Fesoterodine for Overactive Bladder: A Review of the Literature

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ABSTRACT

BACKGROUND: Overactive bladder (OAB) is a chronic condition affecting both men and women, with prevalence increasing with age. Antimuscarinics form the cornerstone of treatment of OAB. Fesoterodine, a nonselective muscarinic-receptor antagonist, was approved by the US Food and Drug Administration in late 2008 for once daily, oral administration in the treatment of OAB to relieve the symptoms of urinary urge incontinence, urgency, and frequency.

OBJECTIVE: The aim of this review was to provide an overview of the mechanism of action of and clinical trial data for fesoterodine, and to discuss the present status of fesoterodine in the management of OAB.

METHODS: The MEDLINE and Google Scholar databases were searched (June 1, 1999–December 1, 2009) using the terms fesoterodine, overactive bladder, and muscarinic antagonists. Full-text articles in English were selected for reference, and articles presenting the mechanism of action, pharmacokinetics, and data from clinical trials were included. The parameters measured were tolerability, efficacy, and health-related quality of life (HRQoL). Trials involving animals and Phase I studies were excluded.

RESULTS: The initial literature search yielded 48 papers. A total of 20 articles fulfilled the inclusion criteria. In two 12-week, randomized, multicenter, Phase III clinical trials involving patients with increased micturition frequency and urgency and/or urinary urge incontinence (n = 836 and 1132 in each trial), both fesoterodine 4 and 8 mg were associated with significantly improved symptoms of OAB (frequency of micturition, urgency, and urge incontinence) compared with placebo (P < 0.05).

In a post hoc analysis of pooled data of the Phase III trials, HRQoL improved significantly with both doses. In a 12-week, Phase IIIb trial, fesoterodine 4 and 8 mg led to treatment satisfaction in ~80% of patients (of 516 enrolled) who were initially unsatisfied with their previous treatment.


KEY WORDS: overactive bladder, fesoterodine, muscarinic antagonists.
INTRODUCTION

Overactive bladder (OAB) has been defined by the Standardisation Sub-Committee of the International Continence Society as urgency, with or without urge incontinence, usually with frequency and nocturia. OAB is a highly prevalent symptom complex. In a population-based survey of 16,776 men and women aged ≥40 years conducted by Milsom et al in 6 countries, by telephone or direct interview, the prevalence of OAB in Europe was estimated to be 15.6% in men and 17.4% in women, with an overall prevalence of 16.6%. In a survey of 11,740 Americans, overall prevalence of OAB was 16.0% in men and 16.9% in women. The symptoms and reduced quality of life (QoL) associated with OAB cause distress in many patients. OAB is a chronic condition occurring in both men and women, with a prevalence that increases with advancing age. The pathophysiology of OAB is complex. It is primarily caused by detrusor overactivity, defined as involuntary contractions of the detrusor muscle during the bladder filling phase as a result of continuous and increasing afferent activity from the bladder. During normal function, the bladder should be relaxed as urine fills it. The cause of OAB is unknown; however, 3 main theories of detrusor overactivity have been proposed. The myogenic theory suggests that partial denervation of the detrusor results in alterations in the properties of the detrusor muscle cells leading to increased excitability and, therefore, producing increases in involuntary pressure. The neurogenic theory suggests that damage to central inhibitory pathways can unmask primitive voiding reflexes that trigger detrusor overactivity. A third theory, the autonomic bladder hypothesis, was proposed in 2004. It suggests that detrusor overactivity is a consequence of inappropriate activation or modulation of phasic activity.

OAB is not purely a bladder condition, but may also involve pelvic floor—muscle dysfunction and behavioral issues. No drug can ever correct all facets of this multifactorial disorder. In almost all OAB groups, no curative treatment can be offered. The principles of treatment are to increase voided volume, decrease urgency, and reduce urinary urge incontinence (UUI) episodes. Current treatments include lifestyle interventions, bladder training and pelvic floor exercises, pharmacotherapy, and surgery.

Acetylcholine released from cholinergic nerves stimulates muscarinic receptors and mediates the main part of the voiding contraction in humans. There are 5 different subtypes of muscarinic receptors (M1–M5). They are all widely distributed throughout the body. In the human bladder, the M2 and M3 receptors can be found, with the ratio being 3:1, respectively. Despite the predominance of M2 receptors, several investigators have found that the pharmacologically defined M3 receptors mediate bladder contraction. The complexity of the muscarinic regulation of bladder function makes the relative importance of the different muscarinic-receptor subtypes difficult to assess.

