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Comparison of fesoterodine and tolterodine in patients with overactive bladder

Christopher R. Chapple, Philip E. Van Kerrebroeck*, Klaus-Peter Jünemann†, Joseph T. Wang‡ and Marina Brodsky‡

*The Royal Hallamshire Hospital, Sheffield, UK, *University Hospital Maastricht, Maastricht, the Netherlands, †Christian-Albrechts-Universität Kiel, Kiel, Germany, and ‡Pfizer Inc, New York, NY, USA*

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OBJECTIVE

To compare, in a post hoc analysis of a phase III trial, the maximum recommended doses of fesoterodine (8 mg) and tolterodine (4 mg) for improving overactive bladder (OAB) symptoms and health-related quality of life (HRQoL), as fesoterodine effectively reduces OAB symptoms vs placebo.

PATIENTS AND METHODS

Eligible patients with frequency (≥eight voids/24 h) and either urgency (≥six episodes over 3 days) or urgency urinary incontinence (UUI; ≥three episodes over 3 days) were randomized to placebo, fesoterodine 4 or 8 mg, or tolterodine extended-release (ER) 4 mg for 12 weeks; fesoterodine 4 mg data were published elsewhere. Patients completed a 3-day bladder diary in which they recorded the time of each void, voided volume (VV), and the severity of urgency. A post hoc inferential analysis was conducted on the primary endpoint (voids/24 h), the two co-primary endpoints (UUI episodes/24 h and treatment response), several secondary endpoints (severe urgency plus UUI per 24 h, mean VV (MVV)/void, and continent days/week), HRQoL, using the King's Health Questionnaire (KHQ) and the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF), and self-reported bladder-related problems. A subanalysis also assessed all endpoints for patients who were incontinent at baseline. Tolerability and safety were assessed by evaluating adverse events, residual urine volume, laboratory variables and treatment withdrawals.

RESULTS

By week 12, patients with OAB in both active-treatment groups showed significant improvements in most bladder diary variables and treatment response rates compared with placebo. Fesoterodine 8 mg was statistically significantly better than tolterodine ER 4 mg for improving UUI episodes, severe urgency plus UUI, mean VV, and number of continent days/week. In addition, the fesoterodine and tolterodine ER groups showed significantly greater improvements in HRQoL than the placebo group, with positive changes in most domains of the KHQ and an improvement in ICIQ-SF score. The fesoterodine 8-mg group had statistically significant improvements over placebo in eight of nine KHQ domains. A major improvement in the severity of bladder-related problems was reported by 39% of the fesoterodine 8 mg and 34% of the tolterodine ER groups vs 25% of those on placebo ($P \leq 0.01$). Results for the subgroup of incontinent patients at baseline were similar to the overall results. Adverse events reported most commonly with active treatment included dry mouth, constipation, dry eye, dry throat, and nausea.

CONCLUSIONS

Both fesoterodine and tolterodine ER significantly improved OAB symptoms and HRQoL, with statistically significant advantages for fesoterodine 8 mg compared with tolterodine ER on several important endpoints.

KEYWORDS

overactive bladder, incontinence, quality of life, antimuscarinic

INTRODUCTION

Fesoterodine is a new antimuscarinic agent for treating overactive bladder (OAB); it acts functionally as a pro-drug and is rapidly and extensively converted by nonspecific esterases to its primary active metabolite, 5-hydroxymethyl tolterodine (5-HMT) [1]. Fesoterodine is not detectable in plasma after oral dosing [2]. 5-HMT is also the major active metabolite of tolterodine, but it is formed from tolterodine via cytochrome P450 (CYP) 2D6-mediated oxidation in the liver. Because both tolterodine and 5-HMT are potent muscarinic receptor antagonists, the overall effect of tolterodine is the combined result of both moieties. The ratio of tolterodine to 5-HMT is affected by a patient's CYP2D6 genotype and relevant drug interactions, which can result in pharmacokinetic variability [3]. A subset of individuals (up to 10% of whites and up to 19% of blacks) [4] lack CYP2D6 enzyme activity and are referred to as 'poor metabolizers'; the remainder of the population is referred to as 'extensive metabolizers'. In the former, 5-HMT plasma levels are virtually undetectable after tolterodine administration [3]. Because fesoterodine does not require CYP2D6 metabolism for activation, it has the potential for less pharmacokinetic variability than tolterodine extended-release (ER).

