SYSTEMATIC REVIEW

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Flexible dosing with fesoterodine 4 and 8 mg: a systematic review of data from clinical trials

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SUMMARY

Aims: To systematically review dose-escalation data from flexible-dose studies of fesoterodine and summarise factors associated with dose-escalation decisions. **Methods:** A PubMed search was conducted using the terms (fesoterodine AND flexible dose), with no limits. Articles were included if they contained fesoterodine dose-escalation data for efficacy or safety outcomes or factors associated with dose-escalation decisions. **Results:** Of 13 articles identified by the search, 10 articles (six clinical studies) met inclusion criteria. In flexible-dose trials of fesoterodine, 51–63% of subjects initially receiving fesoterodine 4 mg opted for dose escalation to fesoterodine 8 mg. Escalators generally reported significantly more severe overactive bladder (OAB) symptoms, greater OAB symptom bother and worse health-related quality of life at baseline than non-escalators. Escalators demonstrated less treatment benefit with fesoterodine 4 mg than non-escalators. Non-escalators generally had a higher rate of dry mouth and constipation with fesoterodine 4 mg than escalators. The decision to escalate appeared to be determined by the efficacy/tolerability responses; fesoterodine escalators demonstrated a lower sensitivity (less efficacy and fewer adverse events) before their decision to escalate. By study end (8–11 weeks after escalation decision), the efficacy and tolerability profiles were similar in escalators and non-escalators. **Conclusions:** Data from flexible-dose studies provide strong evidence that fesoterodine provides treatment benefit to individual subjects with OAB because of its true dose–response effect. In clinical practice, it can be worthwhile to escalate to fesoterodine 8 mg in individual subjects who require additional efficacy benefit.

Review criteria
A PubMed search of the literature on flexible-dose fesoterodine was conducted. We summarised the dose-escalation data for efficacy and safety outcomes and factors associated with dose-escalation decisions.

Message for the clinic
The results from clinical trials of flexible-dose fesoterodine (4 and 8 mg) are consistent with the idea that the dose–response curve differs between individual patients. The dose–response effect of fesoterodine in the treatment of OAB symptoms provides clinicians with valuable information for achieving the optimal balance between efficacy and tolerability with a flexible-dose regimen in individual patients, including elderly patients.

Introduction

Overactive bladder (OAB) is defined by the International Continence Society as urgency, with or without urgency urinary incontinence (UUI), usually with daytime frequency and nocturia (1–2). OAB symptoms can have a marked negative impact on patient-reported health-related quality of life (HRQL) (3–5). The primary goals of pharmacologic therapy for OAB are to relieve OAB symptoms and to improve HRQL (6).

Fesoterodine, an antimuscarinic for the treatment of OAB symptoms, including UUI, urgency and frequency, was developed in two once-daily doses, 4 and 8 mg, which provides dose flexibility for treatment individualisation (7–10). The recommended starting dose of fesoterodine is 4 mg once daily, but the dose may be increased to 8 mg once daily based on individual response and tolerability (11). With these two available doses, the fesoterodine dose can be adjusted to achieve the optimal therapeutic balance between efficacy and tolerability based on each subject's clinical response.

In two phase 3 pivotal trials, subjects with OAB treated with fixed-dose fesoterodine 4 or 8 mg demonstrated significant improvement in OAB symptoms and HRQL compared with subjects treated with placebo (9,10,12). A dose–response relationship was suggested by the generally greater efficacy of fesoterodine 8 mg over fesoterodine 4 mg. A *post hoc* analysis of pooled phase 3 data demonstrated that fesoterodine significantly decreased OAB symptoms, including UUI episodes, in a dose-dependent fashion, with fesoterodine 8 mg providing significant additional benefit compared with fesoterodine 4 mg (13). Another *post hoc* analysis of pooled phase 3 data demonstrated that subjects with greater UUI severity at baseline had a significantly greater improvement with fesoterodine 8 mg vs. fesoterodine 4 mg, whereas the improvement in UUI between those

receiving the 4-mg and 8-mg dose was not significant in subjects with less severe UUI severity at baseline (14).

A 12-week, randomised, double-blind, placebo-controlled trial (Evaluation of urinary urgency Incontinence in patients Given fesoterodine 8 mg vs. fesoterodine 4 mg in a Head-to-head efficacy Trial; EIGHT) prospectively confirmed that fixed-dose fesoterodine 8 mg demonstrates significantly greater efficacy than fesoterodine 4 mg for reducing UUI episodes and other OAB symptoms (15). Significantly greater patient-reported improvements in symptom bother and HRQL with fesoterodine 8 mg vs. fesoterodine 4 mg indicated that this difference in efficacy is clinically meaningful to patients with OAB (15).

