Drug Design, Development and Therapy

Does fesoterodine have a role in the treatment of poorly managed patients with overactive bladder?

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Abstract: Overactive bladder (OAB), a clinically defined symptom complex comprising urinary urgency, usually accompanied by urinary frequency and nocturia, with or without urgency incontinence, is common and has a markedly negative impact on the sufferer’s quality of life. Following conservative and lifestyle management, the current pharmacological mainstay of treatment is antimuscarinic therapy. This review explores the role of fesoterodine, a relatively recently introduced antimuscarinic agent, in the treatment of patients who may have had a sub-optimal response to initial therapy, who have switched treatment from tolterodine, or may be at risk of receiving poor treatment because of either multimorbidity or complex polypharmacy.

Keywords: elderly, fesoterodine, overactive bladder, urgency incontinence

Introduction

Overactive bladder (OAB) is a symptom complex comprising lower urinary tract symptoms of urinary urgency, with or without urgency urinary incontinence, usually with frequency and nocturia, and no proven infection or other obvious pathology.¹

Symptoms of OAB are experienced by 11% of the worldwide population over the age of 20 years. This number is expected to increase, in line with population aging, by 20% to 546 million by 2018.² The prevalence of OAB increases with advancing age. The EPIC study found an increase in the prevalence of OAB from 8% in men and 9% in women under 30 years to 15% and 16%, respectively, in those aged 65–69 years, and a further increase to 21% and 22%, respectively, in older community-dwelling adults aged 70 years and over.³

Available evidence from longitudinal studies suggests that OAB symptoms appear to progress in terms of both prevalence and severity in men and women. In men interviewed in 1992 and again in 2003, the proportion with OAB increased from 15.6% to 44.4% and the proportion with urgency incontinence increased from 1.9% to 7.4%.⁴ A similar pattern was observed in women over a 16-year period, with a marked overall increase in the prevalence of urge incontinence from 17% to 26%.⁵

OAB has a proven negative impact on health-related quality of life, and affected people score significantly worse than their age-matched counterparts without OAB in the domains of physical and social functioning.⁶,⁷ In addition to having an effect on occupational, physical, psychological, and social well-being, the economic cost attributable to managing the condition is significant. OAB sufferers in the US visit their physicians more often and have more urinary tract infections than those without the condition, and in 2007, the average annual costs of OAB were estimated at $1,925 per person.
($1,433 in direct medical costs, $66 in direct nonmedical costs, and $426 in indirect costs). Applying these costs to the 34 million people with reported OAB in the US, results in total national costs of $65.9 billion, and by 2020 this is predicted to rise to $82.6 billion.\textsuperscript{8,9} However, not everyone with symptoms will, according to the results of a UK study, want to seek health care for their symptoms, and these cost projections may reflect the “worst case scenario”.\textsuperscript{10}

Lifestyle changes and conservative therapies (fluids, caffeine, obesity, bladder retraining, pelvic floor muscle exercises) are the starting point for treatment of OAB. Should these measures prove ineffective, antimuscarinics currently remain the mainstay of pharmacological treatment for OAB.\textsuperscript{11} However, antimuscarinic therapy is not always effective, and adherence in the community is low, with many people stopping their medication because of either adverse events or inefficacy. The agents available also vary in their propensity to be associated with adverse events, and this in turn has an impact upon perceived efficacy.\textsuperscript{12–14}

What constitutes “poorly managed”?

Challenges in the treatment of OAB comprise medication-related factors such as dosing frequency, dose flexibility, mode of administration, adverse events, and inadequate symptom control, which may require switching of medications to best suit the individual. In addition, there are patient-related factors, including unrealistic expectations of treatment, comorbidity, and issues related to taking regular medication. These factors result in poor adherence and intolerance.\textsuperscript{15,16} Likewise, older people affected by OAB constitute, if not a poorly managed group, then a difficult-to-treat sector of patients who often receive less optimal management than their younger counterparts. Finding a well-tolerated treatment in these patients, who often have concomitant comorbidity and take multiple medications, is difficult. Finally, local factors such as regulations concerning reimbursement and formulary inclusion may contribute to what might be perceived as poor management when regulatory opinion differs from that of clinical experts. This review considers the evidence for use of fesoterodine in patients who have responded suboptimally to other antimuscarinics, the evidence in favor of a switch from tolterodine to fesoterodine, and the evidence regarding the clinical efficacy and safety of fesoterodine in older people.