The efficacy of fesoterodine 4 mg and 8 mg and its effect on health-related quality of life (HRQoL) have previously been assessed in

patients with OAB in a phase III study that also included tolterodine ER 4 mg as an active control [5]. The purpose of the present post hoc analysis was to compare the effects of the maximum recommended doses of fesoterodine (8 mg) and tolterodine ER (4 mg) on OAB symptoms and HRQoL in patients with OAB, both in all patients and only in those who were incontinent at baseline.

PATIENTS AND METHODS

This is a post hoc analysis of data from a multicentre, double-blind, double-dummy, placebo-controlled trial; details of the study design were published previously [6]. Eligible patients (≥18 years old) with frequency and urgency or urgency urinary incontinence (UUI) were randomized to placebo, fesoterodine 4 or 8 mg, or tolterodine ER 4 mg for 12 weeks. Because the purpose of this analysis was to compare the efficacy of the highest recommended doses of fesoterodine (8 mg) and tolterodine ER (4 mg), only data from these two groups and the placebo group are reported here.

Patients were randomized and the process administered by Schwarz BioSciences (Monheim, Germany) according to a computer-generated schedule anticipating a balancing of treatments (equal proportions for placebo, fesoterodine 4 and 8 mg, and tolterodine ER 4 mg) across countries and sites. After successfully completing visit 2, patients were consecutively randomized to one of four treatment arms and assigned sequential randomization numbers, which served as a basis for packaging the trial medication. Placebo tablets were identical in appearance to fesoterodine 4 and 8 mg tablets; placebo capsules were identical to tolterodine ER 4 mg capsules.

Men and women aged ≥18 years with OAB syndrome for ≥6 months were eligible to participate in this study. This included urinary frequency (≥eight voids/24 h), and urinary urgency (≥six episodes during the 3-day diary period) or UUI (≥three episodes during the 3-day diary period). To ensure enrolment of a sufficient number of patients with UUI (pre-specified in the protocol to be 80% of each treatment group), the protocol was amended shortly after the start of the trial to require ≥three UUI episodes to be recorded in the 3-day diary at the end of the placebo run-in for all remaining patients [6]. Also, patients had to report at least moderate bladder problems on a six-point Likert scale.

Exclusion criteria included the presence of lower urinary tract pathology that could, in the investigator's opinion, be responsible for urgency or UI (e.g. significant stress UI, urolithiasis, interstitial cystitis, urothelial tumours); pelvic organ prolapse grade ≥III; clinically relevant BOO; a postvoid residual urine volume of >100 mL; polyuria (>3 L/24 h); symptomatic or recurrent UTIs; current treatment with antimuscarinic agents; a neurogenic cause for OAB; clinically relevant arrhythmia, unstable angina, or a QTcB interval of >500 ms; and current treatment, or treatment within the past 4 weeks, with electrostimulation or bladder training [6].

Efficacy was assessed from the 3-day bladder diaries, which were completed before randomization and at 2, 8 and 12 weeks after initiating treatment. The primary efficacy endpoint was voiding frequency/24 h. Co-primary endpoints included UUI episodes/24 h (assessed only in patients who were incontinent at baseline) and treatment response (a yes/no variable derived from a four-point Treatment Benefit Scale) [7]. Secondary efficacy endpoints included mean voided volume (MVV) per void, urgency episodes/24 h, continent days/week (data normalized from the 3-day bladder diary; assessed only in patients who were incontinent at baseline), severity of urgency, and severe urgency plus UUI (assessed only in patients who were incontinent at baseline). Patients recorded the time of each urgency episode and void, VV, and the severity of urgency, as 1 (none, normal voiding), 2 (mild; 'could have postponed micturition for as long as necessary without fear of wetting myself'); 3 (moderate; 'could have postponed micturition for a short while without fear of wetting myself'); and 4 (severe; 'could not postpone micturition, had to rush to the toilet in order not to wet myself').

