CLINICAL INVESTIGATION

Fesoterodine fumarate for the treatment of overactive bladder in the elderly – a review of the latest clinical data

Clin. Invest. (2012) 2(8), 825–833

Overactive bladder is a common and troublesome condition for many older people. Although the first-line treatment for the condition is with behavioral and lifestyle measures, many older people will require pharmacological therapy to successfully manage their condition. Fesoterodine, a relatively new antimuscarinic agent for the treatment of overactive bladder, has been extensively trialed in older people and is associated with a significant improvement in both disease related outcomes and in quality of life. Fesoterodine also appears to be well tolerated in this older group of patients. This review discusses the available evidence for fesoterodine in older people to date.

Keywords: cognitive function • efficacy • fesoterodine • older people • overactive bladder • tolerability • urgency urinary incontinence

Adrian Wagg
Department of Medicine, 1–116 Clinical Sciences Building, 11350–83 Ave, University of Alberta, Edmonton, Alberta, Canada, T6G 2P4
Tel.: +1 780 492 5338
Fax: +1 780 492 2874
E-mail: adrian.wagg@ualberta.com

Overactive bladder (OAB), the lower urinary tract symptom (LUTS) complex consisting of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology is increasingly prevalent in association with increasing age [1–3]. More recent data, assessing the accrual of LUTS in a sample of females and males with time, confirm age as a major risk factor for development of the condition [4,5]. Apart from the impact on quality of life and well-being attributable to LUTS, OAB is associated with a number of health-related problems in older people. Published data show an increased risk of falls and fractures, sleep disturbance, depression, urinary tract infection, and risk of institutionalization associated with urinary incontinence [6–9]. As populations in the developed world age and as the absolute number of people with OAB in the population rises, it is likely that the demand for adequate treatment of the condition will also increase. There appears to be increased expectation of quality of life, and those in their seventh decade of life also appear to be more demanding of healthcare services [10]. Similarly, the financial pressures faced by many economies will require older people to remain in work longer, reinforcing the requirement to stay active and keep conditions such as OAB under control.

OAB management

OAB management consists of lifestyle (fluid management, weight maintenance and physical exercise) and conservative (bladder training, urgency suppression and pelvic floor muscle therapy) techniques [11]. If these methods of management are unsuccessful or unsuitable then pharmacological therapy is the next logical step in treatment, although there are limited data about the superior effects of combining these approaches to management [12]. Until very recently, available drug therapy for urgency incontinence consisted of antimuscarinic compounds, aimed at suppressing the storage symptoms associated with the condition. The

FUTURE SCIENCE part of fsg

pathophysiology of OAB is not completely understood, but it is likely that antimuscarinic drugs act by inhibiting the M_2 and M_3 subtype of muscarinic receptors in the urinary bladder, perhaps leading to a decrease in spontaneous detrusor contractions and an alteration of sensory function in the storage phase of micturition [13].

M_3 receptors are found in many other tissues: the smooth muscle of the bowel, salivary glands, the ciliary muscle of the eye and in the brain, which means that the use of antimuscarinic agents can give rise to anticholinergic-type adverse events, such as dry mouth, constipation and blurred vision [14]. These adverse effects are usually mild to moderate in severity and data suggest that these are generally tolerated by older patients if they are obtaining effective relief of symptoms. There is accumulating evidence suggesting that, perhaps because of the increased severity of urinary incontinence in older people [15], or because of the limited success with behavioral or lifestyle measures in older people, they are more likely to request drug therapy to control their OAB symptoms if the drug therapy is withdrawn [16]. Older people are also more likely to need higher doses of drug to achieve most benefit, particularly in the >75 years old category [17,18]. Given that the limited available human data appear to show that muscarinic receptor expression appears to decline in association with increasing age [19], this suggests that the increased doses required may not be related to the effect at the level of the bladder, as less antimuscarinic agent, rather than more, should be required to achieve complete blockade. This is consistent with changes observed in older versus younger male rats, where detrusor contraction in response to carbachol is reduced [20].

A wide range of drugs of varying vintage are available, all of which have evidence of efficacy and variable data concerning their tolerability [21]. Data on the efficacy of this group of drugs in older people come from either preplanned studies in community dwelling older adults [22–24,101], from a few studies of nursing home residents [25,26] or from *post hoc* pooled analyses of data from older people included in studies of all adults [17,18,27–29]. There are some deficiencies in these data. The majority concern community dwelling fit older people who may not be representative of frail or vulnerable older people and there is limited reporting of the effect of comorbid conditions or coexisting medication. Certainly there is a perception that some side effects of these medications, particularly those concerning the CNS, are poorly reported, most likely because they are not proactively sought [30]. Both tolterodine, fesoterodine and its metabolite, 5-hydroxymethyl tolterodine (5-HMT), have a high level of brain anticholinergic activity *in vitro* and are therefore theoretically likely to be associated with central anticholinergic side effects [31]. However, *in vivo*, the level of the drug in the brain is modulated both by blood–brain barrier penetration, dependent upon the size, lipophilicity and charge of the molecule, and also the rate of active efflux from the CNS by protein-mediated transporter systems, for which fesoterodine is a substrate [32]. Owing to elderly specific concerns, and given the increasing need for effective and safe treatment of the condition, the newer antimuscarinic drug, fesoterodine, has been the subject of extensive investigation in older people. This review discusses the available data on its use.

Who are the elderly?