Although fixed-dose studies are valuable in defining the dose–response effect of a drug, studies with a flexible-dose design better reflect clinical practice (i.e. dosing decision based on the individual's clinical response rather than prespecified dosing protocol) and the benefit/risk profile a treating clinician can expect for an individual patient. The purpose of this article is to systematically review dose-escalation data from flexible-dose studies of fesoterodine and summarise baseline characteristics and therapy response phenotypes of patients who may benefit from a higher dose of OAB medication.

Methods

This systematic review followed the recommendations of the PRISMA statement (16). A PubMed search was conducted on 26 November 2013, using the terms (fesoterodine AND flexible dose), with no limits. The references cited in the retrieved articles also were scanned for additional articles. Articles were included if they contained fesoterodine dose-escalation data for efficacy or safety outcomes or factors associated with dose-escalation decisions. Of the 13 articles identified by the PubMed search, 10 articles (six clinical studies) met inclusion criteria (Figure 1).

Results

Randomised, double-blind, placebo-controlled trials

ClinicalTrials.gov ID: NCT00536484

A 12-week, double-blind, placebo-controlled trial evaluated the effects of flexible-dose fesoterodine in subjects aged ≥ 18 years who reported OAB symptoms (17). Eligible subjects were randomised to fesoterodine 4 mg or placebo once daily. At the end of week 2, in consultation with the investigator, subjects could continue on fesoterodine 4 mg or increase the dose to 8 mg for the remaining 10 weeks (sham dose escalation for placebo). Of 883 subjects (fesoterodine, $n = 438$; placebo, $n = 445$) who received ≥ 1 dose of study medication, 87% completed the trial. At week 2, 63% of the fesoterodine group and 73% of the placebo group chose dose escalation. At week 12, fesoterodine significantly decreased micturitions (primary end-point), UUI episodes and urgency episodes per 24 h compared with placebo (all $p < 0.05$); decreases in nocturnal micturitions and nocturnal urgency episodes were not significant. Scores for all OAB Questionnaire (OAB-q) scales (Symptom Bother and total HRQL) and HRQL domains (Concern, Coping, Sleep and Social Interaction) were significantly improved with fesoterodine vs. placebo at week 12 (all $p < 0.01$). Fesoterodine treatment was generally well tolerated, with dry mouth and constipation the most common adverse events (Table 1).

This flexible-dose trial was not designed to compare fesoterodine 4 mg and 8 mg, so *post hoc* analy-

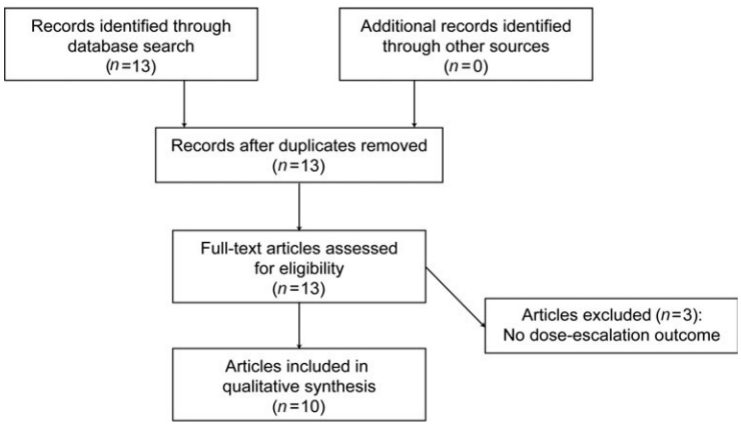

Figure 1 PRISMA flow diagram

Table 1 Randomised, double-blind, placebo-controlled trials of flexible-dose fesoterodine*

Reference (NCT ID)	No. treated (Treatment duration)	Treatment regimen (Once daily)	Key eligibility criteria	Dose escalation	Key efficacy results	Key safety results	Key *post hoc* results (Escalators vs. non-escalators)
Dmochowski et al. (17) Staskin et al. (18) (NCT00536484)	883 subjects (fesoterodine, 438; PBO, 445) received ≥ 1 dose of study drug (12 weeks)	Fesoterodine 4 mg PBO Fesoterodine 8 mg Subjects started on fesoterodine 4 mg; at week 2, could increase dose to 8 mg (sham escalation for PBO) After week 2, dose remained unchanged for remaining 10 weeks	Men and women aged ≥ 18 years with OAB symptoms for ≥ 3 month, ≥ 8 micturitions and ≥ 3 urgency episodes/24 h, and at least moderate bladder-related problems reported on PPBC	*At week 2*: 63% of fesoterodine group and 73% of PBO group opted for dose escalation	*At week 12*: Fesoterodine significantly decreased micturitions, UUI episodes, and urgency episodes/24 h vs. PBO Fesoterodine significantly improved scores for all OAB-q scales and domains vs. PBO	Fesoterodine was well tolerated; most common AEs were dry mouth (26% vs. 8% for PBO) and constipation (11% vs. 6% for PBO); AEs were mostly mild or moderate	*At baseline*: Subject characteristics were similar, except micturitions and urgency episodes/24 h, which were significantly higher for subsequent escalators vs. non-escalators *At week 2*: Subsequent escalators had significantly less improvement in micturitions and urgency episodes/24 h vs. non-escalators; AE rate generally greater for fesoterodine non-escalators vs. escalators *At week 12*: OAB symptom improvements and AE rate generally comparable in fesoterodine escalators and non-escalators
Weiss et al. (19) (NCT00911937)	937 subjects (fesoterodine, 463; PBO, 474) received ≥ 1 dose of study drug (12 weeks)	Fesoterodine 4 mg PBO Fesoterodine 8 mg Subjects started on fesoterodine 4 mg; at week 4, could increase to 8 mg (sham	Men and women aged ≥ 18 years with OAB symptoms, including nocturnal urgency, for ≥ 3 months; ≥ 8 micturitions, ≥ 3 urgency episodes, and 2–8 nocturnal urgency episodes/24 h	*At week 4*: 61% of fesoterodine group and 67% of PBO group opted for dose escalation	*At week 12*: Fesoterodine significantly decreased nocturnal urgency episodes (1° end-point), nocturnal micturitions, total micturitions and urgency episodes/24 h vs. PBO Fesoterodine significantly improved scores for all	Fesoterodine was well tolerated; most common AEs were dry mouth (21% vs. 8% for PBO), constipation (3% vs. 2% for PBO) and headache (2% vs. 1% for	NA

