding difficulty in female patients has yet to be established. Thus, to this date, systematic classification and analysis could not be performed. The initial definition of overactive bladder (OAB) syndrome was made in cases in which one of the three symptoms of frequency, urgency and incontinence was present in the absence of local lesions or metabolic diseases [1]. According to the definition due to the International Continence Society (ICS) in 2002, it is described as urgency, with or without incontinence, usually with frequency and nocturia [2].

Varying definitions of OAB syndrome, coupled to differences in symptom diagnosis and methods of data collection have led to considerable uncertainty as to its actual distribution [3]. Bladder overactivity may occur in all age groups, although its incidence tends to increase with age [4]. According to previous large-scale epidemiological studies its prevalence has been reported to be 9–16% of the population [3]. European studies of patients aged 40 or older have shown approximately 16.6% (male patients: 15.6%, female patients: 17.4%) to suffer from bladder overactivity [5]. Similar results were obtained in the USA [6]. In parallel, the Korean Continence Society (KCS) examined the prevalence of lower urinary tract symptoms including bladder overactivity in 2000 people (male and female subjects) aged 18 years or older using the ICS 2002 definition. According to this study, the overall frequency of

Dedicated to Professor Leonard F. Lindoy, a great chemist, on the occasion of his 75th birthday.

H. W. Kim · J. Z. Lee · D. G. Shin (✉)
Department of Urology, Pusan National University School of Medicine, 1-10, Ami-Dong, Seo-Ku, Busan 602-739, Korea
e-mail: shindong16@hanmail.net

overactive bladder syndrome was shown to be 12.2% (male patients: 10.0%, female patients: 14.3%). Given, however, that most patients regard bladder overactivity as a normal sign of aging and do not consider it as a problem requiring medical treatment, it is likely that the actual incidence is higher.

Bladder overactivity frequently occurs in women, and it is often characterized by chronic progression because women are either unwilling to disclose their problem or are unaware that treatment is possible. In fact, it has been shown that bladder overactivity has had an effect on the quality of life to a greater extent than diabetes mellitus [7–9].

The management of OAB symptoms has relied primarily on pharmacological therapy with or without behavioral therapy or a change of lifestyle [10]. Antimuscarinic agents are the first-line pharmacological treatment for OAB symptoms [11]. Fesoterodine is a nonselective oral antimuscarinic agent for their treatment which is available as a sustained-release formulation in 4- and 8-mg once-daily doses [11]. Fesoterodine itself is inactive and is rapidly and extensively hydrolyzed by nonspecific esterases to its principal active metabolite, 5-hydroxymethyl tolterodine (5-HMT) [12]. 5-HMT is also formed via CYP 2D6 mediated oxidation [12]. The conversion of FESO to 5-HMT bypasses the hepatic CYP pathway, although CYP3A4 and CYP2D6 isozymes are involved in the further inactivation of 5-HMT [3]. Figure 1 shows the chemical structures of antimuscarinic agents.

Previous studies have demonstrated that administering fesoterodine can reduce the distressing symptoms of OAB [13, 14]. Moreover, some studies have shown that the efficacy of fesoterodine is superior to that of tolterodine, which is the first-line pharmacological treatment [13, 15]. The aim of our study was to identify predictors of improved OAB symptoms after administering fesoterodine.

Methods

We selected 109 women aged ≥18 years with OAB symptoms (self assessed), such as urinary frequency, urgency, and urge urinary incontinence (UUI) for ≥3 months before screening and a mean of ≥8 voids/24 h with urgency or UUI reported in 3-day bladder diaries completed at baseline from patients who visited our hospital between January 2010 and December 2010. Patients were excluded if they had: clinically significant hepatic or renal disease; lower genitourinary pathology or surgical treatment responsible for voiding dysfunction; neurological conditions such as stroke, multiple sclerosis, spinal cord injury, or Parkinson's disease; previous history of acute urinary retention requiring catheterization; symptoms of incontinence being predominantly stress UI in the opinion of the investigator; treatment with antimuscarinic OAB medication within 2 weeks before screening; or use of any electrostimulation, bladder training, or pelvic floor exercises within 4 weeks of screening. Patients of childbearing potential who were heterosexually active without using an adequate form of contraception, or who were pregnant, nursing, or with a positive urine pregnancy test were also excluded. We excluded 13 patients due to various reasons, including incomplete medical records ($n = 7$) and current use of anti-muscarinic drugs ($n = 6$) and the remaining 96 patients participated in the study. 4 mg of fesoterodine (Toviaz 4 mg, Pfizer, USA) once a day was administered daily to these patients for 12 weeks.

