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

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OBJECTIVES: To assess the efficacy and safety of flexible-dose fesoterodine in elderly adults with overactive bladder (OAB).

DESIGN: Twelve-week, randomized, double-blind, placebo-controlled trial.

SETTING: Sixty-one outpatient clinics in Europe, Israel, and Turkey.

PARTICIPANTS: Seven hundred ninety-four individuals aged 65 and older (47% male) with OAB symptoms for 3 months or longer, mean of eight or more micturitions and three or more urgency episodes per 24 hours, at least some moderate problems on Patient Perception of Bladder Condition (PPBC), and Mini-Mental State Examination (MMSE) score of 20 or greater.

INTERVENTIONS: Participants were randomized to fesoterodine or placebo for 12 weeks, with stratification according to age (>75 vs $\leq$75) and dosing time (morning vs evening). Participants receiving fesoterodine started on 4 mg and could increase to 8 mg at week 4 or 8 and de-escalate to 4 mg at week 8 (sham escalation for placebo).

MEASUREMENTS: Changes from baseline in bladder-diary variables (primary endpoint, urgency episodes) and patient-reported outcomes including OAB Questionnaire, Treatment Benefit Scale (TBS), PPBC, Urgency Perception Scale (UPS), and OAB Satisfaction Questionnaire (OAB-S); all observed or reported adverse events.

RESULTS: By week 8, 64% of fesoterodine-treated and 71% of placebo-treated participants opted for dose escalation. At week 12, the fesoterodine group had statistically significantly greater improvement than the placebo group in urgency episodes, micturitions, nocturnal micturitions, incontinence pad use, and OAB Questionnaire scores but not urgency urinary incontinence episodes. Responder rates on TBS, PPBC, UPS, and OAB-S were statistically significantly higher with fesoterodine. Improvements in most diary variables and participant-reported outcomes were greater with fesoterodine than placebo in participants in both age groups and when administered in the morning and evening. Rates of dry mouth and constipation were 34% and 9% with fesoterodine and 5% and 3% with placebo, respectively. Rates of adverse events and discontinuations were generally similar in participants in both age groups. There was no change in MMSE score.

CONCLUSION: Fesoterodine was associated with significantly greater improvements in most diary variables and participant-reported outcomes than placebo and was generally well tolerated in older people. **J Am Geriatr Soc 61:185–193, 2013.**

Key words: antimuscarinic; overactive bladder; elderly; fesoterodine; flexible dosing

Overactive bladder (OAB), a symptom complex of urinary urgency often associated with urinary frequency and urgency incontinence and nocturia, affects men and women equally and negatively affects health-related quality of life (HRQL), mental health, and sleep quality.[1–3] The prevalence of OAB increases with advancing age. For example, the prevalence of OAB in the EPIC increased from 8% to 9% in men and women younger than 30 to 15% to 16% in those aged 65 to 69 and 21% to 22% in

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those aged 70 and older.[4,5] The number of individuals with OAB symptoms, including urgency urinary incontinence (UUI), is expected to increase further over time, especially as the proportion of those aged 75 and older in the population increases.[6]

Effective management of OAB in elderly adults is important because of its effects on daily life and potentially serious adverse health consequences, including falls and fractures, institutionalization, and mortality.[7–10] Despite the availability of effective treatments, many individuals do not discuss their OAB symptoms with a physician and remain untreated.[11,12] Although antimuscarinic drugs are first-line pharmacological treatment for OAB,[13] they may be underused in older individuals.[10] A large portion of the data on elderly adults has come from post hoc analyses of OAB clinical trial participants aged 65 and older. Few placebo-controlled studies have prospectively evaluated or reported age-stratified data on the efficacy and safety of antimuscarinics in this population.[14–17]

Significantly greater improvements in OAB symptoms and patient-reported outcomes in the general population with OAB have been demonstrated with fesoterodine 4 and 8 mg than with placebo in fixed- and flexible-dosing clinical trials.[18–21] In a post hoc analysis of data from a fixed-dose trial of individuals with OAB stratified according to age, fesoterodine 4 and 8 mg improved OAB symptoms and HRQL significantly more than placebo in participants younger than 65 and in a group aged 65 to 74; only fesoterodine 8 mg was effective in participants aged 75 and older,[22] although this analysis included a limited number of individuals aged 75 and older.[22] The Study of Fesoterodine in an Aging population (SOFIA) trial was conducted to compare, in the largest planned prospective trial in this population to date, the efficacy and safety of flexible-dose (4 or 8 mg) fesoterodine with placebo in elderly adults with OAB, including a large subgroup older than 75.

METHODS

Study Design

The SOFIA trial consisted of a 12-week double-blind, placebo-controlled phase and a 12-week open-label phase. SOFIA was conducted from June 2008 to September 2010 (Clinicaltrials.gov ID: NCT00798434) at 61 sites in Austria, Belgium, Denmark, Finland, Germany, Israel, Italy, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom in accordance with Good Clinical Practice Guidelines, the Declaration of Helsinki, and local regulatory requirements. The appropriate ethics committees approved the protocol, and all participants provided written informed consent. This article describes the results of the double-blind, placebo-controlled phase of the trial.