Antimuscarinic medications, aimed at blocking cholinergic-receptor activity in the bladder, are the primary pharmacotherapeutic options for OAB. Currently, a variety of antimuscarinics are used for the management of OAB: oxybutynin, tolterodine, propiverine, solifenacin, darifenacin, and trospium chloride. However, antimuscarinics are associated with adverse effects (AEs) (eg, constipation, dry mouth, blurred vision, drowsiness) that impact both compliance and persistence with long-term treatment. None of the currently available medications are ideal in terms of efficacy and tolerability.
Fesoterodine is a novel, competitive, muscarinic-receptor antagonist that has recently been approved for the treatment of OAB as a prolonged-release tablet.\textsuperscript{12}

The aim of this review was to provide an overview of the clinical trial data for fesoterodine and its present status in the management of OAB.

\textbf{METHODS}

A search of the literature was performed using the MEDLINE and Google Scholar databases with the terms \textit{fesoterodine}, \textit{overactive bladder}, and \textit{muscarinic antagonists}. The literature research was limited to English-language clinical trials, meta-analyses, randomized controlled trials (RCTs), reviews, and conference abstracts published from June 1, 1999 to December 1, 2009. Articles were required to present the mechanism of action, pharmacokinetics, and data from clinical trials. The parameters measured were tolerability, efficacy, and health-related QoL (HRQoL). Trials involving animals and Phase I studies were excluded.

\textbf{RESULTS}

\textbf{Search Results}

The initial literature search yielded 48 papers. A total of 20 articles fulfilling the inclusion criteria were selected. These included 4 each of Phase II, III, and IIIb RCTs, 3 post hoc analyses, and 3 clinical trials. In addition to the full articles, the relevant references of the selected articles were obtained.

\textbf{Mechanism of Action}

Fesoterodine is a competitive, specific, and nonselective muscarinic-receptor antagonist. By preventing the binding of acetylcholine to these receptors, it reduces smooth-muscle tone in the bladder, allowing the bladder to retain larger volumes of urine and reducing the number of incontinence episodes.\textsuperscript{13}

\textbf{Chemistry}

Fesoterodine is isobutyric acid 2-((R)-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl) phenyl ester hydrogen fumarate. The empirical formula is $C_{30}H_{41}NO_{7}$. The structural formula is shown in the figure.\textsuperscript{14}

\textbf{Pharmacokinetics}

After oral administration, fesoterodine is well absorbed. It acts as a prodrug. It undergoes rapid and extensive hydrolysis by nonspecific plasma esterases to form its active metabolite, 5-hydroxymethyl tolterodine (5-HMT), which is responsible for its antimuscarinic activity.\textsuperscript{15} 5-HMT is also the active metabolite of tolterodine, but the metabolism is mediated by cytochrome P450 (CYP) 2D6 in liver. Due to rapid conversion, fesoterodine cannot be detected in blood. Bioavailability of the active metabolite is 52%. After single or multiple oral daily doses from 4 to 28 mg, 5-HMT exhibits linear, dose-proportional pharmacokinetics. The $T_{\text{max}}$ of 5-HMT is $\sim$5 hours. No accumulation occurs after multiple-dose administration.
Food does not appear to have a clinically relevant effect on the pharmacokinetics of fesoterodine. 5-HMT has low plasma protein binding (~50%). The mean steady-state volume of distribution after intravenous infusion of 5-HMT is 169 L. 5-HMT is further metabolized in the liver via 2 major pathways involving CYP2D6 and CYP3A4. None of the metabolites contribute significantly to the antimuscarinic activity of fesoterodine. Metabolism via CYP2D6 varies in different individuals. The majority of the population are referred to as extensive metabolizers while a subset of individuals (~7% of whites and ~2% blacks) are considered poor metabolizers. The $C_{\text{max}}$ and AUC of 5-HMT are increased 1.7 and 2.0 times, respectively, in poor metabolizers of CYP2D6 compared with extensive metabolizers. However, mean $T_{\text{max}}$ and $t_{1/2}$ of 5-HMT do not differ with regard to CYP2D6 metabolizer status. Similarly, the extent of systemic accumulation at steady state is similar in extensive and poor metabolizers. The elimination of 5-HMT depends on hepatic metabolism and renal excretion. After oral administration of fesoterodine, ~70% of the administered dose is excreted in urine as metabolites and a smaller amount (~7%) is recovered in the feces. The $t_{1/2}$ of 5-HMT following oral administration is ~7 hours and is ~4 hours following intravenous infusion.

No apparent difference has been observed in the pharmacokinetics of fesoterodine between healthy white or black subjects. The pharmacokinetics of fesoterodine are not significantly influenced by age and gender and no dose adjustment is required. The pharmacokinetics of fesoterodine have not been evaluated in pediatric patients.