Patients underwent urinalysis, 3-day bladder diary recording and a personal interview to identify how they were bothered by urinary symptoms on a scale of 0 to 5 (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = a great deal; 5 = a very great deal) with a standardized OAB V8 questionnaire [16] before and 12 weeks after the medication. OAB was defined as "the presence of urgency with or without incontinence and usually with frequency and nocturia" [17]. During the first visit, the diagnosis of OAB was made when the patient answered "somewhat" or more to any one of the three urge questions in OAB V8 questionnaire (question 2, An uncomfortable urge to urinate?; question 3, A sudden urge to urinate with little or no warning?; question 7, An uncontrollable urge to urinate?), once we had excluded any obvious etiology. The contents of 3-day voiding diary, including maximum voided volume, micturition numbers per day, urgency and incontinence episodes per day, were recorded prior to the second visit. Therefore, the baseline of OAB symptoms came from the OAB V8 questionnaires and 3-day voiding

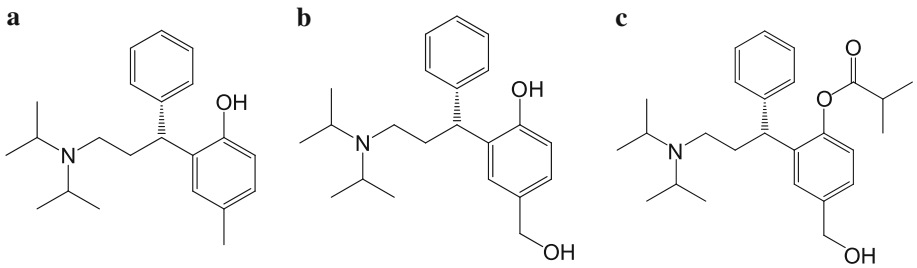

Fig. 1 Chemical structures of antimuscarinic agents

diaries. Following the 12 weeks of medication, women reporting a lower score to any one of the three urge questions were placed into the "Improvement" group. Those who answered the same or greater scale were classified into the "Persistence" group.

Urodynamic studies, including spontaneous uroflowmetry, filling and voiding cystometry were measured before the starting of medication and were performed according to the recommendations by the International Continence Society [18] with a Dantec Duet® urodynamics unit (Dantec Medical, Denmark).

The statistical analysis was performed using Student's *t* test and the difference was considered statistically significant when $P < 0.05$.

Results

The demographic characteristics, such as age, parity, body mass index, occurrence of menopause and duration of symptoms in both groups did not show any statistically significant differences. These are all summarized in Table 1.

After 12 weeks of fesoterodine administration, 79 (82.3%) women experienced absence or improvement of OAB symptoms (improvement group), and 17 (17.7%) women remained unchanged or worsened (persistence group).

We performed a univariate analysis of patients' characteristics and pre-treatment urodynamic parameters to identify potential predictors of OAB improvement after 12 weeks of fesoterodine administration. There were no difference between the two groups with regards to 24-h and nocturnal voiding numbers, UUI numbers and functional bladder capacity ($P > 0.05$; Table 2). There were also no differences in most of pre-treatment urodynamic parameters such as free maximum flow (Free Qmax), maximum detrusor pressure (Pdet.max), detrusor pressure at maximum flow (Pdet Qmax), maximal cytometric capacity (MCC), post void residual (PVR) and volume of first voiding sensation (FS) ($P > 0.05$; Table 3). However, significant differences were found in 24-h urgency numbers ($P < 0.05$), in voiding diary and detrusor overactivity ($P < 0.05$) and in urodynamic studies from which we suggested that these two parameters could be the predictors of post-treatment OAB improvement.

The women with OAB improvement were more likely to have frequent 24-h urgency numbers in their pre-treatment voiding diary and detrusor overactivity during the pre-treatment urodynamics. We found that 24-h urgency numbers and detrusor overactivity were the significant predictors of relief in OAB symptoms after 12 weeks of medication.