Much of the world's population is experiencing profound demographic change. Developed countries are undergoing a graying of their population such that forecasts suggest that for many, the number of people over the age of 65 will shortly outnumber those under the age of 20. The greatest expansion in the number of older people will be in the proportion of those in their ninth decade of life [33]. Whereas aging for many is characterized as "a progressive, generalized impairment of function resulting in a loss of adaptive response to stress (loss of biological reserve) and in a growing risk of age-associated disease" [34], we are witnessing a change in the physical wellness of older people in the 'baby boomer' generation which has led to reductions in late life disability [35]. This means that now, more than ever before, older people constitute a heterogeneous population. Chronological age is simply too unsophisticated a marker with which to label this group. A simple distinction might be drawn between the robust and frail elderly. Frailty as a geriatric concept has a number of definitions which centre on the concept of biological reserve. The frailty phenotype combines impaired physical activity, mobility, balance, muscle strength, motor processing, cognition, nutrition and endurance [36–38]. It is not identical to disability and comorbidity. Among a study of people meeting strict 'phenotypic' criteria for frailty, only 22% also had both comorbidity and disability; 46% had comorbidity without disability; 6% disability without comorbidity and 27% had neither [37]. However, frail people do tend to have a high risk of intercurrent disease, increased disability, hospitalization and death. One may then consider older people in two simplified categories, a largely fitter, community dwelling group and the frail elderly. This review will discuss drug treatment with reference to both groups.

Fesoterodine

Fesoterodine is an orally administered prodrug which is rapidly converted into its active metabolite, 5-HMT, by ubiquitous esterases, largely in the gut, bypassing the hepatic cytochrome pathway. Tolterodine is also converted into this compound, but by routes requiring metabolism by the CYP2D6 enzyme. The advantage gained by use of fesoterodine is that the conversion to 5-HMT is such that the levels of the active metabolite are reasonably predictable and are not dependent upon CYP2D6 metaboliser status. Metabolism is rapid and virtually complete such that fesoterodine is undetectable in the bloodstream after oral dosing. Fesoterodine binds onto muscarinic receptors on both the detrusor and bladder mucosa. 5-HMT has more than ten-times the affinity for muscarinic receptors than its parent compound [39,40]. 5-HMT requires hepatic metabolism via the CYPA4 and CYP2D6 enzymes for its elimination. In patients with moderate hepatic impairment, 5-HMT peak and total exposure are increased approximately 1.4- and 2.1-fold, respectively, and no dose adjustment is recommended. Fesoterodine has not been studied in people with severe hepatic impairment and is not recommended for use in these patients [41]. When fesoterodine 8 mg was given concomitantly with potent CYP3A4 inhibitors such as ketoconazole, 5-HMT exposures increased approximately 2.0–2.5 [41]. Thus, similar restrictions noted for other antimuscarinic agents regarding concomitant treatment with potent inhibitors of CYP3A4 such as ketoconazole exist [42]. However, concomitant administration of moderate CYP3A4 inhibitors, such as fluconazole, does not appear to lead to accumulation of the drug even at the higher, 8-mg dose, although the maximum age of the healthy volunteers in this study, as in all of the pharmacokinetic studies, was 55 years and no data exists in older people [42]. The influence of renal impairment on the pharmacokinetics of fesoterodine has been studied in 16 subjects. The concentration of 5-HMT increases by a factor of 1.4, 1.5 and 2.0 in subjects with mild, moderate, and severe renal impairment, respectively. In this study there was a clear correlation between the renal clearance of 5-HMT and creatinine clearance. The terminal half-life (6–7 h) of 5-HMT was unaffected by renal impairment and the unbound fraction of 5-HMT in plasma was similar across all groups [43]. The pharmacokinetics of single dosing of fesoterodine in people >65 years old, albeit not in those >75 years old has been studied [44]. In this study there was no clinically significant effects of age, race or sex on fesoterodine pharmacokinetics. Additionally, there are data on the effect of warfarin administration in combination with fesoterodine, included here as warfarin is frequently prescribed in older people. In this study, the pharmacokinetics and pharmacodynamics of warfarin 25 mg in healthy adults up to the age of 41 years was unaffected by coadministration of 8-mg fesoterodine [45].

Efficacy of fesoterodine in older people

The efficacy of fesoterodine for the treatment of OAB has been extensively studied in the adult population. A *post hoc* pooled analysis of data in older adults, compiled from older participants in registration trials has been published [17]. The study used data from two randomized, double-blind, double-dummy, placebo-controlled, parallel-arm, 12-week studies, one in Europe and the other in the USA [46,47]. For the analyses, data were stratified into three categories according to subject age: <65, ≥65–<75 and ≥75 years. In both studies, the subjects were randomized to fesoterodine 8 mg, fesoterodine 4 mg, or placebo, all administered once daily. The safety analyses included all subjects in both studies who had taken >1 dose of the trial medication after randomization. Of 1681 people randomized, 620 participants were included in the efficacy analysis (<65 years, n = 1088; ≥65–<75 years, n = 366, >75 years, n = 166). Approximately 90% of the subjects were white, with females outnumbering males by more than threefold. Subject weight, height and BMI was approximately the same across age and treatment groups except that the proportion of males in the ≥65–<75- and ≥75-year age groups was greater than in the <65-year age group. Those aged ≥75 years had significantly more reported urgency urinary incontinence (UUI) episodes at baseline than the younger groups (both $p < 0.0001$), and those aged ≥65–<75 years reported significantly more UUI episodes than those aged <65 years ($p < 0.0049$). Interestingly, objective OAB symptoms only improved at 12 weeks in the group ≥75 years using the higher dose (8 mg) of fesoterodine. The data for 4 mg of fesoterodine failed to reach statistical significance for any bladder diary based variable. After 12 weeks, for those aged <65 years the improvement in UUI episodes was greater with fesoterodine 8 mg than with 4 mg. Also, improvements in micturition frequency and maximum voided volume were greater with fesoterodine 8 mg than with 4 mg among those aged ≥75 years. Compared with placebo, the treatment response rates, as determined from the ratings on the patient-completed Treatment Benefit Scale, were significantly greater at week 12 for those treated with fesoterodine 4 or 8 mg for all age groups. The improvements in the bladder diary variables and treatment response occurred as early as week 2.