Table 1 Continued

Reference (NCT ID)	No. treated (Treatment duration)	Treatment regimen (Once daily)	Key eligibility criteria	Dose escalation	Key efficacy results	Key safety results	Key *post hoc* results (Escalators vs. non-escalators)
		escalation for PBO) After week 4, dose remained unchanged for remaining 8 weeks			OAB-q scales and domains vs. PBO	PBO); AEs were mostly mild or moderate	
Wagg et al. (20) (NCT00798434)	785 subjects (fesoterodine, 392; PBO, 393) received ≥ 1 dose of study drug (12 weeks)	Fesoterodine 4 mg Fesoterodine 8 mg PBO Subjects started on fesoterodine 4 mg; at week 4, could increase to 8 mg; at week 8, could increase or decrease dose (sham increase/ decrease for PBO)	Men and women aged ≥ 65 years with OAB symptoms for ≥ 3 months, ≥ 8 micturitions and ≥ 3 urgency episodes/24 h, at least some moderate bladder-related problems on the PPBC, and MMSE score ≥ 20	*At week 4*: 52% of fesoterodine group and 66% of PBO group opted for dose escalation *At week 8*: 16% of fesoterodine group and 9% of PBO group opted for dose escalation, and 4% and 3% de-escalated, respectively	*At week 12*: Fesoterodine significantly decreased urgency episodes, micturitions and nocturnal micturitions/ 24 h vs. PBO Fesoterodine significantly improved scores for all OAB-q scales and domains vs. PBO	Fesoterodine was generally well tolerated in this elderly population; most common AEs were dry mouth (34% vs. 5% for PBO) and constipation (9% vs. 3% for PBO); AEs were mostly mild or moderate No meaningful change from baseline in MMSE score in either group	NA
DuBeau et al. (22) (NCT00928070)	562 vulnerable elderly subjects (fesoterodine, 281; PBO, 281) received ≥ 1 dose of study drug (12 weeks)	Fesoterodine 4 mg Fesoterodine 8 mg PBO Subjects started on fesoterodine 4 mg; at week 4, could increase dose to 8 mg (sham escalation for PBO); subjects who escalated could return to 4 mg at any time but could not re-escalate	Men and women aged ≥ 65 years with UUI symptoms for ≥ 3 months, ≥ 8 micturitions and ≥ 2 but ≤ 15 UUI episodes/ 24 h, and VES-13 score ≥ 3	*At week 4*: 53% of fesoterodine group and 64% of PBO group opted for dose escalation; 45% of fesoterodine group and 57% of PBO group remained on higher dose through week 12	*At week 12*: Fesoterodine significantly decreased UUI episodes (1° end-point), micturitions, urgency episodes and nocturnal urgency episodes/24 h and significantly improved diary-dry rate vs. PBO Fesoterodine significantly improved scores for OAB-q Symptom Bother and total HRQL scales and Coping and Concern domains vs. PBO	Fesoterodine was generally well tolerated; most common AEs were dry mouth (24% vs. 6% for PBO) and constipation (11% vs. 4% for PBO) in each group and were mostly mild to moderate	NA

*Includes prespecified trial data and any *post hoc* analyses of trial data. AE, adverse event; HRQL, health-related quality of life; MMSE, Mini-Mental State Examination; OAB, overactive bladder; OAB-q, Overactive Bladder Questionnaire; PBO, placebo; PPBC, Patient Perception of Bladder Condition; UUI, urgency urinary incontinence; VES-13, 13-item Vulnerable Elders Survey.