Random assignment to once-daily treatment with fesoterodine or placebo occurred through a centralized system with a 1:1 ratio of fesoterodine to placebo and of morning to evening dosing. Randomization was stratified according to age (≤ 75, >75) with a 1:1 ratio of fesoterodine to placebo within each stratum, with a goal of at least 30% of participants being older than 75. Participants randomized to fesoterodine started with a 4-mg dose and were allowed to increase to 8 mg at weeks 4 and 8; participants who increased from 4 to 8 mg at week 4 could return to the 4-mg dose at week 8. A sham dose escalation and de-escalation procedure was followed for participants randomized to placebo. Pfizer Inc. generated and secured the randomization schedule. The study drug and placebo were identical in appearance; neither the investigators nor the participants were aware of the treatment identity.

Study Population

Men and women aged 65 and older with OAB symptoms for 3 months or longer, a mean of eight or more micturitions and three or more urgency episodes per 24 hours on a 3-day bladder diary at baseline who self-reported at least some moderate problems on the Patient Perception of Bladder Condition (PPBC) questionnaire[23] and had a Mini-Mental State Examination (MMSE)[24] score of 20 or greater, and able to complete micturition diaries and study-related questionnaires and adhere to study procedures were eligible for enrollment. Participants were excluded if they had hypersensitivity to the active substance (fesoterodine fumarate) or to peanut, soya, or any of the excipients; predominant stress incontinence as determined according to the investigator; significant bladder outlet obstruction, previous history of acute urinary retention requiring catheterization, severe voiding difficulties, or active urinary tract infection; clinically significant renal disease; multiple sclerosis or spinal cord injury; treatment with other antimuscarinics within 2 to 3 weeks before baseline; treatment with potent CYP3A4 inhibitors; or intermittent or unstable use of diuretics or alpha-blockers or initiation of treatment within 2 weeks of baseline. Stable, continued use of all other medications, including diuretics, alpha-blockers, and 5α-reductase inhibitors, was permitted.

Assessments and Statistical Analyses

Participants completed 3-day bladder diaries, the OAB Questionnaire (OAB-Q),[25] the PPBC,[23] and the Urgency Perception Scale (UPS)[26] at baseline and weeks 4, 8, and 12. Four items from the OAB Satisfaction Questionnaire (OAB-S; three items from the OAB-S Satisfaction with Control subscale and 1 item from the Expectation subscale) Medication module[27] and the Treatment Benefit Scale (TBS)[28] were completed at week 12. The MMSE[24] was completed at baseline and week 12. Change from baseline to week 12 in the number of urgency episodes per 24 hours was the primary endpoint. Other diary endpoints included change from baseline in number of micturitions, UUI episodes, severe urgency episodes, nocturnal micturitions, and incontinence pads used per 24 hours. Diary-dry rate (proportion of participants reporting any UUI episodes at baseline who reported no UUI episodes before the week 8 and 12 visits) also was determined.

The OAB-Q contains an 8-item Symptom Bother Scale and a 25-item HRQL Scale with four domains (concern, coping, sleep, and social interaction).[25] Scores on each scale and domain are normalized to a scale of 0 to 100.[25] Higher scores on the Symptom Bother Scale reflect greater

bother, and higher scores on the HRQL Scale and domains reflect better HRQL.[25] The minimally important difference (smallest clinically meaningful change from baseline) is 10 points for each OAB-Q scale and domain.[29] The PPBC is a validated single-item questionnaire that participants use to rate the severity of their bladder-related problems on a scale from 1 to 6 (1 = no problems at all, 2 = some very minor problems, 3 = some minor problems, 4 = some moderate problems, 5 = severe problems, 6 = many severe problems).[23] The validated UPS is a single-item instrument with a 3-point scale to assess participant perception of urgency (1 = I am usually not able to hold urine; 2 = I am usually able to hold urine (without leaking) until I reach a toilet if I go to the toilet immediately; 3 = I am usually able to finish what I am doing before going to the toilet (without leaking)).[26] The OAB-S is a validated self-administered instrument that evaluates OAB medication expectations, daily life with OAB, and satisfaction with OAB medication; participants answered items regarding the degree to which their OAB medication met their expectations (1 = greatly exceeds my expectations; 2 = somewhat exceeds my expectations; 3 = exceeds my expectations; 4 = does not quite meet my expectations; 5 = does not meet my expectations at all) and their level of satisfaction with OAB control (1 = very satisfied; 2 = somewhat satisfied; 3 = neither dissatisfied nor satisfied; 4 = somewhat dissatisfied; 5 = very dissatisfied).[27] The TBS is a validated single-item questionnaire that asks participants to rate their level of improvement since beginning treatment on a 4-point scale (1 = greatly improved; 2 = improved; 3 = not changed; 4 = worsened).[28]

The mean treatment difference and standard deviation (SD) used for sample size determination was obtained from an analysis of covariance (ANCOVA) model fitted to mean change from baseline in number of urgency episodes per 24 hours at week 12 from a previous fesoterodine study.[18] Based on a two-sided *t*-test at the 5% significance level, 247 participants were needed in each arm to provide 80% power to detect a difference of 0.82 urgency episodes between fesoterodine and placebo assuming a SD of 3.24. Allowing for 10% attrition in the full analysis set (FAS) (participants randomized and took ≥ 1 doses of study medication and had baseline and postbaseline efficacy data for ≥ 1 endpoints), 550 participants would be required (fesoterodine, n = 275; placebo, n = 275). Based on a prespecified blinded sample size re-estimation with data from approximately 40% of completed participants that indicated a greater variance than expected, the number of participants to be randomized was increased to 790 to maintain a power of 80%.