HRQoL was assessed using the King's Health Questionnaire (KHQ) [8], the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) [9], and a six-point Likert scale assessing the severity of bladder-related problems. The KHQ comprises nine domains; scores range from 0 (best outcome) to 100 (worst outcome). A negative change from baseline indicates improved HRQoL. Changes in KHQ domain scores of ≥5 points (minimally important difference) are considered to be meaningful for the patient [10]. The ICIQ-SF assesses urinary frequency, urine leakage, and the effects these symptoms have on daily life; scores range from 0 (low bother) to 21 (maximum bother). The patients' bladder condition was assessed by responding on the following six-point Likert scale: 'My bladder causes me no (0), very minor (1), minor (2), moderate (3), severe (4), or very severe (5) problems.' A decrease of ≥2 points on this scale was considered a major improvement.

A post hoc inferential analysis was performed for the full-analysis set population (i.e. all randomized patients receiving trial medication for whom a baseline and double-blind treatment measure was obtained for primary, co-primary, and secondary endpoints). Parametric assessment was by analysis of covariance with treatment and region as factors and baseline value as a covariate; nonparametric analysis was conducted using the Wilcoxon rank-sum test. Patients completed the KHQ, the ICIQ-SF, and the bladder condition six-point Likert scale at baseline and end of the study. All efficacy and patient-reported outcomes were also assessed in a subgroup of patients who were incontinent at baseline. Additionally, the least-squares (LS) mean changes from baseline to 2, 8 and 12 weeks were determined for voiding frequency and UUI episodes.

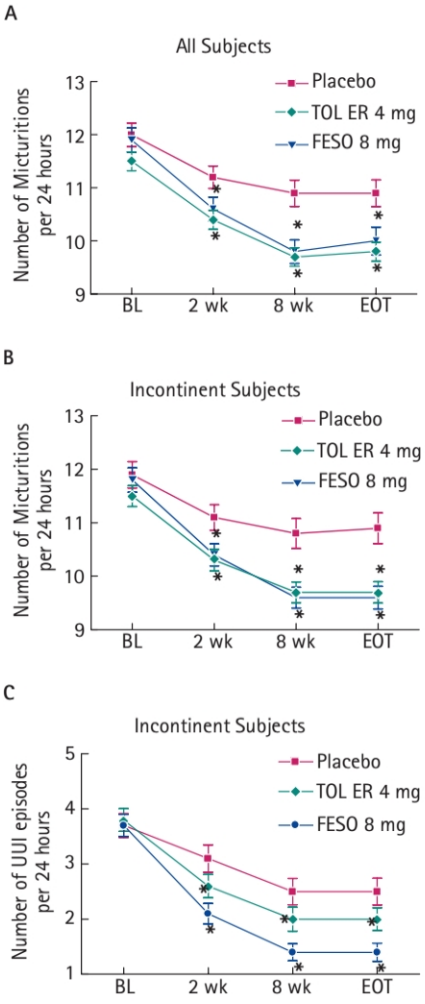
RESULTS

Of 1135 patients enrolled in the parent study, 1132 took study medication (placebo, 283; fesoterodine 4 mg, 272; fesoterodine 8 mg, 287; tolterodine ER 4 mg, 290). Most patients were women (80%) and white (>95%), with a mean (SD) age of 57 (14) years. The mean time since first diagnosis or onset of OAB was 8–9 years, and 80% of patients were incontinent at baseline.

There were treatment-related improvements in the diary variables designated as primary and co-primary endpoints as early as 2 weeks after the start of the study, the first clinical evaluation, that were sustained at 8 weeks and through to the end of the study (Fig. 1). Both the fesoterodine and tolterodine ER groups had significant LS mean changes from baseline for voiding frequency and the number of UUI episodes/24 h vs placebo at all time points.

At the end of the study, treatment with fesoterodine 8 mg resulted in statistically