Safety and efficacy of fesoterodine: clinical trial data

Fesoterodine is a nonselective antimuscarinic agent developed to treat the symptoms of OAB. It is a pro-drug, and is rapidly hydrolyzed by nonspecific esterases to 5-hydroxymethyltolterodine, the main active metabolite of tolterodine. This results in a more predictable pharmacokinetic profile then when tolterodine is given.\textsuperscript{17}

There have been a number of Phase III trials comparing the clinical efficacy of fesoterodine and placebo.\textsuperscript{18–21} Two trials have compared fesoterodine with both tolterodine and placebo.\textsuperscript{20,21} In these studies, only Chapple et al\textsuperscript{22} reported on previously treated patients; here, an average of 41% of patients across the trial had previously been exposed to antimuscarinic agents for OAB. There is no report on the proportion of patients who had discontinued their medication because of either inefficacy or dissatisfaction with treatment. The effect on disease-related variables in these trials is shown in Table 1.

In each study, increasing the dose of fesoterodine from 4 mg to 8 mg was associated with a statistically significant increase in mean voided volume and an increase in number of continent days per week versus placebo. This response has not been consistently shown for other antimuscarinics at variable doses, including tolterodine, solifenacin, and darifenacin.\textsuperscript{22–24}

| Table 1 | Changes in disease-related variables in studies where fesoterodine was compared with tolterodine |
|-------------------------------------------------|-------------------------------------------------|-----------------|-----------------|-----------------|
| Micturitions/24 hours (LS mean change [SE])\textsuperscript{20} | Placebo | Tolterodine 4 mg | Fesoterodine 4 mg | Fesoterodine 8 mg |
| | -0.95 (0.16) | -1.73 (0.16) | -1.76 (0.17) | -1.88 (0.16) |
| Urgency urinary incontinence episodes/24 hours (LS mean change [SE])\textsuperscript{20} | -1.14 (0.15) | -1.74 (0.16) | -1.95 (0.17) | -2.22 (0.16) |
| Urgency episodes/24 hours (LS mean change [SE])\textsuperscript{20} | -1.07 (0.19) | -2.02 (0.19) | -1.88 (0.20) | -2.36 (0.20) |
| Daytime micturitions/24 hours (LS mean change [SE])\textsuperscript{20} | -0.60 (0.14) | -1.35 (0.14) | -1.37 (0.15) | -1.48 (0.14) |
| Nocturnal micturitions/24 hours (LS mean change [SE])\textsuperscript{20} | -0.32 (0.06) | -0.40 (0.06) | -0.39 (0.06) | -0.39 (0.06) |
| Micturitions/24 hours (LS mean change [SE])\textsuperscript{21} | -0.9 (0.1) | -1.50 (0.1) | -1.1 (0.1) | -1.3 (0.1) |
| Urgency urinary incontinence episodes/24 hours (LS mean change [SE])\textsuperscript{21} | -0.6 (0.1) | -1.2 (0.2) | -1.5 (0.1) | -1.7 (0.1) |
| Urgency episodes/24 hours (LS mean change [SE])\textsuperscript{21} | -0.8 (0.2) | -1.6 (0.2) | -1.3 (0.1) | -1.6 (0.1) |

Abbreviations: SE, standard error; LS, least squares.
Fesoterodine dosing, and its rapid conversion by gut esterases to 5-hydroxymethyltolterodine, appears to be associated with a more predictable dose-response relationship. In clinical practice, this should facilitate determination of the most effective dose for the patient, whilst attempting to curtail side effects.

The dearth of direct comparisons between the newer antimuscarinics continues to hamper our ability to make informed decisions about the suitability of individual drugs. Fesoterodine 8 mg was compared with tolterodine 4 mg in studies attempting to show the added benefit of a higher dose of medication, and in some, after a suboptimal response to tolterodine 4 mg.\textsuperscript{25,26} Compared with tolterodine 4 mg extended-release, 8 mg fesoterodine showed significantly greater efficacy in reducing episodes of urgency urinary incontinence (primary endpoint), and in increasing bladder capacity, as measured by mean volume voided. In addition, the diary dry rate at week 12 was also significantly greater in patients receiving fesoterodine 8 mg than in those receiving tolterodine 4 mg extended-release. In self-reported patient assessments of bladder-related problems, ie, urgency, symptom bother, and health-related quality of life, the statistically significant superiority of fesoterodine 8 mg over tolterodine 4 mg extended-release was observed as early as 3 weeks after escalation from fesoterodine 4 mg. This may encourage adherence with treatment, because those with perceived benefit from treatment are more likely to adhere to therapy, particularly older patients.\textsuperscript{12}