In patients with mild or moderate renal insufficiency (creatinine clearance [CrCl] of 30–80 mL/min), $C_{\text{max}}$ of 5-HMT is increased up to 1.5 times compared with healthy subjects. In patients with severe insufficiency (CrCl < 30 mL/min), $C_{\text{max}}$ is increased 2 times compared with healthy volunteers. No dose adjustment is recommended in patients with mild or moderate renal insufficiency. Therefore, a dose of fesoterodine, up to 8 mg once daily, may be administered. However, in patients with severe renal insufficiency, the recommended dose of 4 mg once daily should not be exceeded. In patients with moderate (Child-Pugh B) hepatic impairment, $C_{\text{max}}$ and
AUC of the 5-HMT are increased 1.4- and 2.1-fold, respectively, compared with healthy subjects. No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Fesoterodine has not been studied and is, therefore, not recommended in patients with severe hepatic impairment (Child-Pugh C).18

Drug Interactions
To assess drug–drug interactions of fesoterodine, a CYP3A4 inhibitor (ketoconazole), inducer (rifampicin), and substrates (ethinyl estradiol and levonorgestrel) were administered.19 Concomitant administration of ketoconazole 200 mg twice daily with fesoterodine 8 mg once daily resulted in a 2.0- and 2.3-fold increase in the Cmax and AUC of 5-HMT in CYP2D6 extensive and poor metabolizers, respectively. Therefore, the maximum dose of fesoterodine should be restricted to 4 mg when used concomitantly with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, and clarithromycin. The effects of weak or moderate CYP3A4 inhibitors have not been evaluated in any study.14 Following concomitant administration of rifampicin 600 mg once a day, Cmax and AUC of 5-HMT decreased by ~70% and ~75%, respectively, after oral administration of fesoterodine 8 mg.18 Concomitant administration of CYP3A4 inducers may lead to subtherapeutic plasma levels. In the presence of fesoterodine, there are no changes in the plasma concentrations of combined oral contraceptives containing ethinyl estradiol and levonorgestrel.

Concomitant administration of fesoterodine with other antimuscarinics and other drugs with anticholinergic properties (e.g., amantadine, tricyclic antidepressants) may aggravate AEs such as constipation, dry mouth, drowsiness, and urinary retention. Therefore, caution must be exercised while administering antimuscarinics to patients already receiving fesoterodine.18

Fesoterodine Clinical Trial Data
Clinical Efficacy
In a Phase II, multicenter, double-blind, randomized, placebo-controlled trial by Nitti et al,20 the efficacy, tolerability, and dose-response relationship of sustained-release fesoterodine were studied in patients with OAB (Table I). After a 1-week placebo run-in, 173 patients with ≥8 micturitions/24 hours and ≥2 UUI episodes/week during the run-in period were randomized to receive fesoterodine 4, 8, or 12 mg, or placebo once daily for 8 weeks (44, 47, 39, and 43 patients, respectively). The primary efficacy end point was the number of micturitions per 24 hours. The secondary efficacy end points were UUI episodes per week and mean volume voided (MVV) per micturition. Dose-response relationship was described by fitting a linear regression function test for a nonzero slope with power of ≥80%. Multiple regression analysis showed statistically significant linear dose-response improvement from baseline and placebo in the primary efficacy variable. Statistically significant improvement was observed with fesoterodine 4, 8, and 12 mg compared with placebo (P < 0.04, P = 0.001, and P < 0.007, respectively). The change from baseline to end of treatment in the MVV per micturition was 27.94, 58.96, and 92.34 mL in the fesoterodine 4-, 8-, and 12-mg groups and 4.53 mL in
Table I. Overview of the Phase III clinical trials of fesoterodine for treatment of overactive bladder (OAB).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Dose/Groups</th>
<th>Patients</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitti et al(^{20})</td>
<td>8-Week, Phase II,</td>
<td>Fesoterodine 4, 8, or 12 mg/d</td>
<td>OAB symptoms—≥8 micturitions/24 h and ≥2 urge incontinence episodes/wk</td>
<td>Primary end point: number of micturitions/24 h. Secondary end points: urge incontinence episodes/wk and MVV/ micturition. Dose-response relationship was described by fitting a linear regression function test for a nonzero slope with power of ≥80%.</td>
</tr>
<tr>
<td></td>
<td>multicenter, double-blind,</td>
<td>and placebo</td>
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<tr>
<td></td>
<td>randomized, placebo-controlled trial</td>
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<tr>
<td>Nitti et al(^{21})</td>
<td>12-Week, Phase III,</td>
<td>Fesoterodine 4 or 8 mg/d</td>
<td>Age ≥18 years; OAB symptoms—≥8 micturitions/24 h and ≥6 urgency episodes or ≥3 UUI episodes/24 h</td>
<td>Primary end point: micturitions/24 h (change from week 0 to week 12), UUI episodes/24 h (change from week 0 to week 12), and treatment response from the benefit scale. Secondary efficacy end points: MVV/micturition, daytime micturitions/24 h, urgency episodes/24 h, and continent days/wk.</td>
</tr>
<tr>
<td></td>
<td>multicenter, double-blind,</td>
<td>and placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>randomized, placebo-controlled trial</td>
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</tr>
<tr>
<td>Chapple et al(^{22})</td>
<td>12-Week, Phase III,</td>
<td>Tolterodine ER 4 mg/d,</td>
<td>Age ≥18 years; OAB symptoms—≥8 micturitions/24 h and ≥6 urgency episodes or ≥3 UUI episodes/24 h</td>
<td>Primary end point: micturitions/24 h (change from week 0 to week 12), UUI episodes/24 h (change from week 0 to week 12), and treatment response from the benefit scale. Secondary efficacy end points: MVV/micturition, daytime micturitions/24 h, urgency episodes/24 h, and continent days/wk.</td>
</tr>
<tr>
<td></td>
<td>multicenter, double-blind,</td>
<td>fesoterodine 4 or 8 mg/d,</td>
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<td></td>
<td>randomized, double-dummy,</td>
<td>and placebo</td>
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<td></td>
<td>placebo- and active-controlled,</td>
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<td></td>
<td>parallel-arm trial</td>
<td></td>
<td></td>
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<tr>
<td>Wyndaele et al(^{25})</td>
<td>12-Week, multicenter,</td>
<td>Fesoterodine 4 mg/d for</td>
<td>Age ≥18 years; OAB symptoms for ≥3 months—mean micturition frequency of ≥8 micturitions/24 h and mean number of urgency episodes ≥3 in a 5-day diary</td>
<td>Primary end point: micturitions/24 h (change from week 0 to week 12), UUI episodes/24 h (change from week 0 to week 12), micturition-related urgency episodes/24 h (change from week 0 to week 12), and percentage of patients reporting treatment satisfaction at week 12. Secondary end points: nocturnal micturitions (change from baseline to week 12), severe micturition-related urgency episodes, and frequency-urgency sum/24 h.</td>
</tr>
<tr>
<td></td>
<td>open-label, single-arm,</td>
<td>4 weeks; dose maintained at 4 mg/d or increased to 8 mg/d for the remaining period</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>flexible-dose study</td>
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</tbody>
</table>

