Evaluation of Cognitive Function in Healthy Older Subjects Treated with Fesoterodine

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Abstract

Objective: To evaluate the cognitive effects of fesoterodine 4 and 8 mg versus placebo in healthy older adults. **Methods:** This was an active- and placebo-controlled, double-blind, double-dummy crossover study conducted using healthy volunteers (aged 65–85 years) with baseline Mini–Mental State Examination score ≥ 26. The study comprised 4 treatment periods: fesoterodine 4 mg for 6 days; fesoterodine 4 mg for 3 days followed by fesoterodine 8 mg for 3 days; placebo for 6 days; and placebo for 6 days with alprazolam 1 mg on day 6. The treatment sequence was randomized, with a 3- to 6-day washout between periods. Subjects completed computer-based cognitive assessments and the Rey Auditory Verbal Learning Test on day 1 (before dosing) and day 6 (after dosing) of each period. The primary endpoint was the Detection task; secondary endpoints were the Identification task, 1-card learning task, Continuous Paired Associate Learning task, Groton Maze Learning Task, and the Rey Auditory Verbal Learning Test. **Results:** Among 18 subjects in the per protocol set, changes from baseline to day 6 with fesoterodine 4 and 8 mg were not significantly different from placebo for any endpoint ($P > 0.05$); alprazolam produced significant impairment in all endpoints versus placebo ($P < 0.05$). No serious adverse events were reported; the most common adverse events were dry mouth for fesoterodine and sedation for alprazolam. No sedation was reported with fesoterodine. **Conclusion:** In healthy older adults, fesoterodine 4 and 8 mg once daily had no statistically significant effects versus placebo on any cognitive function assessed, including memory; alprazolam 1 mg produced statistically significant deterioration.

Keywords: fesoterodine; antimuscarinic; elderly; cognition; memory

Introduction

Overactive bladder (OAB) is a syndrome characterized by urinary urgency, with or without urgency incontinence, usually accompanied by frequency and nocturia.[1,2] Overactive bladder is a prevalent condition that affects approximately 11% of men and 13% of women; its prevalence increases with advancing age.[3] Overactive bladder symptoms are associated with increased rates of institutionalization and mortality in older individuals,[4] as well as with comorbidities (eg, falls and fractures) that are a concern in older individuals who may have to rush to the bathroom.[5]

Muscarinic antagonists are first-line pharmacologic treatment for OAB.[6] Individual antimuscarinic agents vary in the muscarinic receptor subtypes with which they interact and in their propensity to cross the blood–brain barrier (BBB), which may affect the agent's safety and tolerability profile.[7] Muscarinic M1 and M2 receptor subtypes are expressed at the highest levels in the prefrontal cortex and hippocampus, which are important for memory, attention, and executive function.[8] Therefore, interaction of an antimuscarinic agent with M1 and M2 receptors in these brain regions could produce impairment of cognitive functions.[9]

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Safety and tolerability are particularly important considerations in older individuals with OAB due to increased permeability of the BBB, changes in hepatic and renal function, and the presence of comorbidities.[10] Additionally, older individuals may be more likely to receive concomitant administration of drugs that may have additive antimuscarinic effects or compete for metabolic resources.[10–12] For example, there is evidence that cumulative anticholinergic effects of multiple drugs may impair short-term memory, executive function, and psychomotor function, in older individuals,[13–16] and concomitant administration of antimuscarinics with drugs that enhance cholingeric activity (cholinesterase inhibitors) may also have a negative impact on activities of daily living.[17] Notably, older individuals with OAB symptoms may have clinically recognizable or even occult neurologic diseases characterized by reductions in cognitive function (eg, Alzheimer's disease) that could be exacerbated by antimuscarinic drugs.[18] Even in the absence of neurological disease, the deleterious effects of drugs acting on the central nervous system (CNS), such as anticholinergics and benzodiazepines, are greater in people aged $>$ 60 years compared with healthy young adults.[19] Thus, there is concern regarding potential CNS adverse events (AEs) in older individuals being treated with antimuscarinics for OAB symptoms.[9]

Fesoterodine is an antimuscarinic agent approved for the treatment of OAB symptoms that is available in 2 doses (4 and 8 mg). Both fixed- and flexible-dose studies have shown that fesoterodine 4 and 8 mg significantly improve bladder diary variables, including micturition frequency, urgency episodes, and urgency urinary incontinence episodes and measures of health-related quality of life (HRQL) compared with placebo.[20–22] A pooled analysis of data from 2 fixed-dose phase 3 studies stratified by subjects' age showed that both fesoterodine 4 and 8 mg effectively treated OAB symptoms and improved HRQL in subjects aged $<$ 75 years, and fesoterodine 8 mg was effective in those aged $\geq$ 75 years. Fesoterodine was generally well tolerated in both younger and older subjects.[23] Similarly, a randomized, double-blind, placebo-controlled, flexible-dose trial of subjects aged $\geq$ 65 years reported significant improvements in most diary variables, symptom bother, and HRQL and significantly higher treatment response rates in the fesoterodine group versus placebo; flexible-dose fesoterodine was well tolerated, with no change in Mini-Mental State Examination (MMSE) score in either group.[24]