The effects of flexible-dose fesoterodine in subjects with OAB who were dissatisfied with previous tolterodine treatment may give some limited insight into its use in poorly managed patients. A 12-week, open-label, flexible-dose study was conducted in 516 adults with OAB (eight or more micturitions and three or more urgency episodes per 24 hours) who had been treated with tolterodine (immediate-release or extended-release) within 2 years of screening and reported being somewhat “dissatisfied” or “very dissatisfied” with tolterodine on the treatment satisfaction question, a single item from the validated Overactive Bladder Satisfaction Questionnaire (OAB-q).\textsuperscript{27} Eleven of the subjects included in this study did not report being dissatisfied with prior tolterodine treatment at the beginning of the study, but inclusion of their data did not alter the conclusions drawn from the study. In addition to prior tolterodine treatment, 216 subjects (42%) had received at least one other antimuscarinic agent prior to enrollment in the study. In addition, 67% of male patients had a history of benign prostatic hyperplasia. Fifty percent of patients opted to increase their dose of fesoterodine from 4 mg to 8 mg at week 4. Treatment with fesoterodine was associated with statistically significant within-group differences from baseline to week 12 with regard to micturitions (12.7–9.7), urgency urinary incontinence episodes, (2.3–0.6), urgency episodes per 24 hours (10.0–5.0), and severe urgency episodes per 24 hours (5.0–1.5). There were also statistically significant improvements in treatment satisfaction, with 1.0% of patients reporting that they were very satisfied or somewhat satisfied with their previous treatment and 80.2% reporting this level of satisfaction with fesoterodine.

In terms of patient perception of bladder condition score following 12 weeks of treatment with fesoterodine, 63.4% reported that they had minor problems or fewer problems compared with pretreatment, and no subjects reported “fewer than moderate problems”. The proportion of subjects who reported that they were usually not able to hold their urine was reduced from 25% at baseline to 6% after 12 weeks, and the proportion who reported being able to finish what they were doing before going to the toilet was increased from 6.8% at baseline to 41% after 12 weeks. The lack of blinding and absence of a placebo arm limit the conclusions that can be drawn from this study: however, unlike objective variables, the study may more closely reflect real clinical practice where outcomes are judged on patient perception and symptom bother.\textsuperscript{28}

A further perspective on difficult-to-treat patients may be gleaned from the AFTER\textsuperscript{29} (Fesoterodine after Tolterodine ER) study, a Pfizer-sponsored trial designed to determine the efficacy and safety of fesoterodine 8 mg versus placebo in patients with OAB and urgency urinary incontinence who have responded suboptimally to tolterodine 4 mg extended-release. This was a 12-week, randomized, double-blind, placebo-controlled, multicenter study for which patients with a suboptimal response to tolterodine were identified by a 2-week, open-label treatment period consisting of daily treatment with tolterodine 4 mg extended-release. At the end of this 2-week period, those with a ≤50% reduction in mean urgency urinary incontinence episodes per 24 hours were randomized 1:1 to fesoterodine (4 mg for 1 week, 8 mg for weeks 2–12) or placebo once daily. The primary efficacy endpoint was the mean change from baseline to week 12 in urgency urinary incontinence episodes per 24 hours. Missing data were imputed using the last observation carried forward technique, and there was a preplanned stepwise analysis whereby a one-sided paired t-test was used to assess the within-group mean reduction from baseline to week 12 in urgency urinary incontinence episodes for fesoterodine 8 mg, and if this was significant, a one-sided test of the between-group
(placebo versus fesoterodine) change in mean number of urgency urinary incontinence episodes per 24 hours was then conducted using an analysis of covariance model. There were statistically significant changes (P<0.0001 for each) from baseline for both placebo (−1.9) and fesoterodine (−2.4), allowing an analysis of between-group change. Those treated with fesoterodine achieved a significantly greater reduction in urgency urinary incontinence episodes per 24 hours than the placebo-treated group (P=0.0079). Fesoterodine was also associated with a statistically significant improvement over placebo in urgency episodes per 24 hours (placebo −2.8 versus fesoterodine −3.5, P=0.0438). There was no statistically significant reduction in micturitions per 24 hours (placebo −1.6 versus fesoterodine −2.0, P=0.0931).