ses were conducted to compare outcomes in subjects who chose to increase their fesoterodine dose to 8 mg (escalators) vs. those who remained on 4 mg (non-escalators) (18). Baseline demographical characteristics were similar between escalators and non-escalators. Baseline disease severity appeared greater among escalators, with micturitions and urgency episodes per 24 h in the fesoterodine group significantly higher among escalators vs. non-escalators. At week 2, before the dose-escalation decision, subjects who subsequently chose fesoterodine dose escalation had significantly less improvement from baseline in micturitions and urgency episodes vs. non-escalators (both $p < 0.001$; Table 1). Improvement in UUI episodes did not differ between fesoterodine escalators and non-escalators, whereas the diary-dry rate (i.e. proportion of subjects with ≥ 1 UUI episode at baseline who report no UUI episodes at subsequent time point) was significantly lower among escalators at week 2 ($p = 0.008$). At week 2, the rate of adverse events was generally greater for fesoterodine non-escalators than escalators. At week 12, improvements in micturitions, UUI episodes, and diary-dry rate were comparable for fesoterodine escalators and non-escalators, whereas improvement in urgency episodes was significantly greater among non-escalators vs. escalators ($p = 0.002$). At week 12, the rates of the most common adverse events (dry mouth, constipation, headache) were similar for fesoterodine escalators and non-escalators (Table 1).

Overall, flexible-dose fesoterodine improved key OAB symptoms and patient-reported outcomes and was generally well tolerated. The decision to escalate to fesoterodine 8 mg appeared to be determined by the efficacy and tolerability responses, with fesoterodine escalators demonstrating a lower sensitivity (less efficacy and fewer adverse events) before their decision to dose escalate.

ClinicalTrials.gov ID: NCT00911937

This 12-week, double-blind, placebo-controlled, multicenter study evaluated the effects of flexible-dose fesoterodine in subjects with self-reported OAB symptoms for ≥ 3 months, including ≥ 8 micturitions, ≥ 3 urgency episodes and ≥ 2 but ≤ 8 nocturnal urgency episodes per 24 h (19). Eligible subjects were randomised to fesoterodine 4 mg or placebo once daily within 4 h of bedtime for 4 weeks. At week 4, the fesoterodine dose could be increased to 8 mg once daily, based on patient treatment response and tolerability (sham dose escalation for placebo). After week 4, no further dose adjustments were permitted. Of 937 subjects (fesoterodine, $n = 463$; placebo, $n = 474$) who took ≥ 1 dose of study medication, 781 completed the study. At week 4, 61% of subjects treated with fesoterodine and 67% of those treated with placebo chose dose escalation.

At week 12, fesoterodine significantly decreased nocturnal urgency episodes ($p = 0.003$; primary end-point), micturitions ($p = 0.001$), nocturnal micturitions ($p = 0.011$) and urgency episodes ($p < 0.001$) per 24 h vs. placebo; the decrease in UUI episodes with fesoterodine was not significant vs. placebo at week 12 (Table 1). Fesoterodine also significantly improved all OAB-q scale and domain scores vs. placebo at week 12 (all $p < 0.05$). Dry mouth, constipation and headache were the most common adverse events in each treatment group (Table 1).

The results of this study indicated that flexible doses of fesoterodine were well tolerated and significantly decreased nocturnal urgency episodes and nocturnal micturitions vs. placebo in subjects with OAB symptoms, including nocturnal urgency.

ClinicalTrials.gov ID: NCT00798434

In the 24-week, multicenter, SOFIA (Study of Fesoterodine In an Aged population) trial, which consisted of a 12-week, randomised, double-blind, placebo-controlled, flexible-dose phase (20) followed by a 12-week, open-label phase (21) (see Open-label trials section below), fesoterodine was evaluated in elderly (aged ≥ 65 years) subjects with OAB symptoms. During the double-blind phase (20), subjects were randomised to fesoterodine 4 mg or placebo once daily. At weeks 4 and 8, subjects could increase the fesoterodine dose to 8 mg based on treatment response and tolerability; subjects who increased the dose at week 4 could decrease at week 8 (sham dose increase/decrease for placebo). During double-blind treatment, 392 subjects received fesoterodine and 393 received placebo, with 52% and 66%, respectively, opting for dose escalation at week 4 (Table 1). At week 8, 16% and 9% of subjects in the fesoterodine and placebo groups, respectively, opted for dose escalation, and 4% and 3% de-escalated.

At week 12, fesoterodine significantly decreased urgency episodes (primary end-point), micturitions and night-time micturitions per 24 h compared with placebo (all $p < 0.01$; Table 1); among subjects with ≥ 1 UUI episode at baseline (46% of subjects), the decrease in UUI episodes was not significant vs. placebo at week 12. Treatment with fesoterodine also significantly improved all OAB-q scale and domain scores compared with placebo at week 12 (all $p < 0.05$). No clinically meaningful change from baseline was observed in the Mini-Mental State Examination (MMSE) score, a test for cognitive impairment, in either treatment group after 12 weeks

of double-blind treatment. Dry mouth and constipation were the most common adverse events for subjects treated with fesoterodine (Table 1).