Discussion

The first line therapies of OAB are behavioral therapy, medical therapy or a combination of both therapies, with about a 70% success rate [19], although in many cases the results were unsatisfactory. Up till now, there have been no reported studies of the relationship between the patient's characteristics and the effectiveness of the therapy. Thus, clinicians had no specific clinical method of predicting the effectiveness of medical treatments in patients with OAB. Our study has proved that the factors such as urgency numbers, detrusor overactivity and increased detrusor pressure do enable prediction of the improvement of OAB symptoms after treating with an anti-muscarinic agent.

Abrams et al. [20] divided OAB patients into two groups, moderate and severe, depending on symptoms such as frequency, numbers of UUI, and bladder capacity before treatment, and compared the effects after the treatment. They reported that in the moderate group, a higher fraction of patients felt subjectively that they were cured. In contrast, a smaller fraction of patients in the severe group felt subjectively that they were cured, despite the fact that the objective variables were improved more significantly compared to those of the moderate group. In our study, comparative studies between the two groups are difficult because the occurrence of urgency in the improvement group was greater than in the other group and the pre-treatment voiding diaries showed that differences in frequency of urination and bladder capacity were not statistically significant. However, the incidence of frequency, nocturia and urgency showed decreases and functional bladder capacity was increased, leading to improvement in objective variables, especially the improvement of

Table 1 Analysis of clinical features in both groups

	Improvement ($n = 79$)	Persistence ($n = 17$)	*P* value
Age (years)	51.4 ± 12.1	53.3 ± 11.2	>0.05
Parity (times)	2.6 ± 1.1	2.7 ± 1.2	>0.05
BMI (kg/m^2)	23.9 ± 2.9	24.1 ± 3.1	>0.05
Menopause (*n*)	42 (58.2%)	12 (70.6)	>0.05
Duration of symptoms (years)	5.2 ± 5.1	5.3 ± 5.2	>0.05

BMI body mass index

Table 2 Pre-treatment voiding diary for both groups

	Improvement ($n = 79$)	Persistence ($n = 17$)	P value
Number of patients (n)	79 (82.3%)	17 (17.7%)	
Frequency (/day)	11.3 ± 2.9	11.0 ± 3.0	>0.05
Nocturia (/night)	2.3 ± 1.5	1.9 ± 1.2	>0.05
Urgency numbers/day	5.6 ± 3.4	3.3 ± 3.0	<0.05
UUI numbers/day	3.1 ± 2.8	2.9 ± 2.9	>0.05
FBC (mL)	298.6 ± 82.9	354.3 ± 148.6	>0.05

UUI urge urinary incontinence, *FBC* functional bladder capacity

Table 3 Pre-treatment urodynamic findings for both groups

	Improvement ($n = 79$)	Persistence ($n = 17$)	P value
Detrusor overactivity (n)	37 (46.8%)	3 (17.6%)	<0.05
Free Qmax (mL/s)	22.8 ± 10.5	20.9 ± 8.8	>0.05
Pdet.max (cm H_2O)	42.7 ± 21.2	47.1 ± 21.5	>0.05
Pdet.Qmax (cm H_2O)	30.9 ± 17.2	32.5 ± 14.1	>0.05
MCC (mL)	355.4 ± 97.2	321.7 ± 104.4	>0.05
PVR (mL)	28.0 ± 30.8	37.8 ± 52.0	>0.05
FS (mL)	143.9 ± 71.8	127.2 ± 93.4	>0.05

Free Qmax free maximum flow, *Pdet.max* maximum detrusor pressure, *Pdet Qmax* detrusor pressure at maximum flow, *MCC* maximal cytometric capacity, *PVR* post void residual, *FS* first sensation

urgency, though the post-treatment voiding diary data is not included in the present study. It means that a diminution in urgency is a principle factor in patient satisfaction.

The contraction of detrusor muscle is mainly mediated by muscarinic receptors and 2 of 5 subtypes such as M2, M3 are distributed throughout the bladder in the ratio of 3:1 [21]. Therefore, the majority of antimuscarinic agents primarily acts on the M3 subtype. Propiverine, one of the commonly used antimuscarinic agents, has smooth muscle relaxation and anticholinergic effects simultaneously and is used for currently treating OAB. Dorschner et al. [22] reported that in OAB patients who were treated with propiverine, frequency was decreased and incontinence was improved in 54% of them. Malone-Lee et al. [23] conducted urodynamic studies in 356 OAB females and 266 (76.1%) appeared to have detrusor overactivity. They reported that invasive procedures such as urodynamic studies were unnecessary because the remedial value of administrating 2.5 mg of oxybutynin twice a day for 6–8 weeks proved to be equal between the detrusor overactivity and non-detrusor overactivity groups.