The more recently reported preplanned trial, the

study of fesoterodine in the aged (SOFIA) [101], was a 12-week randomized, placebo-controlled trial in people with OAB of >65 and >75 years old conducted in Europe. After a 2-week run, subjects were randomized 1:1 to either placebo or fesoterodine. After 4 weeks of therapy, subjects could opt to increase their dose to 8 mg, based on being asked a standardized question about efficacy and the risk of side effects. Subjects could reduce their dose back down to 4 mg at any time during the 12 weeks of the study. Additionally, subjects were stratified 1:1 into day-time and night-time dosing and between subjects >65 and ≥75 years. Recruitment was handled such that 1/3 of randomized subjects were in the latter group. The primary outcome measure in this study was the change in the number of urinary urgency episodes, compared with placebo, between baseline and 12 weeks. Other diary end points included the change from baseline in urinary frequency, UUI episodes, severe urgency episodes, frequency of nocturnal micturition and incontinence pads used per 24 h. Diary-dry rates at 8 and 12 weeks were also calculated. Other assessments comprised the OAB Questionnaire, the Patient Perception of Bladder Condition and the Urgency Perception Scale at baseline and weeks 4, 8 and 12 [48–50]. The OAB Satisfaction Questionnaire and the Treatment Benefit Scale were completed at week 12 [51,52]. The Folstein's Mini Mental State Examination was completed at baseline and week 12 [53].

In SOFIA, 794 people were randomized to fesoterodine (n = 398) or placebo (n = 396). A total of 99.6% were white and, unusually for OAB studies, 47% were men. A total of 46% of subjects reported urgency incontinence episodes at baseline, and 64% had prior treatment with antimuscarinics. At week 4, 52 and 66% of subjects in the fesoterodine and placebo groups opted for dose escalation, respectively. At week 8, 16 and 9% of subjects per subgroup opted for dose escalation and 4 and 3% reduced their dose again. At week 12, the improvement from baseline in urgency episodes (-1.92 vs -3.47; $p < 0.001$), micturitions (-0.93 vs -1.91; $p < 0.001$), nocturnal micturition (-0.27 vs -0.51; $p = 0.003$), severe urgency episodes (-1.55, -2.40; $p < 0.001$), and incontinence pad use were statistically significantly greater with fesoterodine than with placebo. The responses on the Treatment Benefit Scale, OAB Satisfaction Questionnaire, patient perception of bladder condition, and Urgency Perception Scale were also significantly greater in those in the fesoterodine group versus placebo. Efficacy did not differ between day-time and night-time dosing, or between those subjects >65 or >75 years of age. The 12-week placebo-controlled phase was followed by a 12-week open-label phase, reported at the International Continence Society's Annual meeting of 2011. Of the 314 and 341 subjects who received fesoterodine or placebo and completed the double-blind phase, 282 (90%) and 299 (88%) completed the open-label phase. During the open-label phase, clinically significant improvements in the bladder diary variables and patient reported outcomes of SOFIA were achieved in the group who had initially received placebo whereas the group that had received fesoterodine maintained the improvements achieved during the double-blind phase. By week 24, the overall level of improvement in diary variables and the percentage of responders on the Treatment Benefit Scale and OAB Satisfaction Questionnaire were comparable among all subjects regardless of initial treatment group [54].

More recently, reported at the American Urological Association meeting of 2012, fesoterodine has been studied in older people classified as 'vulnerable elderly' according to the Vulnerable Elders Survey [55], which identifies those at risk of death in the following two years. In this 12-week, double-blinded, placebo-controlled study, there were 562 (281 per group; mean age 75 years) subjects with urgency urinary incontinence of more than twice daily. A total of 40% (562/1401) of screened subjects were retained in the study of whom 79% (446/562) completed the trial. Mean reductions in UUI episodes per 24 h at week 12 (baseline adjusted least square mean change of versus placebo -0.65 [0.21]; $p < 0.0018$) and 24-h micturition frequency (baseline adjusted least square mean change versus placebo -0.84 [0.23]; $p < 0.0003$) were significantly greater in the fesoterodine-treated group [56].