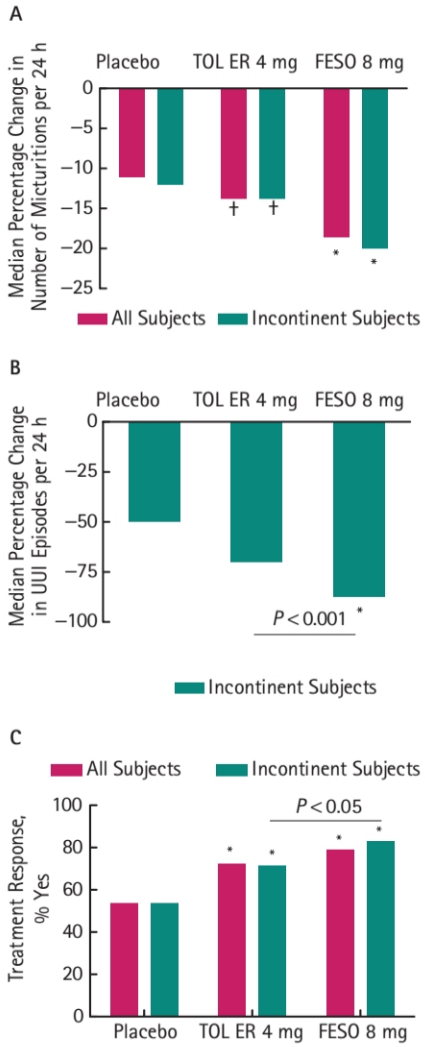
*FIG. 1. LS mean change from baseline in voiding frequency among (A) all patients and (B) patients who were incontinent at baseline; and (C) in UUI episodes among those incontinent at baseline. *P < 0.05 vs placebo.*



significant median percentage improvements of OAB symptoms compared with placebo, including voiding frequency/ 24 h (Fig. 2A), UUI episodes/ 24 h (Fig. 2B), treatment response (Fig. 2C), MVV/void (Fig. 3A), continent days/week (Fig. 3B), urgency episodes/24 h (Fig. 3C), and severe urgency plus UUI (Fig. 3D). Treatment with tolterodine ER also produced significantly greater improvements than with placebo for most efficacy variables, confirming the sensitivity of the study design (Figs 2,3).

By the end of treatment, fesoterodine 8 mg was significantly better than tolterodine ER 4 mg in improving several important endpoints, including UUI episodes/24 h

*FIG. 2. Median percentage change in: the number of (A) voids and (B) UUI episodes (assessed only in those who were incontinent at baseline) per 24 h from baseline to the end of treatment; and (C) treatment response at the end of treatment for placebo, tolterodine ER 4 mg, and fesoterodine 8 mg for all patients and those who were incontinent at baseline. *P < 0.001 vs placebo; †P < 0.05 vs placebo; FESO, fesoterodine; TOL ER, tolterodine ER.*



(Fig. 2B), MVV/void (Fig. 3A), continent days/ week (Fig. 3B), and severe urgency plus UUI (Fig. 3C).

Scores from the KHQ and ICIQ-SF showed a significant improvement in HRQoL for the groups treated with fesoterodine 8 mg and tolterodine ER vs placebo (Table 1). The fesoterodine 8-mg dose produced statistically significant improvements over placebo on

*FIG. 3. LS mean change in: (A) MVV/void, (B) number of continent days/week (assessed only in patients who were incontinent at baseline; data extrapolated from 3-day diary); and the median percentage change in (C) the number of urgency episodes, and (D) severe urgency plus UUI (assessed only in patients who were incontinent at baseline) from baseline to the end of treatment for placebo, tolterodine ER 4 mg, and fesoterodine 8 mg for all patients and those who were incontinent at baseline. *P < 0.001 vs placebo; †P < 0.05 vs placebo.*

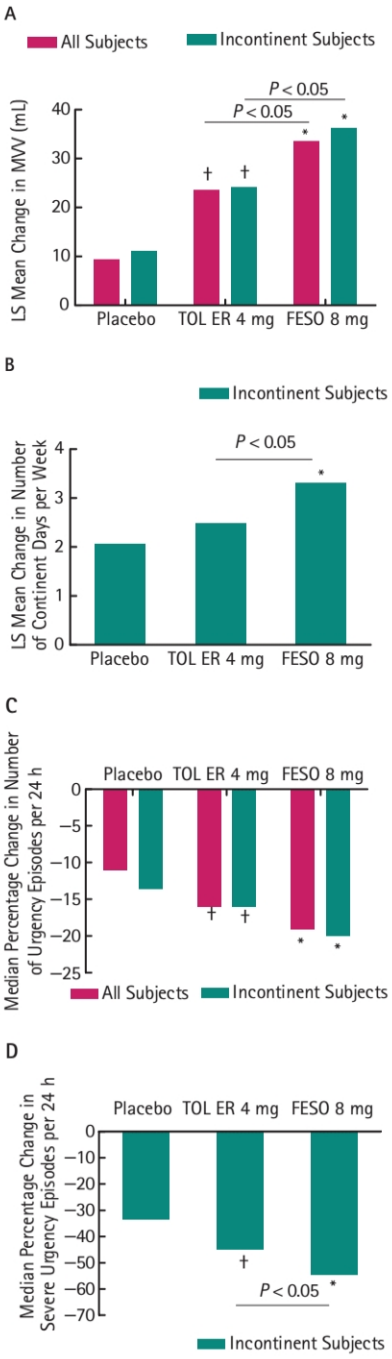


TABLE 1 A summary of HRQoL; the mean changes from baseline for the KHQ and ICIQ-SF for all patients and for incontinent patients only