Detrusor overactivity, the involuntary contraction of the detrusor muscle due to the loss of inhibition within the central or peripheral nerve system, may develop in OAB patients and diagnosis of this symptom is possible by urodynamic studies. Detrusor overactivity is not found in the urodynamic studies of many OAB patients and they are counted as having just 'sensory urgency' according to International Continence Society. This indicates that OAB can be developed from not only the involuntary contraction of the detrusor muscle due to loss of inhibition at the central or peripheral nerve system, but also from increasing afferent stimulation of the central nerve system. Detrusor muscle contractility which gives rise to detrusor overactivity is due to muscarinic receptors of efferent nerves and satisfactory effects can be obtained by administering anticholinergic agents for this condition. In patients with 'sensory urgency', it is thought that the distribution of afferent neuron receptors and the incidence of subtypes in the mucosal and submucosal layers are different from that of efferent nerves [24]. Therefore, to treat patients showing no detrusor overactivity and minimal reactions to existing anti-muscarinic agents, purinic [25, 26] or nicotinic acetylcholine receptors [27, 28] which are currently being actively investigated, and development of agents acting on various receptors and neurotransmitters [29, 30] of the uroepithelium are seen to be needed. For women with bladder outlet obstruction (BOO), a decrease of peak urinary flow velocity and an increase of detrusor power occurs. Recently, Blaivas and Groutz [31] described nomograms of female BOO using peak urinary flow velocity and maximum detrusor power, although different definitions of BOO have been presented by numerous researchers. In our study, maximum detrusor power and detrusor power at peak urinary flow velocity were greater in the persistence group, and even though it was not statistically significant when patients were grouped according to the above-mentioned nomogram, many BOO sufferers were found in the persistence group. The most common causes of BOO in females, found in more than half of the patients, are anatomical factors such as previous urinary incontinence surgery and severe pelvic organ prolapse. However,

the patients included in our study appeared to have functional BOO excluding apparent structural or anatomical disorders such as primary bladder neck obstruction, previous urinary incontinence surgery or pelvic organ prolapse. Hypertrophy of detrusor muscle is one of the changes due to BOO. Braverman and Ruggieri [32] reported that bladder contraction, which usually is activated by subtype M3, switches to M2 with advancing age or existence of BOO. Also, BOO leads to various functional changes of the bladder with detrusor muscle hypertrophy and these changes trigger involuntary contraction of the bladder and thus to instability with clinical symptoms of OAB, such as urgency and urge incontinence. OAB symptoms may occur with increased afferent stimulation which is associated with BOO and changes in the uroepithelium, and various receptors and neurotransmitters are involved in this mechanism. This affects the voiding process which leads to bladder irritation symptoms such as frequency and urgency. Therefore, we conclude that the existing behavioral therapy and use of anti-muscarinic agents may be insufficient for OAB due to BOO, and that what may be necessary is the normalization of the hypertrophied detrusor muscle by relieving BOO, thus decreasing voiding pressure and enabling normalization of alterations in various receptors and neurotransmitters.

These functional alterations of the bladder are slight in patients with low detrusor pressure and absent BOO, who are thus responsive to behavioral therapy and anti-muscarinic agents. Consequently, in our study, it is thought that the number of BOO patients was small in the satisfactory group.

Administering anti-muscarinic agents may induce adverse events such as dry mouth and constipation. Medication may need to be stopped in some cases when these symptoms are severe and these events may influence the patients' satisfaction with the treatment. In our study, the incidence of adverse events was higher in the unsatisfactory group but there were no significant differences compared with other groups. Also, there were no cases where it was necessary to stop the medication due to severe adverse effects. The small size of the unsatisfactory group made it difficult to apply any useful statistical analysis of its results. Further studies with analysis of larger subject groups are needed for definite confirmation of the effects of anti-muscarinic agents in OAB treatment.

Conclusions

The results of our study suggest that women with OAB can expect significant resolution of symptoms with daily administration of fesoterodine. Frequency of urge symptoms and detrusor overactivity were 2 significant predictors of symptom relief. However, all women taking fesoterodine still need to be informed that OAB symptoms might persist after short-term medication. Larger subject groups and longer-term studies, concerned in particular with determination of the optimum dosage of fesoterodine, are needed to identify more predictors and confirm our findings.