Efficacy analyses were conducted using the FAS (an intention-to-treat analysis). The last observation carried forward method was used to impute missing data. Treatment differences in diary outcomes and OAB-Q scores were assessed using ANCOVA, with treatment, center, dosing time, age stratum, and baseline value as covariates. The median treatment difference and 95% confidence interval (CI) for the change from baseline in UUI episodes per 24 hours was calculated using the Hodges-Lehmann estimator,[30] and the *P*-value was based on a two-sided nonparametric van Elteren test[31,32] because UUI data violated normality assumptions. Odds ratios for responder rates on the TBS, OAB-S, PPBC, and UPS were determined using logistic regression, with treatment, center, dosing time, and age stratum as covariates. All statistical tests were two-sided at a 5% significance level. For the TBS, participants reporting that their condition was improved or greatly improved were considered responders. For the OAB-S, participants reporting that OAB medication met or somewhat or greatly exceeded their expectation (Question 5) or that they were very or somewhat satisfied (Questions 9, 10a-d, and 11a-b) were considered responders. Participants reporting improvement on the PPBC or UPS were considered responders for that instrument. The effects of age and dosing time on efficacy outcomes were assessed descriptively. Safety findings were descriptively summarized using the safety population (all randomized participants who took ≥ 1 doses of study drug).

RESULTS

Participants and Dosing

One thousand forty-five individuals were screened, and 794 were randomized to fesoterodine (n = 398) or placebo (n = 396). The safety analysis set (all participants who received ≥ 1 doses of study medication) included 785 participants (fesoterodine, n = 392; placebo, n = 393), and the FAS (all participants who received ≥ 1 doses of study medication and had a baseline and >1 postbaseline measures) included 756 participants (fesoterodine, n = 374; placebo, n = 382). Seventy-eight (20%) participants in the fesoterodine group and 52 (13%) in the placebo group discontinued the study. Reasons for discontinuation included adverse events (fesoterodine, n = 46 (12%); placebo, n = 22 (6%)), insufficient clinical response (fesoterodine, n = 12 (3%); placebo, n = 8 (2%)), no longer willing to participate (fesoterodine, n = 14 (4%); placebo, n = 17 (4%)), and other (fesoterodine, n = 6 (2%); placebo, n = 5 (1%)). Three hundred fourteen (79%) participants in the fesoterodine group and 341 (86%) in the placebo group completed the study.

Participants were predominantly (99.6%) white, and 47% were men (Table 1). Approximately one-third of participants in each group were older than 75. Forty-six percent of participants reported any UUI episodes at baseline, and 64% had been receiving treatment with antimuscarinics before the study. Of the men, 44% receiving placebo and 39% receiving fesoterodine had benign prostatic hyperplasia at baseline; 19.3%, 6.8%, and 2.7% of men had previously received treatment with tamsulosin, finasteride, and doxazosin, respectively.

At week 4, 52% and 66% of participants in the fesoterodine and placebo groups opted for dose escalation, respectively. Dose escalation rates at week 4 were similar in participants aged 75 and younger and older than 75 for fesoterodine (63% and 58%, respectively) and placebo (69% and 73%, respectively). At week 8, 16% and 9% of participants in the fesoterodine and placebo groups opted for dose escalation, and 4% and 3% de-escalated, respectively.

Efficacy

The time courses of the changes from baseline in diary endpoints at weeks 4, 8, and 12 for the fesoterodine and

Table 1. Baseline Demographics and Clinical Characteristics of Treated Participants