Safety & tolerability of fesoterodine in older people

Examining the data from the pooled analysis [17], the most commonly reported adverse events associated with fesoterodine treatment in all age groups were dry mouth, the prevalence of which increased in association with increasing age, and constipation; however, most cases were mild or moderate in severity. Compared with placebo in all age groups, the rate of dry mouth was greater among those receiving fesoterodine 4 mg (<65-years old: 20%; ≥65–<75-years old: 17%, ≥75-years old: 17%) or 8 mg (<65-years old: 33%; ≥65–<75-years old: 35%; ≥75years old: 46%). Dry mouth was predominantly mild in nature for both the 4-mg (<65-years old: 85%; ≥65–<75-years old: 71%; ≥75-years old: 70%) and 8-mg (<65-years old: 61%; ≥65–<75-years old: 67%; ≥75years old: 80%) doses. The rate of constipation was greater among those aged ≥75 years and receiving fesoterodine 4 or 8 mg (10 and 15%) and among those aged ≥65–<75 years

receiving fesoterodine 8 mg (11%) than among the respective placebo age groups (2–3%). The incidence of urinary retention was generally low; 12 subjects, and was slightly greater among the oldest subjects receiving 8-mg fesoterodine. Only one subject, a male in the ≥65–<75-year age group treated with fesoterodine 8 mg, required catheterization. The discontinuation rates were greater for those aged ≥75 years receiving placebo or fesoterodine 4 mg and lower among those aged ≥75 years receiving fesoterodine 8 mg compared with their younger counterparts. Discontinuations due to adverse events occurred in the <65 year group in 2% (placebo), 3% (4 mg) and 7% (8 mg); in the ≥65–<75 group in 3% (placebo), 6% (4 mg) and 8% (8 mg) and in the ≥75 year old group in 12% (placebo), 11% (4 mg) and 9% (8 mg) of cases.

Whilst this study was stratified by age, and compared the results of fesoterodine therapy to those achieved in younger adults, the study did not address adverse events which may be of interest in older people, such as cognitive impairment.

SOFIA revealed dry mouth (33.9 vs 5.3% for drug vs placebo) and constipation (8.9 vs 2.5% for drug vs placebo) to be the most frequent treatment emergent adverse effects in this older group of subjects [101]. The majority of dry mouth, (71% in both groups) was categorized as mild in nature. The rate of adverse events did not vary by day-time or night-time dosing. CNS adverse events, including reported cognitive impairment occurred relatively rarely. A total of 78 fesoterodine-treated (20%) and 52 placebo-treated subjects (13%) discontinued the study prematurely. Discontinuation rates due to adverse events were 12% for fesoterodine and 6% for placebo. Only three subjects in the fesoterodine group discontinued because of cognitive function-related adverse events. There was no change in the Mini Mental State Examination score in or between either group over the 12 weeks of the study. Six people reported urinary retention, including two males within the first 4 weeks of treatment with fesoterodine. Four subjects required catheterization resulting in discontinuation of participation.

The vulnerable elderly study found rates of discontinuation due to adverse events of 5.0% (n = 14/281) for the placebo group and 9.3% (n = 26/281) for the fesoterodine group. Serious adverse events occurred in 6/281 (2.1%) subjects receiving placebo and 8/281 (2.8%) receiving fesoterodine; none were considered treatment-related. In the active treatment group, 9/281 (3.2%) developed urinary retention, three of whom required catheterization [56].

Condition specific quality of life & the elderly

In the pooled analysis of fesoterodine in older people [17], quality of life was measured using the King's Health Questionnaire [57]. At the end of the 12-week study, compared with the baseline and placebo values, there was improvement with active treatment in most domains of the questionnaire. Unlike the bladder diary variables, the improvements with fesoterodine 4 mg were statistically significantly different from placebo among those aged ≥75 years. There was no statistically significant change versus placebo in either the personal relationships or general health perception domains, in common with other similar studies.

Long-term follow-up

A *post hoc* analysis of data from two of the planned open-label extension studies of fesoterodine, published in 2011, which examined those remaining on fesoterodine for up to 36 months following the initial 12 week studies included some older people. The mean age of the sample ranged between 57.4 (SD: 13.0) and 61.1 (SD: 13.4) years. Over the period of the study, out of 185 males and 705 females who entered the extension study, 85 (45.9%) males and 356 (50.4%) females took medication for 24 months. No age-stratified results were reported and thus no conclusions about the longer term tolerability of this medication in older people can be drawn [58].

Cognitive function

Given the demonstrated negative effects of oxybutynin on the cognition of older people [59] and the reported impact of drugs with anticholinergic properties on cognition [60], the effect of fesoterodine on cognitive function compared with placebo, using alprazolam as an active control was assessed in a group of 20 cognitively intact older adults with a mean age 72 years. The study found no detectable impairment of cognition in a variety of cognitive measurements, such as reaction time, visual and verbal learning, executive function and memory, associated with a single dose of either fesoterodine 4 or 8 mg when compared with placebo. Alprazolam was associated with a significant reduction in performance on each test compared with placebo [61].

Discussion

Whereas there are data concerning the efficacy and tolerability of various antimuscarinics in older people (>65 years) from a variety of indirect sources, the efficacy and tolerability of fesoterodine has been prospectively assessed and proven in older people with OAB. Fesoterodine appears to be effective in controlling the symptoms of OAB, both in terms of urinary incontinence episodes and urinary urgency episodes.

Interestingly, the SOFIA trial reported no difference in urgency urinary incontinence episodes between fesoterodine and placebo. This may have been due to the relatively low proportion of those with urgency urinary incontinence, and the low frequency of those episodes at baseline, making a significant impact that much more difficult to achieve. Older people generally report more adverse events than younger people, and this was borne out in the pooled analysis. The number of withdrawals from treatment remained low in both studies, although higher in the older age groups in the pooled analysis, with the exception of the 8-mg dose in the oldest participants, where not only did withdrawal rate remain stable, but was in line with the withdrawal rate for those people on placebo. The number of withdrawals due to adverse events in the SOFIA trial was consistent with the pooled analysis.