In terms of symptom relief, 69% of fesoterodine-treated patients versus 57% of placebo-treated patients (P=0.0027) achieved a 50% reduction in urgency urinary incontinence; 44.1% of placebo-treated patients and 58.9% of fesoterodine-treated patients achieved a 70% reduction in this symptom (P=0.001). Complete resolution of incontinence was achieved in 32.3% of placebo-treated patients versus 39.0% of fesoterodine-treated patients; this difference was not statistically significant. However, significant improvement was seen on the Patient Perception of Bladder Condition questionnaire (P<0.0001) and Urgency Perception Scale (P=0.0095) for fesoterodine over placebo, for all domains of the OAB-q30 (P<0.05), and for symptom bother (placebo −18.1 versus fesoterodine −25.5, P<0.001).

As might be expected, the most commonly reported adverse events were dry mouth (placebo 4.0% versus fesoterodine 16.6%) and constipation (placebo 1.3% versus fesoterodine 3.9%). One of the main criticisms of this study concerns the limited exposure to tolterodine before ascribing a suboptimal response. Although improvements are noted early on with antimuscarinic treatment, in most studies the plateau effect is not achieved for approximately 12 weeks. To what extent the transfer to fesoterodine was truly indicated in this group is unknown.

In a similar vein, but with a markedly different trial design, a post hoc analysis of a retrospective, cross-sectional, observational study (IMPACTA [Assessment of reasons for overactive bladder treatment change])31 reported on factors contributing to treatment change in OAB patients and the degree of satisfaction resulting from that change. This study used the validated Treatment Benefit Scale32 and the Clinical Global Impression of Improvement. Of the 2,038 patients evaluated, 1,407 had been treated previously with antimuscarinic therapy. In this study, 842 patients had previously received tolterodine, 748 of whom had data available for analysis. Older patients were defined as those aged 65 years or older, and comprised 44.1% of the patient population. In the entire group, 69% of those younger than 65 years and 70% of those over 65 years received fesoterodine 8 mg. The majority of those switching from tolterodine to fesoterodine did so because of lack of effectiveness (66.8%), although the details of this are not specified, and the duration of tolterodine treatment prior to the switch is not reported. Adherence was generally low over the 60–68 days of treatment; 33.5% with fesoterodine 8 mg versus 24.9% with fesoterodine 4 mg. The majority of switches were made at the instigation of the study investigators. Overall, 94.4% of patients improved, according to the judgment of the physician, which was in close agreement with the 94.2% of patients who showed improvement on the Treatment Benefit Scale. A significantly higher proportion of patients were either assessed as having improved (Clinical Global Impression of Improvement) or reported improvement on the Treatment Benefit Scale following treatment with fesoterodine 8 mg compared with the 4 mg dose, as might be expected. However, the adverse event rate was not reported for either dose of fesoterodine, with only adverse events precipitating a switch to fesoterodine being reported. The low adherence rate may give some guide to this, but would be confounded by other factors affecting adherence. There was no age differential in terms of the proportion of those who either reported improvement or were assessed as having improved.

The effect of a switch from tolterodine to fesoterodine on patient-reported outcomes has recently been reported in a pooled analysis of two 12-week, double-blind, placebo-controlled, clinical trials.33 At week 12, the analysis showed statistically significant improvements associated with fesoterodine 8 mg over tolterodine 4 mg and placebo for changes in the Patient Perception of Bladder Condition, Urgency Perception Scale, all domains of the OAB-q, and all bladder diary variables, except for nocturnal micturition frequency in women. In men, statistically significant improvements over tolterodine were limited to severe urgency episodes and to the symptom bother domain of the OAB-q. The proportion of men and women who had previously been treated with antimuscarinic agents for OAB was not reported in this study.

The efficacy and safety of flexible-dose fesoterodine in older adults with OAB has been reported in both the randomized, placebo-controlled and open-label follow-up portions of SOFIA (the Study of Fesoterodine in an Aging population).34,35 In this study, 67% of the fesoterodine-treated group (n=392) had received antimuscarinic treatment for OAB prior to entry into the trial; there was no report of reasons for
discontinuation, and it is likely that a proportion of patients would have stopped their previous treatment for the sole purpose of trial entry. However, both portions of the trial reported benefit in fesoterodine-treated patients, that reached statistical significance for the primary outcome, ie, urinary urgency episodes per 24 hours, in the placebo-controlled portion of the trial and the majority of secondary outcomes. There was no statistically significant difference between placebo and fesoterodine with regard to improved resolution of urgency urinary incontinence episodes, which was probably due to a low level of urgency urinary incontinence at trial entry.