Acknowledgments We express our deep appreciation to Dr. Jack M. Harrowfield who has kindly improved the English of our manuscript.

Appendix: OAB Screener

This questionnaire concerns how much you have been bothered by selected bladder symptoms during the past 4 weeks. Please circle the number that best describes the extent to which you were bothered by each symptom during the past 4 weeks. There are no right or wrong answers. Please be sure to answer every question

During the past 4 weeks, how bothered were you by…	Not at all	A little bit	Some what	Quite a bit	A great deal	A very great deal
1. Frequent urination during the daytime hours	0	1	2	3	4	5
2. An uncomfortable urge to urinate	0	1	2	3	4	5
3. A sudden urge to urinate with little or no warning	0	1	2	3	4	5
4. Accidental loss of small amounts of urine	0	1	2	3	4	5
5. Nighttime urination	0	1	2	3	4	5
6. Waking up at night because you had to urinate	0	1	2	3	4	5
7. An uncontrollable urge to urinate	0	1	2	3	4	5
8. Urine loss associated with a strong desire to urinate	0	1	2	3	4	5

References

1. Sand, P.K., Morrow, J.D., Bavendam, T., Creanga, D.L., Nitti, V.W.: Efficacy and tolerability of fesoterodine in women with overactive bladder. Int. Urogynecol. J. **20**, 827–835 (2009)
2. Chapple, C., Kerrebroeck, P.V., Tubaro, A., Haag-Molkenteller, C., Forst, H.-T., Massow, U., Wange, J., Brodsky, M.: Clinical efficacy, safety, and tolerability of once-daily fesoterodine in