MVV = mean voided volume; UUI = urinary urge incontinence; ER = extended release.
the placebo group. Statistically significant changes in the secondary variables were observed 2 weeks after randomization.

In a Phase III, double-blind, randomized, placebo-controlled, multicenter trial by Nitti et al.,\textsuperscript{21} the efficacy and tolerability of fesoterodine 4 and 8 mg were studied in patients with OAB (Table II). Patients included men or women aged ≥18 years with OAB symptoms for ≥6 months with urinary urgency (≥8 micturitions per 24 hours) and UUI (≥6 episodes during the 3-day diary period) or ≥3 episodes of UUI during the 3-day diary period. After a 2-week placebo run-in period, the eligible patients were equally randomized to 1 of 3 groups: fesoterodine 4 mg once daily (n = 282; females, 76%; mean age [range], 59 [21–85] years), fesoterodine 8 mg once daily (n = 279; females, 78%; mean age [range], 59 [23–91] years), or placebo (n = 271; females, 74%; mean age [range], 59 [24–88] years) for 12 weeks. Subjects completed a 3-day bladder diary before randomization, and at 2, 8, and 12 weeks after initiating treatment, in which the time of each micturition, incontinence episode, and urgency episode was recorded. Primary end points included the change from baseline in the number of micturitions and the mean number of UUI episodes per 24 hours and the treatment response, which was derived from a 4-point treatment benefit scale (1 = greatly improved; 2 = improved; 3 = not changed; and 4 = worsened during treatment). The treatment benefit response was considered “Yes” if the score was 1 or 2; “No” if the score was 3 or 4. Secondary efficacy end points were MVV per micturition, and the number of daytime micturitions, nocturnal micturitions, and urgency episodes per 24 hours, and continent days per week. The mean change from baseline in the number of micturitions per 24 hours was statistically significant with fesoterodine 8 mg (−2.09; \( P < 0.001 \)) and fesoterodine 4 mg (−1.61; \( P = 0.032 \)) compared with that of placebo. The mean change from baseline in the number of UUI episodes associated with fesoterodine 8 mg was −2.28 (\( P < 0.001 \) vs placebo) and −1.65 (\( P = 0.003 \) vs placebo) with fesoterodine 4 mg. Patient-reported treatment-response rates with fesoterodine 8 mg (74%; \( P < 0.001 \)) and fesoterodine 4 mg (64%; \( P < 0.001 \)) were statistically significantly higher compared with placebo (45%) at study end. With respect to secondary end points, there was a statistically significant increase in MVV per micturition with fesoterodine 8 mg (mean [SD], 33.6 [4.0] mL; \( P < 0.001 \)) and no significant change with fesoterodine 4 mg (16.5 [4.0] mL) compared with placebo (8.38 [4.1] mL). There was a statistically significant decrease in the number of daytime micturitions associated with fesoterodine 8 mg (−1.54; \( P < 0.001 \) vs placebo) and no significant change with fesoterodine 4 mg (−1.04). There was a statistically significant decrease in the number of nocturnal micturitions associated with fesoterodine 8 mg (−0.58; \( P = 0.013 \) vs placebo) but no statistical difference with fesoterodine 8 mg (−25.0). Both fesoterodine doses led to a statistically significant decrease in the mean number of urgency episodes (8 mg, −2.30 and 4 mg, −1.91; both, \( P < 0.001 \) vs placebo). There was a statistically significant mean change in the number of continent days per week both with 8 and 4 mg fesoterodine (2.80 and 2.33 days) compared with placebo (1.31 days; both, \( P < 0.001 \)).