An obvious strength of the SOFIA trial is that the adverse events affecting cognitive function were reported. Only one subject withdrew from the study due to cognitive impairment thought to be due to active treatment. The Mini Mental State Examination did not change from baseline in a largely unselected group of older people, this perhaps reflects the fact that the instrument may be too insensitive to pick up subtle changes in cognitive state, as observed in studies using this and similar scores examining the impact of bladder antimuscarinics in cognitively impaired older people taking cholinesterase inhibitors for dementia [62,63]. Additionally, in SOFIA, subject to restrictions on newly prescribed antimuscarinics, there was no exclusion that may have limited the total anticholinergic load upon each individual; a factor known to increase the probability of scoring poorly on the Mini Mental State Examination [64]. The available studies provide useful data on the effectiveness and safety of fesoterodine in the community-dwelling elderly and emerging information on vulnerable elderly as defined by the vulnerable elders survey. There is still a need to assess pharmacological treatment of OAB in this group, to reassure clinicians of the comparable efficacy and tolerability and to assess its cognitive safety. As yet, assessment of cognitive safety of the antimuscarinics has, for the most part, been undertaken in cognitively intact older people, and over relatively short periods of time [65]. There is a clear need to systematically examine the effect of these drugs in those who might be more cognitively at risk. Proactive seeking of side effects which may be of more concern in older people, such as delirium and falls is clearly desirable. Despite the available evidence of minimal impact of these drugs in an unselected population, there is often reluctance to prescribe these drugs to older people [66,67]. Additionally, there are no long-term data on the continued efficacy and tolerability or safety of fesoterodine specifically in older people; provision of these data would certainly help in confidently prescribing the drug to older people.

Future perspective

Antimuscarinic medications have remained the first-line pharmacological treatment of OAB since the introduction of oxybutynin over 30 years ago. Since that time there has been refinement in the tolerability and side-effect profiles of medications for OAB, but little additional efficacy over and above that reported with treatment with oxybutynin [21,68]. Whilst undoubtedly of benefit to many people, tolerability and perceived efficacy of these medications is still a problem, leading to many patients stopping their medication. OAB medications are associated with very poor persistence rates in the community, although perhaps less so in older people [69,70]. Many patients also stop their medications due to unrealistic expectations of the results of therapy, a factor which should be modifiable by the health care provider [71]. There is still much that might be done to enhance long-term adherence to these medications and additionally, the efficacy of these medications has yet to be tested in other disease areas common to the older population in which urgency urinary incontinence is writ large, such as stroke, Parkinson's disease and recurrent falls.

Recently, a β-3 receptor agonist, mirabegron, has been studied in OAB [72,73]. Theoretically, mirabegron enhances the relaxation of the detrusor whilst filling, leading to a reduction in the main symptoms of OAB. This medication is not associated with antimuscarinic side effects nor, from available data, does it seem to lead to an excess of hypertension in users versus placebo. Data on pharmacokinetics in healthy volunteers >65 years of age show no age-related effects [74]. Published data from older people included in the clinical trial program suggest equivalent efficacy to younger people in terms of reductions in frequency of micturition and incontinence episodes and the effect size appears to be comparable to that seen with the antimuscarinics [74]. Whether this drug becomes more favored in older people because of the reduction in antimuscarinic side effects associated with its use remains to be seen. Common adverse events associated with mirabegron are dose-related increases in pulse rate and urinary tract infection. There are some other drugs in this class under investigation in varying markets round the world. For the moment, though, for successful pharmacological treatment of this condition; the antimuscarinics are here to stay. For the elderly, at time of writing, there is robust

Executive summary

- Overactive bladder (OAB) is increasingly prevalent in association with increasing age.
- OAB is associated with a number of health-related problems in older people such as an increased risk of falls and fractures, sleep disturbance, depression, urinary tract infection, and risk of institutionalization associated with urinary incontinence.
- OAB management consists of lifestyle and conservative management techniques in addition to pharmacotherapy. There are limited data about the superior effects of a combination approach to management.
- It is believed that antimuscarinic drugs for OAB act by inhibiting the M_2 and M_3 receptors in the urinary bladder, perhaps leading to a decrease in spontaneous detrusor contractions and an alteration of sensory function in the storage phase of micturition.
- Fesoterodine is an orally administered prodrug which is rapidly converted into its active metabolite, 5-hydroxymethyl tolterodine, by ubiquitous esterases, largely in the gut, bypassing the hepatic cytochrome pathway.
- The efficacy of fesoterodine for the treatment of OAB has been studied in a *post hoc* pooled analysis of data in older adults and from preplanned European and American studies of the elderly.
- Fesoterodine is effective in improving the majority of bladder diary-related OAB variables versus placebo and effective in improving subjective patient reported outcome measures and quality of life measures in older people.
- There is no detectable impairment of cognition in a variety of cognitive measurements, such as reaction time, visual and verbal learning, executive function and memory, associated with a single dose of either fesoterodine 4 or 8 mg when compared with placebo in cognitively intact older people.
- In clinical trials, cognition-related treatment adverse events are few. The most frequently reported adverse events are dry mouth and constipation.
- Fesoterodine appears to be an effective option for the treatment of OAB in the elderly.

clinical trial evidence demonstrating the efficacy of fesoterodine in older people.