In SOFIA, 47% of the patients were men, allowing a glimpse into the effect of fesoterodine in OAB with benign prostatic enlargement, from which 41% of the men suffered and for which 28% had pre-existing treatment. There were low discontinuation rates due to urinary retention; in the double-blind phase, six patients reported urinary retention (three men and two women receiving fesoterodine, and one man receiving placebo). Four of the six participants reporting urinary retention required catheterization (three men receiving fesoterodine and one man receiving placebo). Five of the six participants reporting urinary retention discontinued, including all four participants requiring catheterization. In the extension portion of the study, three men in the double-blind placebo/open-label fesoterodine group discontinued due to urinary retention. Adverse effects of dry mouth and constipation in SOFIA were comparable with those reported for other antimuscarinics, although there was a higher discontinuation rate in the fesoterodine-treated and placebo-treated arms of the trial in the over 75-year age group compared with younger groups in other trials with fesoterodine.

Taking things a little further, into the realms of the physically frailer elderly, the recently reported Vulnerable Elders Study utilized the Vulnerable Elders Scale-13 to select older people scoring ≥3 on this scale who had a high level of comorbidity, defining an increased risk of decline and death as well as OAB, who were then randomized to a 12-week, controlled trial of fesoterodine versus placebo. Patients had an option to increase their dose from 4 mg to 8 mg at 4 weeks with no opportunity to decrease the dose after that point. The mean number of comorbid conditions was approximately 8.5 (range 1–27), and 27% of patients had more than eleven concomitant medications at baseline. Here, the primary outcome was urgency incontinence episodes and included patients who had to have a mean of more than two but fewer than 15 urgency urinary incontinence episodes on a 3-day bladder diary at baseline to be eligible for the study. Reduction in urgency urinary incontinence episodes per 24 hours from baseline to week 12 was significantly greater with fesoterodine (−2.84) than with placebo (−2.2, P=0.002). Likewise, there were statistically significant improvements in diary dry rate, nocturnal urgency, micturitions per 24 hours, and pad use associated with fesoterodine. Patient-reported outcomes also improved, with statistically significant improvements over placebo-reported outcomes with regard to patient perception of bladder control score and the OAB-q symptom bother, health-related quality of life, and coping and concern scores at week 12. Twenty-six (9.3%) patients in the fesoterodine group and 14 (5.0%) in the placebo group discontinued treatment because of adverse events. There were no deaths in the study. The most commonly occurring side effects associated with fesoterodine were dry mouth and constipation. The total discontinuation rate was 19.6% in the fesoterodine group and 21.7% in the placebo group. There was no significant change in blood pressure or resting heart rate associated with fesoterodine.

The use of drugs with anticholinergic properties in elderly patients has been associated with a decline in cognition and, in some, an increased risk of incident dementia. Of the antimuscarinics used for OAB in trials, only oxybutynin has been shown to be associated with a negative impact on cognition. Concerns regarding this potential adverse impact have led pharmaceutical manufacturers to undertake studies specifically to examine cognitive function in older people exposed to such agents. In the case of fesoterodine, its effect on cognition has been examined in a randomized crossover study that ensured its subjects were exposed to chronic dosing of the drug at both 4 mg and 8 mg and used alprazolam as an active control. The trial reported on 18 cognitively intact older adults (mean age 72 years) and found no detectable impairment of cognition when assessing executive function, verbal and visual learning, or memory and reaction time with either fesoterodine 4 mg or 8 mg as compared with placebo. In contrast, alprazolam caused a significant reduction in performance on each test. Although a short-term study, and conducted in cognitively intact elderly, some reassurance regarding lack of a significant cognitive effect can be taken from the low level of cognitive side effects reported in SOFIA (three fesoterodine-treated patients, two of whom were thought to be unrelated to treatment) and in the Vulnerable Elders Study (two fesoterodine-treated patients), with no overall change in Mini-Mental State Examination scores over the duration of the study.
Conclusion