In a Phase III, multicenter, randomized, 12-week, double-blind, placebo- and active-controlled trial by Chapple et al.,\textsuperscript{22} the efficacy, tolerability, and safety profile
Table II. Results of the clinical trials of fesoterodine. Data are the least squares mean (SE) change from baseline, unless otherwise indicated.

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Primary End Points</th>
<th></th>
<th>Secondary End Points</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Micturitions per 24 Hours</td>
<td>Treatment Response, Yes, %</td>
<td>No.</td>
<td>Micturitions per 24 Hours</td>
</tr>
<tr>
<td>Chapple et al 22</td>
<td>Fesoterodine 4 mg</td>
<td>-1.76 (0.17)</td>
<td>75</td>
<td>-1.95 (0.17)</td>
<td>27.72 (3.41)</td>
</tr>
<tr>
<td></td>
<td>Fesoterodine 8 mg</td>
<td>-1.88 (0.16)</td>
<td>79</td>
<td>-2.22 (0.16)</td>
<td>33.62 (3.35)</td>
</tr>
<tr>
<td></td>
<td>Tolterodine 4 mg</td>
<td>-1.73 (0.16)</td>
<td>72</td>
<td>-1.74 (0.16)</td>
<td>23.64 (3.31)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>-0.95 (0.16)</td>
<td>53</td>
<td>-1.14 (0.16)</td>
<td>9.37 (3.33)</td>
</tr>
<tr>
<td>Nitti et al 21</td>
<td>Fesoterodine 4 mg</td>
<td>-1.61 (0.18)</td>
<td>64</td>
<td>-1.65 (0.16)</td>
<td>16.5 (4.00)</td>
</tr>
<tr>
<td></td>
<td>Fesoterodine 8 mg</td>
<td>-2.09 (0.18)</td>
<td>74</td>
<td>-2.28 (0.16)</td>
<td>33.6 (4.04)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>-1.08 (0.18)</td>
<td>45</td>
<td>-0.96 (0.17)</td>
<td>8.38 (4.06)</td>
</tr>
</tbody>
</table>

UUI = urinary urge incontinence; MVV = mean voided volume.
of fesoterodine were assessed in patients (N = 1132) with OAB (Table II). Patients aged ≥18 years with ≥8 micturitions per 24 hours and either ≥6 urgency episodes or ≥3 UUI episodes per 24 hours were included in the study. After a 2-week placebo run-in period, the eligible patients were equally randomized to 1 of 4 groups: fesoterodine 4 mg once daily (n = 272; female, 81%; mean [SD] age, 57.1 [13.2] years), fesoterodine 8 mg once daily (n = 287; female, 82%; mean [SD] age, 55.6 [14.1] years), tolterodine extended release (ER) 4 mg once daily (n = 290; female, 78%; mean [SD] age, 57.7 [14.6] years) and placebo (n = 283; female, 81%; mean [SD] age, 56.0 [13.7] years) for 12 weeks. The primary efficacy end points were change from baseline to week 12 in micturitions per 24 hours, in UUI episodes per 24 hours, and treatment response (which was identical to the primary efficacy end point of Nitti et al21). Secondary efficacy end points included MVV per micturition, daytime micturitions per 24 hours, nocturnal micturitions per 24 hours, urgency episodes per 24 hours, and continent days per week (calculated based on a 3-day diary). At the end of treatment, there was a statistically significant reduction in the least squares mean change in number of micturitions per 24 hours from baseline in subjects receiving fesoterodine 4 mg (−1.76; P < 0.001 vs placebo), fesoterodine 8 mg (−1.88; P < 0.001), and tolterodine ER 4 mg (−1.73; P = 0.001). The percentage of subjects who reported a positive treatment response was statistically significantly higher among the subjects receiving fesoterodine 4 mg, fesoterodine 8 mg, and tolterodine ER 4 mg, than placebo (75%, 79%, 72%, and 53%, respectively; all, P < 0.001 vs placebo). At the end of treatment, the mean change from baseline in UUI episodes per 24 hours was statistically significant for patients receiving fesoterodine 4 mg (−1.95; P = 0.001 vs placebo), fesoterodine 8 mg (−2.22; P < 0.001), and tolterodine ER 4 mg (−1.74; P = 0.008). The increase in MVV was 3.0, 3.6, and 2.5 times greater than placebo in subjects receiving fesoterodine 4 mg, 8 mg (both, P < 0.001), and tolterodine ER 4 mg (P = 0.002), respectively. The mean change in daytime micturitions was statistically significant with fesoterodine 4 and 8 mg and tolterodine ER 4 mg compared with placebo (all, P < 0.001). The mean change in the number of urgency episodes per 24 hours was statistically significant with fesoterodine 4 mg (−1.88; P = 0.003 vs placebo), fesoterodine 8 mg (−2.36; P < 0.001), and tolterodine ER 4 mg (−2.03; P < 0.001). The mean increase in the number of continent days per week was statistically significant with fesoterodine 4 mg (2.84; P = 0.007 vs placebo) and fesoterodine 8 mg (3.32; P < 0.001), but not significant with tolterodine ER 4 mg (2.48). The mean change in the number of nocturnal micturitions per 24 hours was not statistically significant in any of the groups compared with placebo.22