Characteristic	Placebo, n = 393	Fesoterodine, n = 392
Sex, n (%)		
Male	188 (48)	179 (46)
Female	205 (52)	213 (54)
Age, mean ± SD (range)	72.8 ± 5.7 (65–89)	72.6 ± 5.8 (65–90)
Weight, kg, mean ± SD (range)	77.4 ± 13.4 (42.7–132.2)	77.6 ± 14.5 (42.0–131.8)
Body mass index, kg/m^2, mean ± SD (range)	28.2 ± 4.6 (17.5–44.9)	27.9 ± 4.6 (16.6–47.8)
Duration of overactive bladder symptoms since diagnosis, years, mean (range)	7.0 (0.3–57.2)	7.4 (0.3–59.8)
Previous antimuscarinic treatment, n (%)[a]		
Tolterodine	73 (18.6)	87 (22.2)
Solifenacin	67 (17.0)	62 (15.8)
Trospium	38 (9.7)	45 (11.5)
Oxybutynin	45 (11.5)	44 (11.2)
Darifenacin	18 (4.6)	7 (1.8)
Propiverine	9 (2.3)	10 (2.6)
Common comorbidities, n (%)		
Hypertension	204 (52)	223 (57)
Other cardiac conditions	95 (24)	78 (20)
Hypercholesterolemia	69 (18)	77 (20)
Osteoarthritis	61 (16)	65 (17)
Diabetes mellitus	54 (14)	54 (14)
Depression	25 (6)	37 (9)
Hypothyroidism	33 (8)	27 (7)
Benign prostatic hyperplasia (men only)	83 (44)	69 (39)
Number of urgency episodes per 24 hours, mean ± SD	8.8 ± 4.0	8.5 ± 3.6
Number of severe urgency episodes per 24 hours, mean ± SD	4.1 ± 4.2	3.5 ± 3.4
Number of micturitions per 24 hours, mean ± SD	12.1 ± 3.1	11.9 ± 2.9
Number of night-time micturitions per 24 hours, mean ± SD	2.9 ± 1.5	2.8 ± 1.5
Number of UUI episodes per 24 hours, median (range)[b]	1.7 (0.3–26.7)	1.3 (0.3–14.3)
Number of incontinence pads used per 24 hours, mean ± SD[c]	3.3 ± 3.2	2.8 ± 2.1
Mini-Mental State Examination score, mean ± SD (range)	28.1 ± 2.0 (20–30)	28.2 ± 1.9 (20–30)

Demographic characteristics based on safety set; clinical characteristics based on full analysis set.
SD = standard deviation.
[a] Participants could have received >1 previous antimuscarinic treatments.
[b] Includes only participants reporting urinary urgency incontinence (UUI) at baseline.
[c] Includes only participants reporting incontinence pad usage at baseline.

placebo groups are shown in Figure 1A–F. At week 12, improvement from baseline in urgency episodes (primary endpoint) ($P < .001$), micturitions ($P < .001$), nocturnal micturitions ($P = .003$), severe urgency episodes ($P < .001$), and incontinence pad use ($P = .01$) was significantly greater with fesoterodine than placebo but not median change in UUI episodes ($P = .73$) in the 46% of patients with any UUI episodes at baseline (Figure 1A–F). Mean number of urgency episodes per 24 hours decreased from 8.5 at baseline to 4.6 at week 12 in the fesoterodine group and from 8.8 to 6.3 in the placebo group. Mean number of micturitions per 24 hours decreased from 11.9 at baseline to 9.8 at week 12 in the fesoterodine group and from 12.1 to 10.9 in the placebo group. Mean number of nocturnal micturitions per 24 hours decreased from 2.8 to 2.2 in the fesoterodine group and from 2.9 to 2.6 in the placebo group. Mean number of severe urgency episodes per 24 hours decreased from 3.5 to 1.1 in the fesoterodine group and from 4.1 to 2.3 in the placebo group. Mean number of incontinence pads used per 24 hours (for those using them at baseline) decreased from 2.8 to 1.8 in the fesoterodine group and from 3.3 to 2.7 in the placebo group. Median number of UUI episodes per 24 hours (for those with UUI >0 at baseline) decreased from 1.3 to 0.0 in the fesoterodine group and from 1.7 to 0.0 in the placebo group. The diary-dry rate at weeks 8 and 12 for participants with any UUI episodes at baseline was 53% with fesoterodine and 45% with placebo (odds ratio = 1.52, 95% confidence interval=0.91–2.53; $P = .11$).

The odds of a patient-reported treatment response on the TBS, OAB-S, PPBC, and UPS were significantly greater in participants in the fesoterodine group than for those receiving placebo ($P < .001$ for TBS, OAB-S, and PPBC; $P = .001$ for UPS) (Figure 2A). Improvements in scores on the OAB-Q Symptom Bother ($P < .001$) and HRQL ($P < .001$) scales and the coping ($P < .001$), concern ($P < .001$), sleep ($P = .003$), and social interaction ($P = .02$) domains were significantly greater for fesoterodine than placebo (Figure 2B).

Improvements in all outcomes were greater with fesoterodine than with placebo in participants aged 65 to 75 or older than 75 for all outcomes, and the magnitude of the difference between fesoterodine and placebo was generally similar in both age groups (Table 2), although for some outcomes, the magnitude of change from baseline was somewhat smaller in participants older than 75, particularly in the placebo group. Dosing time (morning vs evening) did not influence differences between fesoterodine and placebo. For example, mean changes from baseline in urgency episodes were −3.8 for fesoterodine and −2.7 for placebo with morning dosing and −3.9 for fesoterodine and −2.3 for placebo with evening dosing; TBS response rates were 70% for fesoterodine and 40% for placebo with morning dosing and 65% for fesoterodine and 46% for placebo with evening dosing. Similar results with morning and evening dosing were also demonstrated for all other study outcomes (data not shown).