Whilst there is limited direct evidence of the efficacy of fesoterodine in patients with a well-defined suboptimal response to other antimuscarinic agents, fesoterodine appears to fulfill a role in the treatment of those who may not reach optimal efficacy with tolterodine. There are no stratified analyses comparing the efficacy of fesoterodine in patients who have previously received antimuscarinic treatment, and thus we are unable to draw any specific conclusions in this group of patients. In terms of groups that may be at risk of poorly managed OAB, such as the elderly and medically complex patients, fesoterodine has an impressive portfolio of prospectively planned trials supporting its efficacy and safety. Additionally, treatment with fesoterodine in these circumstances is associated with improved quality of life for people affected by OAB.

Disclosure

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References

1. Abrams PH, Fall M, Cardozo L, et al. The standardization of terminology of lower urinary tract function: report from the standardization subcommittee of the International Continence Society. Neurourol Urodyn. 2002;21(2):167–178.
2. Irwin DE, Kopp ZS, Agateb T, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int. 2011;108(7):1132–1138.
3. Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol. 2006;50(6):1306–1314.
4. Malmsten UG, Molander U, Peeker R, Irwin DE, Milsom I. Urinary incontinence, overactive bladder, and other lower urinary tract symptoms in Sweden: a longitudinal population-based survey in men aged 45–103 years. Eur Urol. 2010;58(1):149–156.
5. Wennberg AL, Molander U, Peeker R, Irwin DE, Milsom I. Urinary incontinence, overactive bladder, and other lower urinary tract symptoms in women. Eur Urol. 2009;55(4):783–791.
6. Milsom I, Kaplan SA, Coyne KS, Sexton CC, Kopp ZS. Effect of bothersome overactive bladder symptoms on health-related quality of life, anxiety, depression, and treatment seeking in the United States: results from EpiLUTS. Urology. 2012;80(1):90–96.
7. Coyne KS, Kvasz M, Ireland AM, Milsom I, Kopp ZS, Chapple CR. Urinary incontinence and its relationship to mental health and health-related quality of life in men and women in Sweden, the United Kingdom, and the United States. Eur Urol. 2012;61(1):88–95.
8. Wagner TH, Hu TW, Bentkover J, et al. Health-related consequences of overactive bladder. Am J Manag Care. 2002;8(Suppl 19):S598–S607.
9. Ganz ML, Smalrza AM, Krukski TL, et al. Economic costs of overactive bladder in the United States. Urology. 2010;75(3):526–532.
10. McGrother CW, Donaldson MM, Shaw C, et al. Storage symptoms of the bladder: prevalence, incidence and need for services in the UK. BJU Int. 2004;93(6):763–769.
11. Andersson KE, Chapple CR, Cardozo L, et al. Pharmacological treatment of overactive bladder: report from the International Consultation on Incontinence. Curr Opin Urol. 2009;19(4):380–394.
12. Wagg A, Compion G, Fahey A, Siddiqui E. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. BJU Int. 2012;110(11):1767–1774.
13. Haab F, Castro-Diaz D. Persistence with antimuscarinic therapy in patients with overactive bladder. Int J Clin Pract. 2005;59(8):931–937.
14. Buser N, Ivie S, Kessler TM, Kessels AG, Bachmann LM. Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses. Eur Urol. 2012;62(6):1040–1060.
15. Basra RK, Wagg A, Chapple C, et al. A review of adherence to drug therapy in patients with overactive bladder. BJU Int. 2008;102(7):774–779.
16. Noe L, Neuringer R, Patel B, Williamson T. The implications of poor medication persistence with treatment for overactive bladder. Manag Care Interface. 2004;17(11):54–60.
17. Malhotra B, Guan Z, Wood N, Gandelman K. Pharmacokinetic profile of fesoterodine. Int J Clin Pharmacol Ther. 2008;46(11):556–563.
18. Khullar V, Rovner ES, Dmochowski R, Nitti V, Wang J, Guan Z. Fesoterodine dose response in subjects with overactive bladder syndrome. Urology. 2008;71(5):839–843.
19. Nitti VW, Dmochowski R, Sand PK, et al. Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. J Urol. 2007;178(6):2488–2494.
20. Chapple C, Van Kerrebroeck P, Tubaro A, et al. Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. Eur Urol. 2007;52(4):1204–1212.
21. Sand PK, Morrow JD, Bavendam T, Creanga DL, Nitti VW. Efficacy and tolerability of fesoterodine in women with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct. 2009;20(7):827–835.
22. Van Kerrebroeck PF, Amarenco G, Thurrow JF, et al. Dose-ranging study of tolterodine in patients with detrusor hyperreflexia. Neurourol Urodyn. 1998;17(5):499–512.
23. Cardozo L, Amarenco G, Pushkar D, et al. Severity of overactive bladder symptoms and response to dose escalation in a randomized, double-blind trial of solifenacin (SUNRISE). BJU Int. 2013;111(5):804–810.
24. Hill S, Khullar V, Wyndaele JJ, Lheritier K. Dose response with darifenacin, a novel once-daily M3 selective receptor antagonist for the treatment of overactive bladder: results of a fixed dose study. Int Urogynecol J Pelvic Floor Dysfunct. 2006;17(3):239–247.
25. Herschorn S, Swift S, Guan Z, et al. Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. BJU Int. 2010;105(1):58–66.
26. Kaplan SA, Schneider T, Foote JE, Guan Z, Carlsson M, Gong J. Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: a prospective, head-to-head, placebo-controlled trial. BJU Int. 2011;107(9):1432–1440.
27. Pauilt E, Evans CJ, Espindle D, Kopp Z, Brubaker L, Abrams P. Development and validation of the Overactive Bladder Satisfaction (OAB-S) Questionnaire. Neurourol Urodyn. 2008;27(3):179–190.
28. Wyndaele JJ, Goldfischer ER, Morrow JD, et al. Effects of flexible-dose fesoterodine on overactive bladder symptoms and treatment satisfaction: an open-label study. Int J Clin Pract. 2009;63(4):560–567.
29. Cardozo L, Kaplan S, Herschorn S, et al. A Randomised Controlled Trial of Fesoterodine in Subjects with Overactive Bladder and Suboptimal Response to Tolterodine Extended Release: Results from the AFTER Study. European Association of Urology (EAU) Annual Meeting; March 15–19, 2013; Milan, Italy. Abstract 740.
30. 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(6):563-574.