A post hoc analysis of Phase III trials by Khullar et al23 suggested that fesoterodine was associated with significantly reduced OAB symptoms, including urgency and UUI, in a dose-dependent manner. Fesoterodine 8 mg was associated with a statistically significant improvement in most bladder-diary variables (P < 0.05) compared with fesoterodine 4 mg, with the exception of micturition frequency, for which a numerical, though not statistically significant, decrease was observed.

Another post hoc analysis by Chapple et al24 concluded that the maximum recommended dose of fesoterodine (8 mg) was significantly (P < 0.05) more effective than...
the maximum recommended dose of tolterodine ER (4 mg) for improving several important OAB outcomes including incontinence, MVV per void, number of continent days per week, and severe urgency plus UUI.

The efficacy and tolerability of flexible-dose fesoterodine in patients with OAB was assessed by Wyndaele et al. in a 12-week, multicenter, open-label, single-arm, flexible-dose study (Table III). Patients aged ≥18 years (n = 516; female, 77%; mean age, 60 years) with OAB symptoms for ≥3 months, mean micturition frequency of ≥8 micturitions per 24 hours, and mean number of urgency episodes ≥3 per 24 hours, who were dissatisfied with previous tolterodine or tolterodine ER treatment (within 2 years of screening) were enrolled. Patients reported being "somewhat dissatisfied" or "very dissatisfied" with tolterodine treatment on the treatment satisfaction question (TSQ), a single item from the validated Overactive Bladder Satisfaction Questionnaire. All of these patients were administered fesoterodine 4 mg once daily for the first 4 weeks. After that, the dose could either be maintained at 4 mg or increased to 8 mg once daily for the remaining 8 weeks. Statistically significant improvements from baseline to week 12 were observed in the mean number of micturitions, UUI episodes, and urgency episodes (all, P < 0.001). Statistically significant improvements in nocturnal micturitions, severe urgency episodes, and frequency-urgency total were also observed at week 12 compared with baseline (all, P < 0.001). After 12 weeks, 80% of patients who responded to the TSQ reported being satisfied with fesoterodine, with 38% being "very satisfied." At that time, 83% of subjects reported improvement on the Patient Perception of Bladder Condition (PPBC) questionnaire. The percentage of subjects with many severe, severe, and moderate problems were 17.9%, 50.1%, and 32.0%, respectively. After 12 weeks, 3.1%, 8.8%, and 24.6% had many severe, severe, and moderate problems. Also, 26.3%, 28.1% and 9.0% of subjects had minor, very minor, or no problems. Mean PPBC scores decreased (improved) significantly from 4.9 at baseline to 3.1 at week 12 (P < 0.001). Improvement in mean scores on the Urgency Perception Scale was statistically significant at week 12 (from 1.8 at baseline to 2.4 at week 12; P < 0.001).