Flexible doses of fesoterodine significantly decreased key OAB symptoms, improved HRQL and were well tolerated in elderly subjects with OAB. No new safety concerns were observed with flexible-dose fesoterodine treatment in this elderly population.

ClinicalTrials.gov ID: NCT00928070

A 12-week, randomised, double-blind, placebo-controlled, flexible-dose, multicenter trial was conducted in vulnerable elderly subjects (22), defined as those aged ≥ 65 years with a score of ≥ 3 on the 13-item Vulnerable Elders Survey (VES-13) (24). The VES-13 is a validated measure on which individuals self-rate their health, limitations in physical function and functional disabilities. Subjects with VES-13 scores ≥ 3 have a fourfold greater risk of death or functional decline over a 2-year period compared with subjects with scores < 3 (23). Eligible subjects had self-reported OAB symptoms for ≥ 3 months before screening, including ≥ 2 and ≤ 15 UUI episodes and ≥ 8 micturitions per 24 h. Subjects with moderate to very severe cognitive impairment (an MMSE score < 20 (24)) were excluded. Subjects were randomised to fesoterodine 4 mg or placebo once daily for the first 4 weeks, after which, in consultation with the investigator, the fesoterodine dose could be increased to 8 mg for the remaining 8 weeks (sham dose escalation for placebo). During the last 8 weeks of the study, the fesoterodine dose could be decreased to 4 mg at any time.

Of the 562 subjects (fesoterodine, $n = 281$; placebo = 281; mean age, 75 years) who received ≥ 1 dose of study medication, most (fesoterodine, 53%; placebo, 64%) opted to increase their dose at week 4. At week 12, 45% of subjects receiving fesoterodine and 57% of those receiving placebo remained on the higher dose. At 12 weeks of treatment, the decreases from baseline in the mean number of UUI episodes (primary end-point), micturitions and urgency episodes per 24 h were significantly greater with fesoterodine vs. placebo (Table 1). Improvements from baseline to week 12 in scores on the OAB-q Symptom Bother and total HRQL scales and the Concern and Coping domains were significantly greater with fesoterodine than placebo (all $p \leq 0.02$). Dry mouth and constipation were the most common adverse events, with most cases mild or moderate in nature. At week 12, no significant change from baseline was demonstrated in cognitive function, as assessed with the MMSE.

These results indicated that a flexible-dose fesoterodine regimen significantly improved UUI episodes, other OAB symptoms and HRQL compared with placebo and was generally well tolerated in vulnerable elderly subjects with OAB. No new safety concerns were identified in this vulnerable elderly population.

Open-label trials

ClinicalTrials.gov ID: NCT00425100

In a 12-week, open-label, multicenter study, the effects of flexible-dose fesoterodine were investigated in subjects aged ≥ 18 years who were at least somewhat dissatisfied with tolterodine immediate release or tolterodine extended release treatment within the previous 2 years (25). Eligible subjects reported OAB symptoms for ≥ 3 months, including ≥ 3 urgency episodes and ≥ 8 micturitions per 24 h at baseline and at least moderate bladder problems on the Patient Perception of Bladder Condition (PPBC). After a 2-week washout period, subjects received fesoterodine 4 mg once daily for 4 weeks. At the end of week 4, based on subjective assessment of efficacy and tolerability by the subject and the investigator, subjects could remain on fesoterodine 4 mg or increase the dose to 8 mg. At week 4, approximately 50% of 516 treated subjects opted for dose escalation to fesoterodine 8 mg.

At week 12, significant decreases from baseline were demonstrated in the primary end-points (i.e. UUI episodes, micturitions and urgency episodes per 24 h; all $p < 0.0001$ vs. baseline; Table 2). The percentage of subjects who reported satisfaction with fesoterodine treatment on the single-item OAB Satisfaction Questionnaire (26) (primary end-point) was 79.8% at week 12. Significant decreases from baseline also were observed in secondary end-points, including nocturnal micturitions and severe urgency episodes per 24 h at week 12 (both $p < 0.0001$). Scores on the two OAB-q scales and all OAB-q HRQL domains showed significant ($p < 0.0001$) and clinically meaningful (≥ 10-point change) improvements by week 12. Dry mouth and constipation were the most commonly reported adverse events (Table 2).

A *post hoc* analysis of data from this study evaluated the efficacy and tolerability of fesoterodine among subjects who chose to increase their fesoterodine dose (escalators) vs. those who remained on fesoterodine 4 mg (non-escalators) (27). The age and gender of subjects at baseline were similar between the 255 escalators and 258 non-escalators in the safety-analysis set. Escalators self-reported significantly ($p < 0.05$) higher mean baseline levels of OAB symptoms (except UUI episodes) and worse OAB symptom bother and HRQL vs. non-escalators. Although significant (all $p < 0.0001$) improvements compared with baseline were demonstrated in all bladder diary variables at

week 4 (before dose-escalation decision) for both subsequent escalators and non-escalators, mean improvements in these end-points (except UUI episodes) and the diary-dry rate were significantly (all $p < 0.05$) greater for non-escalators vs. escalators at week 4 (Table 2).