subjects with overactive bladder. Europ. Urol. **52**, 1204–1212 (2007)
3. Nitti, V.W., Dmochowski, R., Sand, P.K., Forst, H.-T., Haag-Molkenteller, C., Massow, U., Wang, J., Brodsky, M., Bavendam, T.: Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. J. Urol. **178**, 2488–2494 (2007)
4. Kraus, S.R., Ruiz-Cerdá, J.L., Martire, D., Wang, J.T., Wagg, A.S.: Efficacy and tolerability of fesoterodine in older and younger subjects with overactive bladder. Urology **76**, 1350–1357 (2010)
5. Cardozo, L., Khullar, V., El-Tahtawy, A., Guan, Z., Malhotra, B., Staskin, D.: Modeling dose-response relationships of the effects of fesoterodine in patients with overactive bladder. BMC Urol. **10**, 14 (2010)
6. Ellsworth, P., Berriman, S.J., Brodsky, M.: Fesoterodine: a new agent for treating overactive bladder. Amer. J. Managed Care. **15**, 4 (2009)
7. Herschorn Sender, J., Jones, S., Oelke, M., MacDiarmid, S., Wang, J.T., Guan, Z.: Efficacy and tolerability of fesoterodine in men with overactive bladder: a pooled analysis of 2 phase III studies. Urology. **75**, 1149–1155 (2010)
8. Meek, P.D., Evang, S.D., Tadrous, M., Roux-Lirange, D., Triller, D.M., Gumustop, B.: Overactive bladder drugs and constipation: a meta-analysis of randomized, placebo-controlled trials. Dig. Dis. Sci. **56**, 7–18 (2011)
9. Wyndaele, J.-J., Goldfischer, E.R., Morrow, J.D., Gong, J., Tseng, L.-J., Guan, Z., Choo, M.-S.: Effects of flexible-dose fesoterodine on overactive bladder symptoms and treatment satisfaction: an open-label study. Int. J. Clin. Pract. **63**, 560–567 (2009)
10. Ellsworth, P.: Fesoterodine for the treatment of urinary incontinence and overactive bladder. Ther Clin Risk Manag **5**, 869–876 (2009)
11. Van Kerrebroeck, P.E.V., Heesakkers, J., Berriman, S., Aiyer, L.P., Carlsson, M., Guan, Z.: Long-term safety, tolerability and efficacy of fesoterodine treatment in subjects with overactive bladder symptoms. Int. J. Clin. Pract. **64**, 584–593 (2010)
12. Malhotra, B.K., Crownover, P.H., La Badie, R., Glue, P., MacDiarmid, S.A.: The pharmacokinetic profile of fesoterodine 8 mg with daytime or nighttime dosing. Eur. J. Clin. Pharmacol. **66**, 171–176 (2010)
13. Chapple, C.R., Van Kerrebroeck, P.E., Jünemann, K.-P., Wang, J.T., Brodsky, M.: Comparison of fesoterodine and tolterodine in patients with overactive bladder. BJU Int. **102**, 1128–1132 (2008)
14. Goldman, H.B., Morrow, J.D., Gong, J., Tseng, L.-J., Schneider, T.: Early onset of fesoterodine efficacy in subjects with overactive bladder. BJU Int. **107**, 598–602 (2010)
15. Herschorn, S., Swift, S., Guan, Z., Carlsson, M., Morrow, J.D., Brodsky, M., Gong, J.: Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. BJU Int. **105**, 58–66 (2009)
16. Acquadro, C., Kopp, Z., Coyne, K.S., Corcos, J., Tubaro, A., Choo, M.S.: Translating overactive bladder questionnaires in 14 languages. Urology. **67**, 536–540 (2006)
17. Rosier, P., Ulmsten, U., van Kerrebroeck, P., Victor, A., Wein, A.: The standardization of terminology of lower urinary tract function: report from the standardisation sub-committee of the international continence society. Neurourol. Urodyn. **21**, 167–178 (2002)
18. Abrams, P., Blaivas, J.G., Stanton, S.L.: The standardization of terminology of low urinary tract function recommended by the International Continence Society. Int. Urogynecol. J. **1**, 45–58 (1990)
19. Milsom, I., Abrams, P., Cardozo, L., Roberts, R.G., Thuroff, J., Wein, A.J.: How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int. **87**, 760–766 (2001)
20. Kelleher, C.J., Reese, P.R., Pleil, A.M., Okano, G.J.: Health-related quality of life of patients receiving extended-release tolterodine for overactive bladder. Am. J. Manag. Care **8**, S608–S615 (2002)
21. Liberman, J.N., Hunt, T.L., Stewart, W.F.: Health-related quality of life among adults with symptoms of overactive bladder: results from a US community-based survey. Urology **57**, 1044–1050 (2001)
22. Coyne, K., Revicki, D., Hunt, T.: Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. Qual. Life Res. **11**, 563–574 (2002)
23. Kim, U.H., Kim, Y.H., Kim, M.E.: The prevalence and quality of life of overactive bladder and urinary incontinence in young women. Korean J. Urol. **45**, 543–550 (2004)
24. Abrams, P., Wein, A.J.: Introduction: overactive bladder and its treatments. Urology. **55**, 1–27 (2000)
25. Milsom, I., Stewart, W., Thuroff, J.: The prevalence of overactive bladder. Amer. J. Manag. Care. S565–S573 (2000)
26. Stewart, A.L., Hays, R.D., Ware Jr., J.E.: The MOS short form general health survey. Reliability and validity in a patient population. Med. Care **26**, 724–735 (1998)
27. Elving, L.B., Foldspang, A., Lam, G.W., Mommsen, S.: Descriptive epidemiology of urinary incontinence in 3, 100 women age 30–59. Scand. J. Urol. Nephrol. Suppl. **125**, 37–43 (1989)
28. Goepel, M., Hoffmann, J.A., Piro, M., Rubben, H., Michel, M.C.: Prevalence and physician awareness of symptoms of urinary bladder dysfunction. Eur. Urol. **41**, 234–239 (2002)
29. Lapitan, M.C., Chye, P.L.: The epidemiology of overactive bladder among females in Asia: a questionnaire survey. Int. Urogynecol. J. Pelvic. Floor Dysfunct **12**, 226–231 (2001)
30. Jackson, S.: The patient with an overactive bladder symptoms and quality of life issues. Urology. **50**(6A Suppl), 18–22 (1997)
31. Komaroff, A.L., Fagioli, L.R., Doolittle, T.H.: Health status in patients with chronic fatigue syndrome and in general population and disease comparison groups. Am. J. Med. **101**, 281–290 (1996)
32. Braverman, A.S., Ruggieri, M.R.Sr.: Hypertrophy changes the muscarinic receptor subtype mediating bladder contraction from M3 toward M2. Amer. J. Physiol. Regul. Integr. Comp. Physiol. **285**, R701–R708 (2003)