**Effect on HRQoL**

A post hoc inferential analysis assessed treatment-related effects on HRQoL based on the King's Health Questionnaire (KHQ), International Consultation on Incontinence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean No. at Baseline</th>
<th>Mean No. at Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micturitions/24 h</td>
<td>12.7</td>
<td>9.7</td>
</tr>
<tr>
<td>Urgency episodes/24 h</td>
<td>10.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Severe urgency episodes/24 h</td>
<td>5.0</td>
<td>1.5</td>
</tr>
<tr>
<td>UUI episodes/24 h</td>
<td>2.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Nocturnal micturitions</td>
<td>2.6</td>
<td>1.8</td>
</tr>
</tbody>
</table>

UUI = urinary urge incontinence.
Questionnaire Short Form (ICIQ-SF), and a 6-point Likert scale (0 = no problems to 5 = very severe problems), to rate the severity of problems related to their bladder condition, and treatment response (a yes/no variable derived from a 4-point treatment-benefit scale). Patients completed the scales at baseline and end of study. The KHQ is a 33-item, multidimensional, disease-specific questionnaire with 9 domains: role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, severity/coping, incontinence impact, and general health perception. The ICIQ-SF assesses the effects of urinary frequency and urine leakage on daily life. The Likert scale assesses the bladder condition.

There was a statistically significant change in HRQoL in patients with OAB receiving fesoterodine 4 or 8 mg once daily compared with those receiving placebo. The group that received fesoterodine 8 mg had statistically significant improvements compared with placebo in 8 of 9 KHQ domains (ie, all except for general health perception). Patients receiving fesoterodine 4 mg or tolterodine ER 4 mg had statistically significant improvements compared with placebo in 7 of 9 KHQ domains. Patients receiving fesoterodine 8 mg had significantly better results than those receiving 4 mg in 2 domains (ie, emotions and severity/coping; both, \( P < 0.05 \)); however, there was no statistically significant difference between patients receiving fesoterodine 8 mg and those receiving tolterodine ER 4 mg. Improvements considered meaningful to the patients (ie, change from baseline of \( \geq 5 \) points) were found in all active treatment groups in all but one KHQ domain (ie, general health perception). All active treatment groups reported a statistically significant improvement in the ICIQ-SF score compared with placebo \( (P < 0.001) \), and there were no statistical differences between active treatment groups. At the end of the study, the Likert scale scores ranged from 2.3 to 2.8 (indicating minor problems) compared with a mean of \( \sim 3.6 \) at the baseline (moderate to severe problems). The percentage of patients with an improvement of \( \geq 2 \) points with fesoterodine 4 mg (33%), fesoterodine 8 mg (38%), and tolterodine ER 4 mg (34%) was statistically significant compared with placebo (all, \( P < 0.001 \)).

The percentage of patients reporting a positive treatment response was statistically significant in those receiving fesoterodine 4 or 8 mg once daily compared with those receiving placebo \( (P < 0.001) \). Wyndaele et al used the Overactive Bladder Questionnaire (OAB-q), which comprises an 8-item Symptom Bother scale and a 25-item HRQoL scale with 4 domains (concern, coping, sleep, and social interaction). The mean change in the OAB-q Symptom Bother score, in total HRQoL, and all 4 domains of HRQoL from baseline to week 12 was statistically significant (all, \( P < 0.001 \)).

**Safety and Tolerability**

The safety and tolerability profile of fesoterodine was studied in 3 Phase III trials. In the Phase II trial by Nitti et al, the safety profile of fesoterodine was investigated. It was reported that dry mouth, headache, and gastrointestinal symptoms were the most common AEs. The treatment was discontinued by 2.27%, 4.25%, 12.80%, and 4.65% in patients receiving fesoterodine 4, 8, and 12 mg, and placebo, respectively, due to AEs. The Phase III trial by Nitti et al reported that treatment-emergent AEs occurred in 61%, 69%, and 55% of subjects receiving fesoterodine 4
and 8 mg, and placebo, respectively. The most frequently reported AE was mild to moderate dry mouth, reported by 16%, 36%, and 7% of subjects in the fesoterodine 4 and 8 mg, and placebo groups. Urinary retention occurred in 1.41%, 2.15%, and 0.36% of patients receiving fesoterodine 4 and 8 mg and placebo. Other reported AEs were constipation, urinary tract infection, and headache. Chapple et al\textsuperscript{22} reported dry mouth in 16.9%, 21.7%, 33.8%, and 7.15% of patients receiving tolterodine ER 4 mg, fesoterodine 4 and 8 mg, and placebo. Severe dry mouth was reported by 3.0% of patients in the 8-mg fesoterodine group. Other than dry mouth, no AE was reported in >5% of subjects. Other reported AEs were constipation, headache, and nasopharyngitis. Wyndaele et al\textsuperscript{25} reported dry mouth (23%) and constipation (5%) as the most common AEs. Urinary retention requiring catheterization was reported in one female patient who was receiving fesoterodine 8 mg.