At week 12, significant improvements vs. baseline were again observed for all bladder diary variables among escalators and non-escalators, but no significant differences were demonstrated between the mean improvements in bladder diary variables (except urgency episodes) and the diary-dry rate for escalators vs. non-escalators. Improvements from baseline at week 12 in scores for the OAB-q Symptom Bother scale and the Coping, Sleep and Social Interaction domains were similar for escalators and non-escalators, whereas OAB-q total HRQL and Concern domain scores were significantly better in non-escalators vs. escalators (all $p < 0.05$). Furthermore, no significant difference was seen between escalators and non-escalators in the percentage of subjects reporting satisfaction with fesoterodine treatment at week 12 (escalators, 78%; non-escalators, 82%). The most common adverse events in both escalators and non-escalators during the study were dry mouth and constipation (Table 2). The rate of study discontinuation was 14% for non-escalators vs. 7% for escalators; no escalator discontinued because of lack of efficacy.

These results indicated that treatment with flexible-dose fesoterodine significantly improved OAB symptoms, patient-reported HRQL, and treatment satisfaction and was well tolerated in subjects who were dissatisfied with previous treatment with tolterodine. Subjects who chose dose escalation at week 4 achieved additional OAB symptom improvement after dose escalation. At week 12, OAB symptom improvement and the incidence of adverse events were similar among escalators and non-escalators.

ClinicalTrials.gov ID: NCT00806494

The 12-week, open-label SAFINA (Study Assessing Flexible-dose fesoterodine IN Adults) study was conducted to determine the efficacy and safety of flexible doses of fesoterodine in subjects with OAB treated in the United Kingdom healthcare system (28). After 12 weeks of flexible-dose treatment with fesoterodine, a 4-week period of no treatment was conducted to assess changes in efficacy outcomes after drug cessation (30). Eligible subjects were aged ≥ 18 years and had self-reported OAB symptoms for ≥ 3 months, including ≥ 8 micturitions and ≥ 3 urgency episodes per 24 h, and reported at least some moderate problems on the PPBC. Subjects were treated with fesoterodine 4 mg once daily for the first 4 weeks, after which they could opt to increase the dose to 8 mg after consultation with the investigator. No further dose adjustments were permitted after week 4.

Of the 331 subjects who were treated with fesoterodine, 195 (59%) increased the fesoterodine dose from 4 mg to 8 mg at week 4 (28). The most common reason for escalating the fesoterodine dose was an insufficient treatment response (93%). At week 12, clinically meaningful improvements from baseline were observed in micturitions (mean [95% CI]: −3.3 [−3.6, −2.9]; primary end-point), urgency episodes (−5.1 [−5.6, −4.6]) and UUI episodes (−1.6 [−2.0, −1.3]) per 24 h with flexible-dose fesoterodine (Table 2). OAB-q Symptom Bother scale scores were improved from baseline and most subjects reported satisfaction (77%), much benefit (57%) and a willingness to continue (75%) with fesoterodine treatment at week 12. The most common adverse events were dry mouth (30%), constipation (9%) and diarrhoea (9%). At week 16, 4 weeks after treatment cessation, the frequency of OAB symptoms increased and patient-reported outcomes deteriorated to week 4 values or worse (29).

A prespecified stepwise logistic regression analysis conducted to evaluate factors associated with fesoterodine dose escalation at week 4 indicated that smaller improvement in micturitions and poorer response on the PPBC were significantly associated with dose escalation (28). At week 12, improvements in most outcomes were similar in escalators and non-escalators.

Flexible doses of fesoterodine in a clinical practice setting in the United Kingdom were efficacious and well tolerated, with most subjects reporting satisfaction and a willingness to continue fesoterodine treatment. Subjects who escalated the fesoterodine dose at week 4 had a poorer clinical response at week 4 than subjects who did not escalate. However, at week 12, improvements in efficacy outcomes were comparable between dose escalators and non-escalators. OAB symptoms and HRQL deteriorated after 4 weeks of treatment cessation; subjects reporting the greatest perceived treatment benefit after 12 weeks of treatment with fesoterodine had the greatest deterioration.