	Patients					
	All			Incontinent at baseline		
Instrument/domain	Placebo	TOL ER	FESO	Placebo	TOL ER	FESO
No. of patients	279	283	276	203	213	217
KHQ						
Severity (coping)	−9.0	−12.6*	−14.0*	−10.8	−14.9*	−15.8*
Emotions	−10.1	−16.3*	−17.4*	−11.3	−17.3*	−18.6*
Role limitations	−11.8	−22.1*	−21.7*	−12.4	−23.2*	−23.7*
Physical limitations	−11.4	−19.7*	−21.7*	−11.1	−20.5*	−23.3*
Social limitations	−8.7	−14.1*	−15.4*	−9.5	−15.7*	−16.2*
Sleep/energy	−9.6	−11.7	−13.6*	−10.4	−12.5	−15.3*
Personal relationship	−6.2	−10.4	−11.9*	−6.8	−12.7*	−12.3
Incontinence Impact	−16.1	−23.3*	−24.6*	−17.7	−23.8*	−26.5*
General health	−3.8	−4.3	−4.0	−5.5	−4.5	−4.3
ICIQ-SF	−2.55	−3.95*	−4.41*	−3.12	−4.56*	−5.29*

*FESO, fesoterodine; TOL ER, tolterodine ER. *P < 0.05 vs placebo.*

TABLE 2 Treatment-related adverse events occurring in ≥2% of patients and more frequently than with placebo, as n (%)

Adverse event	Placebo	Tolterodine ER 4 mg	Fesoterodine 8 mg
No. of patients	283	290	287
Dry mouth	20 (7.1)	49 (16.9)	97 (33.8)
Constipation	4 (1.4)	8 (2.8)	13 (4.5)
Dry eye	0	1 (<1)	12 (4.2)
Nasopharyngitis	7 (2.5)	10 (3.4)	5 (1.7)
Fatigue	1 (<1)	10 (3.4)	1 (<1)
Dry throat	0	3 (1)	8 (2.8)
Increased alanine aminotransferase	1 (<1)	0	6 (2.1)
Nausea	1 (<1)	6 (2.1)	4 (1.4)

eight of the nine domains assessed, including Sleep/Energy and Personal Relationships. By comparison, tolterodine ER-treated patients reported statistically significant improvements over placebo in six of nine KHQ domains. Both fesoterodine 8 mg and tolterodine ER treatment resulted in a ≥5-point improvement from baseline, which constitutes a meaningful change for the patient [10], for all domains except General Health. A major improvement in the severity of bladder-related problems from baseline to the end of treatment was reported by 39% of fesoterodine 8 mg and 34% of tolterodine ER patients ($P = 0.01$ for both groups vs placebo), compared with 25% on placebo. The results were similar in patients who were incontinent at baseline (Table 1).

Adverse events reported in ≥2% of patients in the active-treatment groups and occurring more frequently than placebo included dry mouth, constipation, dry eye, dry throat, and elevated levels of alanine aminotransferase (Table 2). More patients treated with fesoterodine 8 mg had dry mouth than those receiving tolterodine ER or placebo. Most cases of dry mouth were mild or moderate; 3% of patients on fesoterodine 8 mg reported severe dry mouth. Similarly, more patients on fesoterodine 8 mg reported constipation than those receiving tolterodine ER or placebo; most cases were mild to moderate.

Overall, 3.2% of patients discontinued the study prematurely because of an adverse event: placebo, 2%; tolterodine ER 4 mg, 3%; fesoterodine 8 mg, 5%. Among the reasons for discontinuation was urinary retention, which occurred in 1% of patients in the fesoterodine 8-mg group, and required catheterization in one patient; no patients receiving tolterodine ER or placebo discontinued due to urinary retention, and none required catheterization. Although the incidence of dry mouth in the fesoterodine 8 mg group was higher than that in the tolterodine ER group, only one patient (<1%) in either group withdrew because of dry mouth. One patient (0.3%) in the fesoterodine 8-mg group discontinued because of constipation; no patients in the tolterodine ER or placebo groups discontinued because of constipation.