Conclusion

Antimuscarinic therapy is likely to remain first-line pharmacological therapy for OAB. There is an increased need to show efficacy and safety of these drugs in older people. The condition affects more of them and is, perhaps, more severe in older people. There are increasing numbers of older people in the populations of the developed world and expectations of healthy aging are changing. Fesoterodine shows evidence of efficacy in the community-dwelling elderly and has data in 'older' old people, albeit not in those who might be described as frail. Fesoterodine also appears to be tolerable in this age group and treatment with fesoterodine does not lead to an excess of adverse events related to cognitive dysfunction in a largely unselected group of older adults.

Financial & competing interests disclosure

A Wagg has received financial support for research, lecturing and consultancy from Astellas Pharma, Inc., Pfizer, Inc., SCA and Watson Pharmaceuticals, Inc. In addition, he is a trustee of the International Continence Society. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

References

1 Haylen BT, de Ridder D, Freeman RM *et al.* An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol. Urodyn.* 29(1), 4–20 (2010).

2 Coyne KS, Sexton CC, Thompson CL *et al.* The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study. *BJU Int.* 104(3), 352–360 (2009).

3 Stewart WF, Van Rooyen JB, Cundiff GW *et al.* Prevalence and burden of overactive bladder in the United States. *World J. Urol.* 20(6), 327–336 (2003).

4 Wennberg AL, Molander U, Fall M, Edlund C, Peeker R, Milsom I. A longitudinal population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in women. *Eur. Urol.* 55(4), 783–791 (2009).

5 Malmsten UG, Molander U, Peeker R, Irwin DE, Milsom I. Urinary incontinence, overactive bladder, and other lower urinary tract symptoms: a longitudinal population-based survey in men aged 45–103 years. *Eur. Urol.* 58(1), 149–156 (2010).

6 Burgio K, Ouslander JG. Effects of urge urinary incontinence on quality of life in older people. *J. Am. Geriatr. Soc.* 47(8), 1032–1033 (1999).

7 Brown JS, McGhan WF, Chokroverty S. Comorbidities associated with overactive bladder. *Am. J. Manag. Care* 6(Suppl. 11), S574–S579 (2000).

8 Thom DH, Haan MN, Van Den Eeden SK. Medically recognized urinary incontinence and risks of hospitalization, nursing home admission and mortality. *Age Ageing* 26(5), 367–374 (1997).

9 Sexton CC, Coyne KS, Thompson C, Bavendam T, Chen CI, Markland A. Prevalence and effect on health-related quality of life of overactive bladder in older americans: results from the epidemiology of lower urinary tract symptoms study. *J. Am. Geriatr. Soc.* 59(8), 1465–1470 (2011).

10 Bowling A, Mariotto A, Evans O. Are older people willing to give up their place in the queue for cardiac surgery to a younger person? *Age Ageing* 31(3), 187–192 (2002).

11 Burgio KL. Behavioral treatment options for urinary incontinence. *Gastroenterology* 126(Suppl. 1), S82–S89 (2004).

12 Burgio KL, Goode PS, Richter HE, Markland AD, Johnson TM 2nd, Redden DT. Combined behavioral and individualized drug therapy versus

individualized drug therapy alone for urge urinary incontinence in women. *J. Urol.* 184(2), 598–603 (2010).

13 Banakhar MA, Al-Shaiji TF, Hassouna MM. Pathophysiology of overactive bladder. *Int. Urogynecol. J.* doi:10.1007/s00192-012-16 (2012) (Epub ahead of print).

14 Abrams P, Andersson KE, Buccafusco JJ *et al.* Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. *Br. J. Pharmacol.* 148(5), 565–578 (2006).

15 Perry S, Shaw C, Assassa P *et al.* An epidemiological study to establish the prevalence of urinary symptoms and felt need in the community: the Leicestershire MRC Incontinence Study. Leicestershire MRC Incontinence Study Team. *J. Public Health Med.* 22(3), 427–434 (2000).

16 Choo MS, Song C, Kim JH *et al.* Changes in overactive bladder symptoms after discontinuation of successful 3-month treatment with an antimuscarinic agent: a prospective trial. *J. Urol.* 174(1), 201–204 (2005).

17 Kraus SR, Ruiz-Cerda JL, Martire D, Wang JT, Wagg AS. Efficacy and tolerability of fesoterodine in older and younger subjects with overactive bladder. *Urology* 76(6), 1350–1357 (2010).

18 Wagg A, Wyndaele JJ, Sieber P. Efficacy and tolerability of solifenacin in elderly subjects with overactive bladder syndrome: a pooled analysis. *Am. J. Geriatr. Pharmacother.* 4(1), 14–24 (2006).

19 Michel MC, Barendrecht MM. Physiological and pathological regulation of the autonomic control of urinary bladder contractility. *Pharmacol. Ther.* 117(3), 297–312 (2008).

20 Zhao W, Aboushwareb T, Turner C *et al.* Impaired bladder function in aging male rats. *J. Urol.* 184(1), 378–385 (2010).

21 Kessler TM, Bachmann LM, Minder C *et al.* Adverse event assessment of antimuscarinics for treating overactive bladder: a network meta-analytic approach. *PLoS ONE* 6(2), e16718 (2011).

22 Chapple C, DuBeau C, Ebinger U, Rekeda L, Viegas A. Darifenacin treatment of patients >or= 65 years with overactive bladder: results of a randomized, controlled, 12-week trial. *Curr. Med. Res. Opin.* 23(10), 2347–2358 (2007).