ClinicalTrials.gov ID: NCT00798434

To assess the long-term efficacy and safety of flexible-dose fesoterodine in elderly subjects with OAB, subjects who completed the 12-week, randomised, double-blind, placebo-controlled phase of the SOFIA trial (20) were eligible for a 12-week, open-label, extension phase (21). During the open-label phase of the trial, all subjects received treatment with fesoterodine. Subjects who received fesoterodine during the double-blind treatment phase maintained their dose (4 or 8 mg) during the open-label phase. Subjects

Table 2 Open-label trials of flexible-dose fesoterodine*

Reference (NCT ID)	No. treated (Treatment duration)	Treatment regimen (Once daily)	Key eligibility criteria	Dose escalation	Key efficacy results	Key safety results	Key *post hoc* results (Escalators vs. non-escalators)
Wyndaele et al. (25) Wyndaele et al. (27) (NCT00425100)	516 subjects received ≥ 1 dose of fesoterodine (12 weeks)	Fesoterodine 4 mg Fesoterodine 8 mg Subjects started on fesoterodine 4 mg; at week 4, could increase dose to 8 mg for remaining 8 weeks	Men and women aged ≥ 18 years with OAB symptoms for ≥ 3 months, ≥ 8 micturitions and ≥ 3 urgency episodes/24 h, and at least some moderate bladder-related problems on the PPBC; previously treated with tolterodine for OAB within 2 years of screening and reported somewhat or very dissatisfied with tolterodine	*At week 4:* 50% of subjects opted for dose escalation to fesoterodine 8 mg	*At week 12:* Fesoterodine significantly decreased UUI episodes, micturitions and urgency episodes/24 h from baseline; 80% reported satisfaction with fesoterodine treatment (1° end-points) Fesoterodine significantly improved scores for all OAB-q scales and domains vs. baseline, with all scores exceeding minimally important difference (≥ 10-point change)	Fesoterodine was well tolerated; most common AEs were dry mouth (23%) and constipation (5%), with most of these AEs mild or moderate	*At baseline:* Subsequent escalators had significantly worse values for all diary variables (except UUI episodes) and worse OAB-q scores than non-escalators *At week 4:* Improvements in all diary variables were significantly greater and the diary-dry rate was significantly higher (62% vs. 42%) in subsequent non-escalators vs. escalators *At week 12:* Improvements in all diary variables were comparable and the diary-dry rate was similar (67% vs. 60%) in non-escalators and escalators, respectively OAB-q Symptom Bother scale and Coping, Sleep and Social Interaction domain scores were similar for escalators and non-escalators; total HRQL and Concern domain scores were significantly better in non-escalators vs. escalators The most common AEs were dry mouth (escalators, 24%;

Table 2 Continued

Reference (NCT ID)	No. treated (Treatment duration)	Treatment regimen (Once daily)	Key eligibility criteria	Dose escalation	Key efficacy results	Key safety results	Key *post hoc* results (Escalators vs. non-escalators)
							non-escalators, 23%) and constipation (escalators, 5%; non-escalators, 5%)
Cardozo et al. (28) Khullar et al. (29) (NCT00806494)	331 subjects received ≥ 1 dose of fesoterodine (12 weeks)	Fesoterodine 4 mg Fesoterodine 8 mg Subjects started on fesoterodine 4 mg; at week 4, could increase dose to 8 mg for remaining 8 weeks	Men and women aged ≥ 18 years with OAB symptoms for ≥ 3 months, ≥ 8 micturitions and ≥ 3 urgency episodes per 24 h and at least some moderate bladder-related problems on the PPBC	*At week 4:* 59% of subjects opted for dose escalation to fesoterodine 8 mg; 93% of escalators reported insufficient clinical response as reason for dose escalation			*At week 4*: Generally less improvement in OAB symptoms and OAB-q Symptom Bother score in escalators than non-escalators. *At week 12:* Improvements in OAB symptoms and OAB-q Symptom Bother score were similar in escalators and non-escalators
Wagg et al. (21) (NCT00798434)	654 subjects from DB phase (DB fesoterodine, 313; DB PBO, 341) received ≥ 1 dose of open-label fesoterodine (12 weeks open-label after 12 weeks DB)	DB fesoterodine: maintained dose (4 mg or 8 mg) during the open-label phase DB PBO: started on fesoterodine 4 mg with option to increase to 8 mg at week 16 or 20 During 24-week SOFIA trial, only 1 dose increase and 1 dose decrease were allowed	Men and women aged ≥ 65 years with OAB symptoms for ≥ 3 months, ≥ 8 micturitions and ≥ 3 urgency episodes/ 24 h, at least some moderate bladder-related problems on PPBC, and MMSE score ≥ 20	*At week 20 (week 8 of open-label phase),* 53% of subjects treated with DB fesoterodine and 51% of subjects treated with DB PBO were receiving fesoterodine 8 mg	*At week 24 (week 12 of open-label phase):* OAB symptoms and HRQL improvements were maintained in subjects who had received DB fesoterodine; efficacy outcome improvements in DB PBO subjects were similar to active-treatment group at week 12 of DB phase	Most common AEs during open-label phase were dry mouth (DB fesoterodine, 7%; DB PBO, 28%) and constipation (DB fesoterodine, 2%; DB PBO, 6%)	NA