Safety

The most frequently reported all-cause adverse events in the fesoterodine group were dry mouth and constipation (Table 3). The incidence of these adverse events was similar with morning and evening dosing. Central nervous system adverse events occurred rarely. The majority of adverse events were mild or moderate (fesoterodine, 94%; placebo, 98%). No meaningful mean change from baseline (fesoterodine, n = 374; placebo, n = 382) to week 12 (fesoterodine, n = 341; placebo, n = 356) in MMSE score was observed in the fesoterodine (0.24 ± 1.76) or placebo

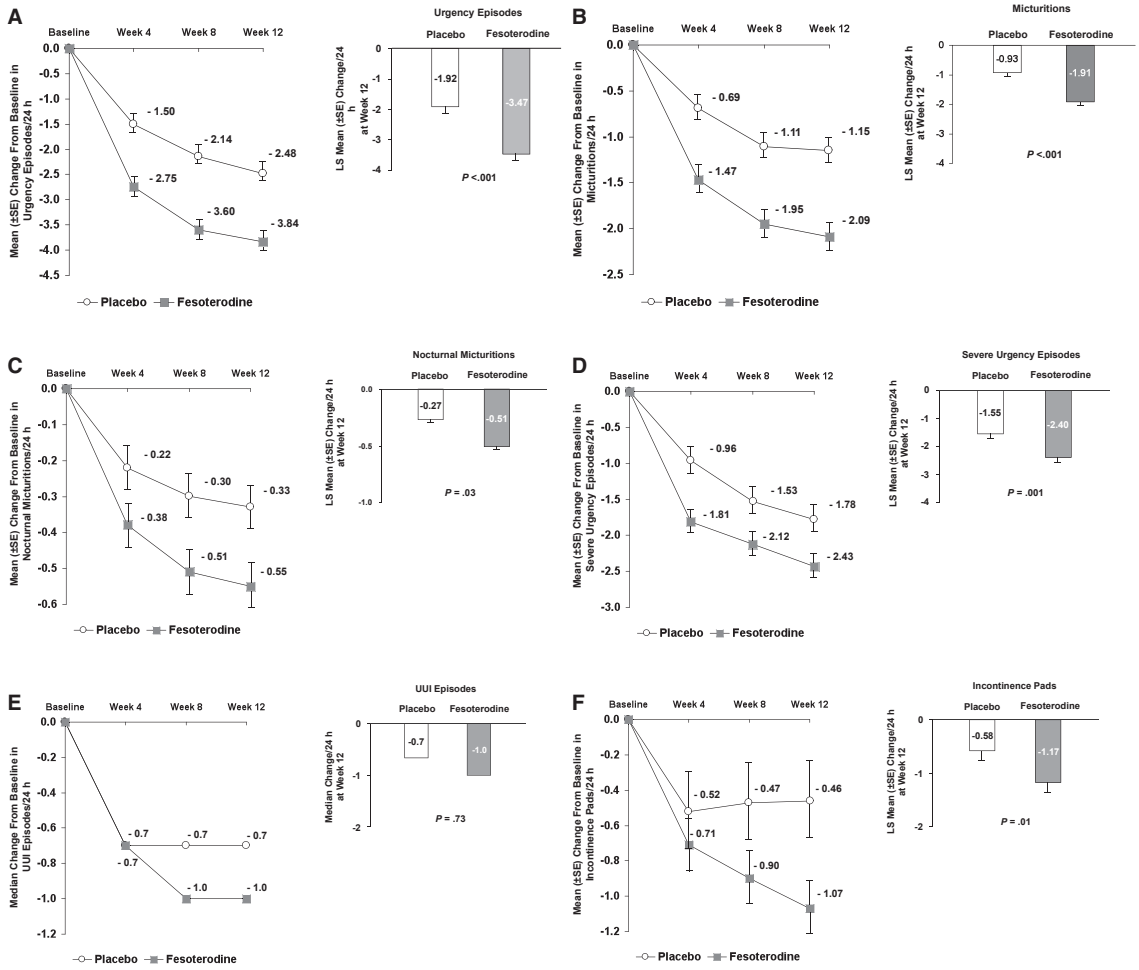

Figure 1. Time course of changes from baseline in diary endpoints and change from baseline to week 12 for (A) urgency episodes per 24 hours (primary endpoint), (B) micturitions per 24 hours, (C) nocturnal micturitions per 24 hours, (D) severe urgency episodes per 24 hours, (E) urgency urinary incontinence episodes per 24 hours, and (F) incontinence pad use per 24 hours. LS = least squares; SE = standard error.

(0.23 ± 1.82) group. Mean MMSE scores at week 12 were 28.4 (range 20–30) in the fesoterodine group and 28.3 (range 19–30) in the placebo group. No clinically relevant changes from baseline were observed in vital sign measurements in either group. Two deaths occurred (fesoterodine, n = 1: abscess, appendicitis perforated; placebo, n = 1: metastatic colon cancer); neither death was considered related to treatment.