23 Szonyi G, Collas DM, Ding YY, Malone-Lee JG. Oxybutynin with bladder retraining for detrusor instability in elderly people: a randomized controlled trial. *Age Ageing* 24(4), 287–291 (1995).

24 Dorschner W, Stolzenburg JU, Griebenow R *et al.* Efficacy and cardiac safety of propiverine in elderly patients – a double-blind, placebo-controlled clinical study. *Eur. Urol.* 37(6), 702–708 (2000).

25 Wagg A, Khullar V, Marscall-Kehrel D *et al.* Assessment of fesoterodine treatment in older people with overactive bladder: results of SOFIA, a double blind, placebo controlled pan-European trial. Presented at: *Meeting of the Euopean Urology Association*. 880 (2010).

26 Ouslander JG, Schnelle JF, Uman G *et al.* Does oxybutynin add to the effectiveness of prompted voiding for urinary incontinence among nursing home residents? A placebo-controlled trial. *J. Am. Geriatr. Soc.* 43(6), 610–617 (1995).

27 Lackner TE, Wyman JF, McCarthy TC, Monigold M, Davey C. Randomized, placebo-controlled trial of the cognitive effect, safety, and tolerability of oral extended-release oxybutynin in cognitively impaired nursing home residents with urge urinary incontinence. *J. Am. Geriatr. Soc.* 56(5), 862–870 (2008).

28 Newman DK. The MATRIX study: evaluating the data in older adults. *Director* 16(3), 15–19 (2008).

29 Malone-Lee JG, Walsh JB, Maugourd MF. Tolterodine: a safe and effective treatment for older patients with overactive bladder. *J. Am. Geriatr. Soc.* 49(6), 700–705 (2001).

30 Sand PK, Johnson Ii TM, Rovner ES, Ellsworth PI, Oefelein MG, Staskin DR. Trospium chloride once-daily extended release is efficacious and tolerated in elderly subjects (aged >/= 75 years) with overactive bladder syndrome. *BJU Int.* 107(4), 612–620 (2011).

31 Paquette A, Gou P, Tannenbaum C. Systematic review and meta-analysis: do clinical trials testing antimuscarinic agents for overactive bladder adequately measure central nervous system adverse events? *J. Am. Geriatr. Soc.* 59(7), 1332–1339 (2011).

32 Jakobsen SM, Kersten H, Molden E. Evaluation of brain anticholinergic activities of urinary spasmolytic drugs using a high-throughput radio receptor bioassay. *J. Am. Geriatr. Soc.* 59(3), 501–505 (2011).

33 Chancellor MB, Staskin DR, Kay GG, Sandage BW, Oefelein MG, Tsao JW. Blood–brain barrier permeation and efflux exclusion of anticholinergics used in the treatment of overactive bladder. *Drugs Aging* 29(4), 259–273 (2012).

34 Kinsella K, He W. An aging world: 2008. International Population Reports. P95/09-1 (2009).

35 Kirkwood TBL. The evolution of ageing. *Rev. Clin. Gerontol.* 5, 3–9 (1995).

36 Martin LG, Schoeni RF, Andreski PM. Trends in health of older adults in the United States: past, present, future. *Demography* 47(Suppl.), S17–S40 (2010).

37 Ferrucci L, Guralnik JM, Studenski S *et al.* Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. *J. Am. Geriatr. Soc.* 52(4), 625–634 (2004).

38 Fried L, Tangen C, Walston J *et al.* Frailty in older adults: evidence for a phenotype. *J. Gerontol. A Biol. Sci. Med. Sci.* 56(3), M146–M156 (2001).

39 Mansfield KJ, Chandran JJ, Vaux KJ *et al.* Comparison of receptor binding characteristics of commonly used muscarinic antagonists in human bladder detrusor and mucosa. *J. Pharmacol. Exp. Ther.* 328(3), 893–899 (2009).

40 Ney P, Pandita RK, Newgreen DT, Breidenbach A, Stohr T, Andersson KE. Pharmacological characterization of a novel investigational antimuscarinic drug, fesoterodine, *in vitro* and *in vivo*. *BJU Int.* 101(8), 1036–1042 (2008).

41 Malhotra B, Guan Z, Wood N, Gandelman K. Pharmacokinetic profile of fesoterodine. *Int. J. Clin. Pharmacol. Ther.* 46(11), 556–563 (2008).

42 Malhotra B, Dickins M, Alvey C *et al.* Effects of the moderate CYP3A4 inhibitor, fluconazole, on the pharmacokinetics of fesoterodine in healthy subjects. *Br. J. Clin. Pharmacol.* 72(2), 263–269 (2011).

43 Malhotra B, Gandelman K, Sachse R, Wood N. Assessment of the effects of renal impairment on the pharmacokinetic profile of fesoterodine. *J. Clin. Pharmacol.* 49(4), 477–482 (2009).

44 Malhotra BK, Wood N, Sachse R. Influence of age, gender, and race on pharmacokinetics, pharmacodynamics, and safety of fesoterodine. *Int. J. Clin. Pharmacol. Ther.* 47(9), 570–578 (2009).

45 Malhotra B, Alvey C, Gong J, Li X, Duczynski G, Gandelman K. Effects of fesoterodine on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. *Br. J. Clin. Pharmacol.* 72(2), 257–262 (2011).

46 Chapple C, Van Kerrebroeck P, Tubaro A *et al.* Clinical efficacy, safety, and tolerability

of once-daily fesoterodine in subjects with overactive bladder. *Eur. Urol.* 52(4), 1204–1212 (2007).