DISCUSSION

This post hoc analysis of bladder diary variables from a phase III trial [6] shows that the maximum recommended dose of fesoterodine (8 mg) is significantly more effective than the maximum recommended dose of tolterodine ER (4 mg) in improving several important OAB outcomes, including incontinence, MVV/void, number of continent days/week, and severe urgency plus UUI. Urgency, incontinence, and MVV are three of five bladder variables that have been shown to be central to OAB [11]. Numerical differences in favour of fesoterodine 8 mg on the other endpoints (voiding frequency, number of urgency episodes/24 h, and rate of treatment response) were not statistically significant. It is possible that the total number of urgency episodes was not statistically significant because the urgency measurement scale used in this trial did not include UUI, the ultimate expression of urgency.

In the present study, treatment with tolterodine ER provided significantly greater improvements than placebo for most efficacy variables, confirming the sensitivity of the study design. The magnitude of the improvement in OAB symptoms with tolterodine ER was generally consistent with that reported in previous trials [12–14].

Because HRQoL is thought to be worse in patients with UUI than in those who have urgency only, it might be expected that HRQoL improvements with treatment would be greater in patients who were incontinent at baseline. However, a subanalysis of patients incontinent at baseline revealed no apparent differences on HRQoL or bladder diary variables between this group and the overall study population. These findings suggest that all OAB symptoms, not just incontinence, can be bothersome and can diminish the HRQoL of those affected [15–17].

Although the incidence of dry mouth with fesoterodine 8 mg (34%) was higher than that with tolterodine ER 4 mg (17%), the related discontinuation rate was low and similar. Only one patient in each of the fesoterodine 8 mg and tolterodine ER groups discontinued the trial because of dry mouth. This suggests that most cases of dry mouth did not bother patients enough to discontinue (indeed, most cases were categorized as mild or moderate). The incidence of constipation in the fesoterodine 8-mg group (4.5%) was higher than in the tolterodine ER 4 mg group (2.8%).

Limitations of the present study include that this was a post hoc analysis of a study which was not powered for a comparison between active treatments or for HRQoL; prospective studies are currently underway. Another shortcoming of the study is the urgency classification; there is no consensus on whether to measure urgency by episodes or with a graduated scale, and whether UUI should be a part of the urgency continuum or a discrete event. The scale used in this study allowed for four choices, i.e. none, mild, moderate, or severe urgency. Ratings of mild, moderate and severe were equally counted as urgency episodes, which was suboptimal. A separate assessment of category 4 urgency combined with UUI episodes (Fig. 2D) clearly shows that not only was this urgency (characteristic of OAB) significantly reduced by active therapy, but that fesoterodine 8 mg was more effective than tolterodine ER on this endpoint. The use of different methods to document urgency makes it difficult to compare the present results to previously published tolterodine ER studies.

In conclusion, both fesoterodine 8 mg and tolterodine ER are safe and well tolerated, and they provide statistically significant improvements in OAB symptoms and HRQoL. The maximum recommended dose of fesoterodine (8 mg) provides additional benefit compared with the maximum recommended dose of tolterodine ER (4 mg) on several important endpoints, including reduction in UUI episodes and increase in MVV/void, thus offering an alternative treatment option for patients with OAB.

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CONFLICT OF INTEREST

Philip E. Van Kerrebroeck and Christopher R. Chapple are Study Investigators funded by the Sponsor, and Joseph T. Wang and Marina Brodsky are Employees of the Sponsor.

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Correspondence: Christopher Chapple, Honorary Professor of Urology, Sheffield Hallam University, Glossop Road, Sheffield S10 2 JF, UK.
e-mail: c.r.chapple@shef.ac.uk

Abbreviations: **OAB**, overactive bladder; **5-HMT**, 5-hydroxymethyl tolterodine; **CYP**, cytochrome P; **ER**, extended-release; **HRQoL**, health-related quality of life; **(U)UI**, (urgency) urinary incontinence; **LS**, least squares; **MVV**, mean voided volume; **ICIQ-SF**, International Consultation on Incontinence Questionnaire-Short Form; **KHQ**, King's Health Questionnaire.