Seventy-eight fesoterodine-treated participants (20%) and 52 placebo-treated participants (13%) discontinued the study prematurely; discontinuation rates due to adverse events were 12% (46/392) for fesoterodine and 6% (22/393) for placebo. The most common adverse event leading to discontinuation was dry mouth (fesoterodine, n = 11; placebo, n = 1). Two participants (<1%) in the fesoterodine group withdrew from the study because of constipation. Three participants in the fesoterodine group discontinued because of cognitive function–related adverse events, one each for cognitive disorder, amnesia, and confusional state; the latter two were considered, in the opinion of the site investigator, to be unrelated to study drug.

Six participants reported urinary retention (three men and two women receiving fesoterodine; one man receiving placebo), including two men within the first 4 weeks of treatment with fesoterodine. Four of the six participants reporting urinary retention required catheterization (three men receiving fesoterodine; one man receiving placebo). Five of the six participants reporting urinary retention discontinued because of this adverse event (fesoterodine, n = 4; placebo, n = 1), including all four participants requiring catheterization.

DISCUSSION

Potential concerns of clinicians regarding the safety and tolerability of antimuscarinic drugs in elderly adults may result in the undertreatment of older people with OAB, despite its increasing burden in this group and even though older individuals are more likely to request pharmacological treatment for their OAB symptoms.[33] The results of the SOFIA trial show that fesoterodine was associated with statistically significantly and clinically greater improvements in urgency episodes, micturition frequency, and patient-reported outcomes than placebo in elderly adults with OAB. Improvements in urgency episodes and treatment response rates were greater with fesoterodine than placebo with morning and evening dosing and for

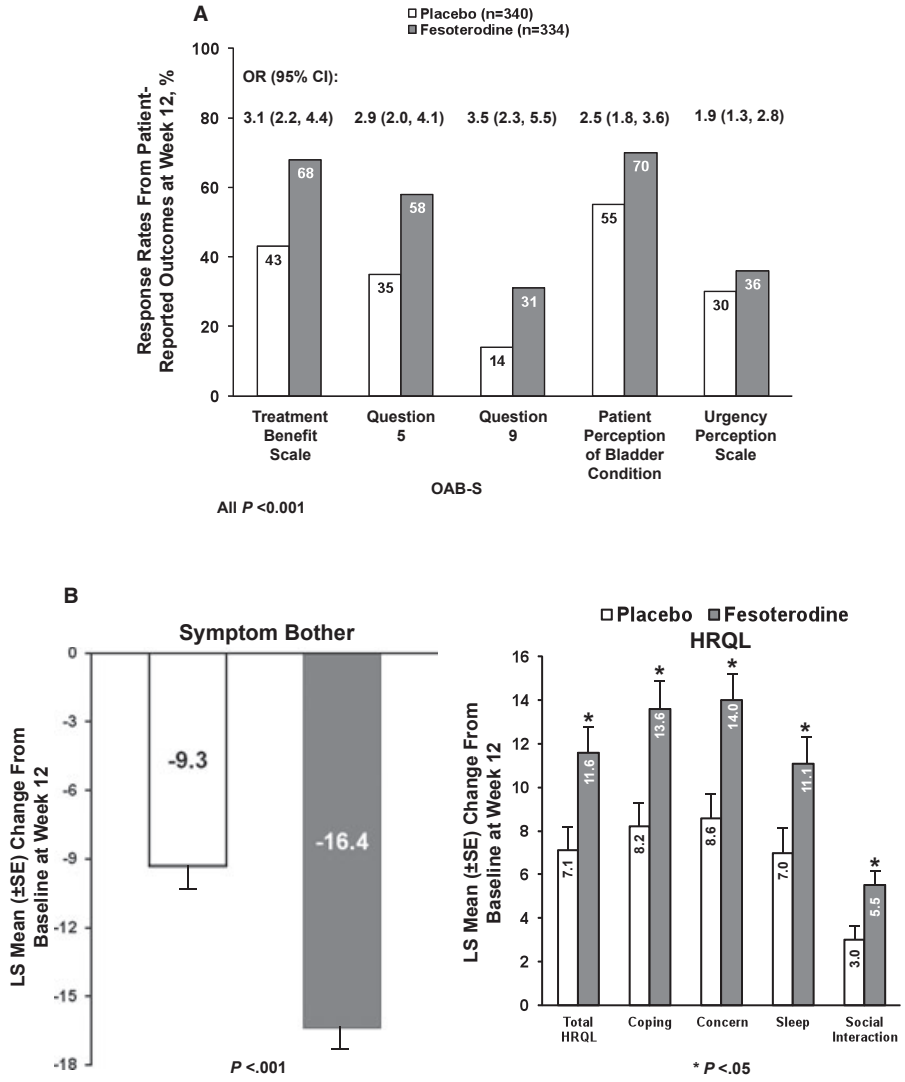

Figure 2. Response rates on (A) patient-reported outcomes at week 12 and (B) mean change from baseline to week 12 in Overactive Bladder Questionnaire scores. CI = confidence interval; HRQL = health-related quality of life; LS = least squares; OAB-S = OAB Satisfaction Questionnaire; OR = odds ratio; SE=standard error.