Fesoterodine treatment was not associated with any clinically relevant changes in vital signs (eg, heart rate, blood pressure) or in laboratory parameters. Fesoterodine 4 and 8 mg once daily was generally well tolerated, and the number of patients who discontinued due to the AEs was low in both clinical trials.\textsuperscript{21,22}

**Dosage and Administration**

Fesoterodine is indicated for the treatment of OAB to relieve symptoms of urge incontinence, urgency, and frequency.\textsuperscript{14,18} The recommended starting dose of fesoterodine is 4 mg once daily; however, it may be increased to 8 mg once daily depending on individual response and tolerability.\textsuperscript{14} The daily dose of fesoterodine should not exceed 4 mg in patients with severe renal insufficiency (CrCl <30 mL/min) and those taking potent CYP3A4 inhibitors such as ketoconazole, itraconazole, and clarithromycin.\textsuperscript{18}

**Contraindications**

Fesoterodine is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma.\textsuperscript{14,18} It is also contraindicated in patients with severe hepatic impairment (Child Pugh C) and known hypersensitivity to the drug or its ingredients.

**Precautions**

Caution needs to be exercised in patients with the following: clinically significant bladder outlet obstruction (risk of urinary retention); gastrointestinal obstructive disorders (eg, pyloric stenosis); decreased gastrointestinal motility, such as those with severe constipation; severe ulcerative colitis; toxic mega colon; myasthenia gravis; and controlled narrow-angle glaucoma.

**Discussion**

Based on this review of the literature, fesoterodine is a well-tolerated agent and the pharmacokinetics of its active moiety, 5-HMT, are robust and largely independent of CYP pharmacogenetics. The maximum recommended dose of fesoterodine (8 mg) provided additional benefit compared with the maximum recommended dose of tolterodine ER (4 mg) on several important end points, including reduction in UUI epi-
sodes and increase in MVV per void. Fesoterodine, which was granted US Food and Drug Administration approval in October 2008, is an additional treatment option for patients with OAB. The Scottish Medicines Consortium, based on its assessment, advises that fesoterodine should be used as a second-line agent in the National Health Service for Scotland in view of less expensive antimuscarinics being available.

Fesoterodine is the newest oral drug available for treatment of OAB. Unlike the CYP2D6-mediated metabolism of tolterodine to 5-HMT, the formation of 5-HMT by fesoterodine is mediated by nonspecific and ubiquitous esterases. Moreover, multiple metabolic (comparable contributions from CYP3A4 and CYP2D6) and renal excretion pathways are involved in the elimination of 5-HMT. Therefore, the effects of patient intrinsic (hepatic/renal impairment) and extrinsic factors (CYP3A4 or CYP2D6 inhibition) on the pharmacokinetics of fesoterodine are only modest. This may generate an advantage compared with tolterodine.

A pooled post hoc analysis of the Phase III trials found that fesoterodine 8 mg was significantly more efficacious than fesoterodine 4 mg for improving UII episodes, MVV per micturition, continent days per week, and subject-reported treatment response after 12 weeks. The trial by Wyndaele et al suggested similar results in the real-world clinical condition. When fesoterodine was used in the flexible dosing regimen, there was a significant improvement in OAB symptoms and HrQoL measures. The clinical trials of fesoterodine have some limitations. First, the only study with an active comparator (tolterodine ER) was not powered to detect a statistical difference between fesoterodine and the comparator. Although the comparative results were not available from this Phase III trial, the open-label trial by Wyndaele et al found that, at 12 weeks, 80% of subjects who responded to the TSQ and who were dissatisfied with their previous treatment (tolterodine ER), reported being satisfied with fesoterodine treatment; 38% reported being very satisfied. Second, the duration of the studies was just 12 weeks. Although supportive open-label extension studies are ongoing, it is difficult to draw conclusions on efficacy from interim results. Third, the Wyndaele et al trial was an open-label, nonrandomized, dose-escalation study without a control group. Fourth, in the Wyndaele et al trial, no comparison was drawn between the subjects who received the 4-mg dose throughout the study with subjects who escalated to the 8-mg dose at week 4. Fifth, there were no data provided for the reasons for the dose escalation in the same trial. Lastly, in both the Phase III trials, patients with OAB of neurogenic origin were not included, therefore limiting the knowledge about the use of fesoterodine in a very large group of patients with OAB.

The prolonged-release formulation of fesoterodine offers an advantage of less frequent dosing and, consequently, better patient compliance. The benefit of pharmacotherapy for OAB must be a balance between efficacy and tolerability. The availability of 2 different doses of fesoterodine (4 and 8 mg) allows for an opportunity to find an optimal balance between efficacy and tolerability in individual patients. The efficacy of fesoterodine can be tested in patients unsatisfied with tolterodine treatment.

This was an attempt to review the available literature regarding fesoterodine, a relatively new molecule. A number of clinical trials are currently under way to explore the efficacy, tolerability, and safety profile in comparison with established treatments.
for OAB. A final word about the use of fesoterodine would be possible once the data from these studies are available.

CONCLUSION
A review of the literature suggests that fesoterodine is an efficacious and well-tolerated treatment option for patients with OAB.

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