31. Castro D, Miranda P, Sánchez-Ballester F, Arumi D, Lizarraga I, Ebel C; grupo de estudio Impacta. [Assessment of reasons for overactive bladder treatment change]. Actas Urol Esp. 2011;35(2):73-79. Spanish.

32. Colman S, Chapple C, Nitti V, Haag-Molkenteller C, Hastedt C, Massow U. Validation of treatment benefit scale for assessing subjective outcomes in treatment of overactive bladder. *Urology.* 2008;72(4):803–807.

33. Ginsberg D, Schneider T, Kelleher C, et al. Efficacy of fesoterodine compared with extended release tolterodine in men and women with overactive bladder. *BJU Int.* 2013;112(3):373–385.

34. Wagg A, Khullar V, Marschall-Kehrel D, et al. Flexible-dose fesoterodine in elderly adults with overactive bladder: results of the randomized, double-blind, placebo-controlled study of fesoterodine in an aging population trial. *J Am Geriatr Soc.* 2013;61(2):185–193.

35. Wagg A, Khullar V, Michel MC, Oelke M, Darekar A, Bitoun CE. Long-term safety, tolerability and efficacy of flexible-dose fesoterodine in elderly patients with overactive bladder: open-label extension of the SOFIA trial. *Neurourol Urodyn.* March 4, 2013. [Epub ahead of print.]

36. Dubeau CE, Kraus SR, Griebling TL, et al. Effect of fesoterodine in vulnerable elderly subjects with urgency incontinence: a double-blind, placebo-controlled trial. *J Urol.* August 31, 2013. [Epub ahead of print.]

37. Wagg A. The cognitive burden of anticholinergics in the elderly – implications for the treatment of overactive bladder. *Eur Urol Rev.* 2012;7(1):42–49.

38. Katz IR, Sands LP, Bilker W, DiFilippo S, Boyce A, D’Angelo K. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. *J Am Geriatr Soc.* 1998;46(1):8–13.

39. Kay GG, Maruff P, Scholfield D, et al. Evaluation of cognitive function in healthy older adults treated with fesoterodine. *Neurourol Urodyn.* 2011;30(6):961–963.

40. Folstein MF, Robins LN, Helzer JE. The Mini-Mental State Examination. Arch Gen Psychiatry. 1983;40(7):812.