participants aged 75 and younger and those older than 75. The safety profile of fesoterodine in this older population was similar to that reported in previous studies, with no new safety concerns and a low rate of discontinuation due to constipation. The rate of urinary retention was low, especially for this population, although it was higher in participants who received fesoterodine (n = 5, 1.3%) than in those who received placebo (n = 1, 0.3%). The number of participants who required catheterization (n = 3, 0.8% vs n = 1, 0.3%) and the number who discontinued the study because of urinary retention (n = 4, 1.0% vs n = 1, 0.3%) were also higher with fesoterodine than placebo. The overall discontinuation rates in the fesoterodine (19.9%) and placebo (13.2%) groups in the present study were at the high end of the range of discontinuation rates observed in fesoterodine (10–21%) and placebo (9–15%) arms of trials conducted in younger participants;[18,19,34,35] discontinuation rates in the present study were slightly higher in participants older than 75 in both treatment groups.

In this largely cognitively intact group of older people, few adverse events related to cognitive function were observed, and there was no change in the MMSE scores of participants. Although the individual may not report cognitive dysfunction related to antimuscarinics, it is reassuring that fesoterodine appeared to be largely cognitively safe in this population of community-dwelling older adults. A recent study showed no adverse effect of fesoterodine on memory or executive function in a group of cognitively intact older adults,[36] despite the high anticholinergic activity of the metabolite of fesoterodine: 5-hydroxymethyl tolterodine.[37]

Unlike typical studies of antimuscarinics for OAB, this study included a large proportion of men (47%), which is consistent with epidemiological data on the prevalence of OAB.[5] Of the men in this trial, 41% had benign prostatic enlargement recorded as a coexisting medical condition. In addition, the study population differed with regard to the low proportion of participants with UUI (46%) at baseline, because UUI was not an inclusion criterion of the

Table 2. Week 12 Outcomes in Participants Aged 65 to 75 and Older Than 75

Outcome	65–75		>75	
	Placebo, n = 259	Fesoterodine, n = 254	Placebo, n = 123	Fesoterodine, n = 120
Diary variable per 24 hours				
Urgency episodes, mean ± SD	−2.7 ± 4.3	−4.0 ± 4.2	−1.9 ± 5.0	−3.5 ± 3.8
Severe urgency episodes, mean ± SD	−1.7 ± 3.0	−2.3 ± 2.8	−2.0 ± 5.3	−2.7 ± 3.8
Micturitions, mean ± SD	−1.3 ± 2.6	−2.3 ± 2.2	−0.8 ± 2.6	−1.7 ± 2.5
Nighttime micturitions, mean ± SD	−0.3 ± 1.1	−0.6 ± 1.1	−0.3 ± 1.2	−0.5 ± 1.2
UUI episodes, median[a]	−1.0	−1.0	−0.7	−1.0
Incontinence pad use, mean ± SD[b]	−0.5 ± 3.4	−1.1 ± 1.8	−0.3 ± 1.8	−1.1 ± 1.7
Treatment benefit scale responder, n/N (%)	112/234 (48)	153/225 (68)	34/106 (32)	73/109 (67)
Overactive bladder satisfaction questionnaire responder, n/N (%)				
Question 5	102/249 (41.0)	137/235 (58.3)	24/110 (21.8)	63/113 (55.8)
Questions 9, 10a–d, 11a–b	43/248 (17.3)	78/234 (33.3)	6/110 (5.5)	29/113 (25.7)
Patient perception of bladder condition responder, n/N (%)	153/258 (59.3)	184/253 (72.7)	56/122 (45.9)	78/120 (65.0)
Urgency perception scale responder, n/N (%)	82/258 (31.8)	93/254 (36.6)	32/122 (26.2)	43/120 (35.8)
Overactive bladder questionnaire, mean ± SD change from baseline				
Symptom bother	−13.3 ± 19.8	−19.0 ± 20.5	−9.7 ± 21.0	−17.1 ± 23.2
Health-related quality of life				
Total	10.1 ± 17.5	14.0 ± 16.8	8.4 ± 21.3	11.7 ± 18.9
Coping	11.4 ± 21.3	16.3 ± 20.6	8.9 ± 25.8	14.3 ± 23.3
Concern	12.3 ± 19.9	17.1 ± 19.5	9.0 ± 24.3	12.2 ± 21.3
Sleep	9.9 ± 21.2	11.4 ± 20.7	8.1 ± 24.0	13.2 ± 22.6
Social interaction	4.8 ± 17.5	7.9 ± 16.5	6.4 ± 20.8	5.3 ± 19.1

SD = standard deviation.

[a] Includes only participants with any urgency urinary incontinence (UUI) episodes in baseline diary.

[b] Includes only participants using incontinence pads at baseline.