47 Nitti VW, Dmochowski R, Sand PK *et al.* Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. *J. Urol.* 178(6), 2488–2494 (2007).

48 Coyne K, Revicki D, Hunt T *et al.* Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. *Qual. Life Res.* 11(6), 563–574 (2002).

49 Coyne KS, Matza LS, Kopp Z, Abrams P. The validation of the patient perception of bladder condition (PPBC): a single-item global measure for patients with overactive bladder. *Eur. Urol.* 49(6), 1079–1086 (2006).

50 Cardozo L, Coyne KS, Versi E. Validation of the urgency perception scale. *BJU Int.* 95(4), 591–596 (2005).

51 Piault E, Evans CJ, Espindle D, Kopp Z, Brubaker L, Abrams P. Development and validation of the Overactive Bladder Satisfaction (OAB-S) Questionnaire. *Neurourol. Urodyn.* 27(3), 179–190 (2008).

52 Colman S, Chapple C, Nitti V, Haag-Molkenteller C, Hastedt C, Massow U. Validation of Treatment Benefit Scale for assessing subjective outcomes in treatment of overactive bladder. *Urology* 72(4), 803–807 (2008).

53 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatric Res.* 12(3), 189–198 (1975).

54 Wagg A, Khullar V, Marschall-Kehrel D *et al.* Efficacy and tolerability of fesoterodine in older people with overactive bladder: results of the open-label phase of the SOFIA trial. Presented at: *International Continence Society.* Glasgow, UK, 2 September 2011.

55 Saliba D, Elliott M, Rubenstein LZ *et al.* The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. *J. Am. Geriatr. Soc.* 49(12), 1691–1699 (2001).

56 DuBeau CE, Ouslander JG, Johnson TM. Fesoterodine is effective and well tolerated in vulnerable elderly subjects with urgency incontinence: a double-blind, placebo-controlled study. Presented at: *Annual Meeting American Urology Association.* GA, USA, 19–22 May 2012.

57 Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. *Br. J. Obstet. Gynaecol.* 104(12), 1374–1379 (1997).

58 Scarpero H, Sand PK, Kelleher CJ, Berriman S, Bavendam T, Carlsson M. Long-term safety, tolerability, and efficacy of fesoterodine treatment in men and women with overactive bladder symptoms. *Curr. Med. Res. Opin.* 27(5), 921–930 (2011).

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

60 Lechevallier-Michel N, Molimard M, Dartigues JF, Fabrigoule C, Fourrier-Réglat A. Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. *Br. J. Clin. Pharmacol.* 59(2), 143–151 (2005).

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

62 Sink KM, Thomas J 3rd, Xu H, Craig B, Kritchevsky S, Sands LP. Dual use of bladder anticholinergics and cholinesterase inhibitors: long-term functional and cognitive outcomes. *J. Am. Geriatr. Soc.* 56(5), 847–853 (2008).

63 Isik AT, Celik T, Bozoglu E, Doruk H. Trospium and cognition in patients with late onset Alzheimer disease. *J. Nutr. Health Aging* 13(8), 672–676 (2009).

64 Mulsant BH, Pollock BG, Kirshner M, Shen C, Dodge H, Ganguli M. Serum anticholinergic activity in a community-based sample of older adults: relationship with cognitive performance. *Arch. Gen. Psychiatry* 60(2), 198–203 (2003).

65 Pagoria D, O'Connor RC, Guralnick ML. Antimuscarinic drugs: review of the cognitive impact when used to treat overactive bladder in elderly patients. *Curr. Urol. Reports* 12(5), 351–357 (2011).

66 Campbell N, Perkins A, Hui S, Khan B, Boustani M. Association between prescribing of anticholinergic medications and incident delirium: a cohort study. *J. Am. Geriatr. Soc.* 59(Suppl. 2), S277–S281 (2011).

67 Gomes T, Juurlink DN, Ho JM, Schneeweiss S, Mamdani MM. Risk of serious falls associated with oxybutynin and tolterodine: a population based study. *J. Urol.* 186(4), 1340–1344 (2011).

68 Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *Eur. Urol.* 54(3), 543–562 (2008).

69 Basra RK, Wagg A, Chapple C *et al.* A review of adherence to drug therapy in patients with overactive bladder. *BJU Int.* 102(7), 774–779 (2008).

70 Wagg A, Compion G, Fahey A, Siddiqui E. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. *BJU Int.* doi: 10.1111/j.1464-410X.2012.11023.x. (2012) (Epub ahead of print).

71 Brubaker L, Fanning K, Goldberg EL *et al.* Predictors of discontinuing overactive bladder medications. *BJU Int.* doi: 10.1111/j.1464-410X.2009.09035.x (2009) (Epub ahead of print).

72 Andersson KE. Pharmacotherapy of the overactive bladder. *Discov. Med.* 8(42), 118–124 (2009).

73 Tyagi P, Tyagi V, Chancellor M. Mirabegron: a safety review. *Expert Opin. Drug Safety* 10(2), 287–294 (2011).

74 Astellas Pharma Global Development, Inc. Advisory Committee Briefing Document: Mirabegron (YM178) for the treatment of overactive bladder. NDA 202611 (2012).

■ Website

101 Centers for Disease Control and Prevention. Health, USA, 2003. www.cdc.gov/nchs/products/pubs/pubd/hus/highlits.pdf. (Accessed 11 June 2004)