*Includes prespecified trial data and any *post hoc* analyses of trial data. AE, adverse event; DB, double-blind; HRQL, health-related quality of life; MMSE, Mini-Mental State Examination; OAB, overactive bladder; OAB-q, Overactive Bladder Questionnaire; PBO, placebo; PPBC, Patient Perception of Bladder Condition; UUI, urgency urinary incontinence.

who received placebo during the double-blind phase were started on fesoterodine 4 mg with an option to increase to 8 mg at week 16 or week 20. Throughout the 24-week SOFIA trial, subjects were allowed only 1 dose increase and 1 dose decrease. At week 20 of open-label treatment, 53% of subjects who were treated with fesoterodine in the double-blind phase and 51% of subjects who were treated with placebo in the double-blind phase chose to increase or maintain their fesoterodine dose at 8 mg for the remainder of the study; 89% of subjects completed the open-label phase of the study.

During the 12 weeks of open-label treatment, improvements in OAB symptoms and HRQL were maintained in elderly subjects who had received fesoterodine during the previous double-blind phase (Table 2). The improvements in efficacy outcomes observed during 12 weeks of open-label fesoterodine treatment in elderly subjects who had received placebo during the double-blind phase were similar to those demonstrated by the active-treatment group at week 12 of double-blind treatment. Dry mouth and constipation were the most common adverse events during open-label treatment with fesoterodine (Table 2). These results indicated that long-term treatment with flexible-dose fesoterodine is an effective and well-tolerated approach to the management of OAB symptoms in elderly individuals.

Discussion

The evidence from this systematic review of clinical trials of flexible-dose fesoterodine provides valuable insights on the benefit of dose escalation for individual subjects with OAB symptoms. In flexible-dose trials of fesoterodine, 51% to 63% of subjects initially receiving fesoterodine 4 mg opted for dose escalation to fesoterodine 8 mg. Overall, subjects who subsequently opted for dose escalation from fesoterodine 4 mg to 8 mg generally reported significantly more severe OAB symptoms and greater OAB symptom bother and worse HRQL at baseline (i.e. before starting treatment with fesoterodine 4 mg) than subjects who opted to remain on the 4-mg dose (18,27). Subjects who opted for dose escalation also demonstrated less evidence of a treatment benefit with fesoterodine 4 mg before the opportunity to increase their dose than subjects who opted not to dose escalate (18,27,28). Subjects who opted to maintain the 4-mg dose generally had a higher incidence of adverse events, particularly dry mouth and constipation, during treatment with fesoterodine 4 mg (i.e. before the dose escalation decision point) than subjects who escalated to fesoterodine 8 mg (18,27,28). However, by the end of these flexible-dose trials (i.e. 8–11 weeks after the dose-escalation decision), the efficacy and tolerability profiles were similar in escalators and non-escalators (18,27,28).

Collectively, the data from these flexible-dose studies confirm the results of fixed-dose studies and provide strong evidence that fesoterodine provides treatment benefit to individual subjects with OAB because of its true dose–response effect. In fixed-dose studies, in which subjects are randomised to either fesoterodine 4 mg or 8 mg, subjects receiving the higher dose show greater improvement in efficacy outcomes and a higher incidence of adverse events. In flexible-dose studies, which better reflect the use of fesoterodine in clinical practice, subjects who opt to receive fesoterodine 4 mg or fesoterodine 8 mg generally show similar improvements in efficacy and safety outcomes by study end. The finding that dose escalators have more severe baseline symptoms, together with smaller improvements in efficacy outcomes and fewer adverse events during treatment with fesoterodine 4 mg, suggests a need for more effective treatment. This is supported by the results of the SAFINA study, in which the predominant reason for escalating to fesoterodine 8 mg was an insufficient clinical response (28). Therefore, unless intolerability is demonstrated with fesoterodine 4 mg, it can be worthwhile to escalate the fesoterodine dose to 8 mg in individual subjects to obtain an additional efficacy benefit without a marked increase in adverse events.

These findings from clinical trials of flexible-dose fesoterodine are consistent with the idea that the dose–response curve differs between individual subjects (30). Subjects with high drug sensitivity may experience sufficient efficacy on a lower dose of drug but experience unacceptable tolerability on a higher dose. In contrast, subjects with low drug sensitivity may experience insufficient efficacy on a lower dose but experience increased benefit with acceptable tolerability on a higher dose. As a result, adverse event rates reported in fixed-dose studies should not be interpreted as indicative of adverse event rates with flexible-dose regimens.

In clinical practice, each patient's perspective on the goals of treatment with respect to OAB symptom relief and tolerable adverse events should be discussed and considered when making treatment decisions. Patient–clinician discussions of treatment expectations are an important component in the optimal management of OAB symptoms. This approach, together with the evidence supporting the dose–response effect of fesoterodine in the treatment of OAB symptoms, provides clinicians with valuable information for achieving the optimal balance between efficacy and tolerability with a flexible-dose regimen in individual patients, including elderly patients.

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