Table 3. Adverse Events and Reasons for Discontinuation

Adverse Event and Reason for Discontinuation	Placebo			Fesoterodine		
	65–75, n = 267	>75, n = 126	Total, n = 393	65–75, n = 264	>75, n = 128	Total, n = 392
	n (%)					
Adverse event						
Any adverse event	91 (34.1)	51 (40.5)	142 (36.1)	171 (64.8)	73 (57.0)	244 (62.2)
Any serious adverse event	5 (1.9)	4 (3.2)	9 (2.3)	10 (3.8)	4 (3.1)	14 (3.6)
Dry mouth	12 (4.5)	9 (7.1)	21 (5.3)	101 (38.3)	32 (25.0)	133 (33.9)
Mild	7 (2.6)	8 (6.3)	15 (3.8)	72 (27.3)	23 (18.0)	95 (24.2)
Moderate	4 (1.5)	1 (0.8)	5 (1.3)	21 (8.0)	7 (5.5)	28 (7.1)
Severe	1 (0.4)	0	1 (0.3)	8 (3.0)	2 (1.6)	10 (2.6)
Constipation	5 (1.9)	5 (4.0)	10 (2.5)	25 (9.5)	10 (7.8)	35 (8.9)
Dizziness	3 (1.1)	1 (0.8)	4 (1.0)	8 (3.0)	6 (4.7)	14 (3.6)
Nasopharyngitis	4 (1.5)	5 (4.0)	9 (2.3)	10 (3.8)	2 (1.6)	12 (3.1)
Headache	4 (1.5)	1 (0.8)	5 (1.3)	10 (3.8)	1 (0.8)	11 (2.8)
Urinary tract infection	5 (1.9)	2 (1.6)	7 (1.8)	5 (1.9)	5 (3.9)	10 (2.6)
Diarrhea	1 (0.4)	4 (3.2)	5 (1.3)	5 (1.9)	5 (3.9)	10 (2.6)
Dyspepsia	2 (0.7)	0	2 (0.5)	6 (2.3)	3 (2.3)	9 (2.3)
Fatigue	10 (3.7)	0	10 (2.5)	8 (3.0)	1 (0.8)	9 (2.3)
Nausea	3 (1.1)	1 (0.8)	4 (1.0)	5 (1.9)	4 (3.1)	9 (2.3)
Hypertension	6 (2.2)	2 (1.6)	8 (2.0)	7 (2.7)	0	7 (1.8)
Back pain	6 (2.2)	2 (1.6)	8 (2.0)	1 (0.4)	1 (0.8)	2 (0.5)
Reason for Discontinuation	34 (12.7)	18 (14.3)	52 (13.2)	50 (18.9)	28 (21.9)	78 (19.9)
All-cause adverse events	15 (5.6)	7 (5.6)	22 (5.6)	29 (11.0)	17 (13.3)	46 (11.7)
Insufficient clinical response	5 (1.9)	3 (2.4)	8 (2.0)	7 (2.7)	5 (3.9)	12 (3.1)
Consent withdrawn	11 (4.1)	6 (4.8)	17 (4.3)	11 (4.2)	3 (2.3)	14 (3.6)
Other	3 (1.1)	2 (1.6)	5 (1.3)	3 (1.1)	3 (2.3)	6 (1.5)

All-causality adverse events occurring in ≥2% of total participants in either treatment group (safety population).

study. These population differences may account for the lack of a significant improvement in UUI episodes with fesoterodine, which has been demonstrated in previous studies in younger predominantly female populations.[18,19] The low rate of discontinuation due to urinary retention suggests a favorable safety profile of fesoterodine in older men.

The efficacy and safety profiles of fesoterodine in the SOFIA trial support the favorable benefit:risk ratio of antimuscarinic drugs in older adults with OAB reported in previous trials.[14–17] In addition, the study provides valuable data for individuals older than 75, indicating that fesoterodine is effective and well tolerated in this elderly subgroup. These results in this subgroup support those of the post hoc analysis of data from two randomized, fixed-dose, placebo-controlled studies that indicated that the 4- and 8-mg doses of fesoterodine effectively treated OAB symptoms in individuals younger than 75, with the 8-mg dose being most effective in those aged 75 and older.[22] These findings, together with the high rate of dose escalation with fesoterodine in the present study and in previous flexible-dose fesoterodine studies,[20] suggest that some elderly adults require higher doses of medication to achieve effective relief of OAB symptoms, contrary to commonly held beliefs about drug treatment in elderly adults.[38]

One potential limitation of this study is that the mean MMSE score of the participants at baseline was approximately 28 in both treatment groups, suggesting that the participants were functioning at a high level even though the inclusion criteria required a score of only 20. Nevertheless, there were 18 participants in the fesoterodine group and 22 participants in the placebo group with MMSE scores less than 25 at baseline. Additionally, participants had to be outpatients and had to be able to complete micturition diaries and study-related questionnaires, which may have precluded the enrollment of individuals with much cognitive impairment, which may also limit the generalizability of the results.

Treatment with fesoterodine was associated with statistically significantly greater improvements than placebo in most bladder-diary variables in elderly adults with OAB. The statistically significantly greater improvement or higher response rates on self-reported outcomes suggest that the improvements in diary variables were meaningful to the individuals experiencing them. Improvements in all outcomes were greater with fesoterodine than with placebo regardless of dosing time or age stratum. Fesoterodine treatment was generally well tolerated in elderly and very elderly adults with few central nervous system adverse events.

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