After oral administration, fesoterodine is rapidly and extensively converted by ubiquitous esterases to its active metabolite, 5-hydroxymethyl tolterodine (5-HMT).[7] 5-HMT has been shown to have low lipophilicity, which limits the propensity of 5-HMT to cross the BBB, and is a substrate of the P-glycoprotein (P-gp) efflux transporter, which may limit CNS penetration through active removal of molecules that do cross the BBB.[7,25] Although the low degree of CNS penetration of 5-HMT has been confirmed in vivo in rats[25] and via observation that the incidence of CNS AEs in human subjects with OAB in fesoterodine clinical trials has been no greater than placebo,[20,22] the potential of fesoterodine to impair cognitive functioning in older populations has not been assessed. The objective of the present 6-week study was to assess cognitive function using sensitive, specific, validated methodology in healthy older volunteers after oral administration of fesoterodine 4 and 8 mg compared with placebo. Because 5-HMT does not cross the BBB and no cognitive impairment or CNS AEs have been observed previously after treatment with fesoterodine, we hypothesized that fesoterodine would not induce impairment in attention, memory, or executive function in this psychopharmacological challenge. To ensure the experiment was sufficiently sensitive to cognitive change in the older adults, we included a positive-control treatment (alprazolam 1 mg) that is often prescribed for use in older adults and known to reliably induce acute and reversible impairment in cognitive domains known to be impacted by anticholinergics in adults at the recommended therapeutic doses.[26]

Materials and Methods

Study Design and Subjects

In this randomized, positive- and placebo-controlled, double-blind, double-dummy, 4-way crossover study, healthy volunteers aged 65 to 85 years who scored $\geq$ 26 on the MMSE at baseline were enrolled at 1 site in the United States (ClinicalTrials.gov ID NCT01161472). Subjects with cognitive impairment due to any concurrent condition or who were taking concomitant medications that may cause cognitive impairment were excluded. The cognitive effect of alprazolam 1 mg compared with placebo was used as a positive control to assess the sensitivity of the methodology used.[27,28]

The study comprised 4 treatment periods: fesoterodine 4 mg for 6 days with matching alprazolam placebo on day 6; fesoterodine 4 mg for 3 days followed by fesoterodine 8 mg for 3 days with matching alprazolam placebo on day 6; matching fesoterodine placebo for 6 days with matching alprazolam placebo on day 6; and matching fesoterodine placebo for 6 days with alprazolam 1 mg on day 6. Subjects were randomized in a 1:1:1:1 ratio to one of 4 cross-over sequences,

with 4 treatment periods in each sequence arranged in a Williams' square. There was a 3- to 6-day washout period between each treatment period.[29–31] Total study duration was 6 weeks. All treatments were administered once daily; subjects were confined to the study site for the night prior to cognitive assessment. Compliance with the dosing regimen was evaluated at each cognitive assessment via collection of unused study drug.

Measures

Subjects were administered a validated computer-based cognitive test battery (CogState)[32] and the Rey Auditory Verbal Learning Test (RAVLT)[33] on day 1 (before dosing) and day 6 (after dosing) of each treatment period (Table 1). The primary endpoint was performance on the Detection task, a test of psychomotor function and processing speed in which a subject must respond as quickly as they can to the presence of a visual stimulus. Secondary endpoints were performance on the Identification task (a test of visual attention or vigilance in which the subject must decide whether a card presented is red), One Card Learning task (a test of visual learning and memory in which the subject must decide whether or not they have seen each card before), Continuous Paired Associate Learning (CPAL) task (a test of visual learning and memory in which subjects must learn a set of 6 associations between abstract patterns and locations), and the Groton Maze Learning Task (GMLT; a measure of executive function in which the subject must locate and learn a pathway hidden beneath a 10×10 grid) and the Rey Auditory Verbal Learning Test (RAVLT; a test in which the subject must learn a set of 15 unrelated spoken words on 5 learning trials). Previous studies suggest that the practice effects should be minimal for these tests under the design employed in the current study.[34] Safety was monitored throughout the study based on treatment-emergent adverse events (TEAEs), assessments of vital signs, and physical examination.

Statistical Methods

The sample size estimation to ensure that the study had sufficient statistical power to detect statistically significant differences between active treatment and placebo was based on data from previous crossover studies using the CogState cognitive testing battery in healthy volunteers. Approximately 20 subjects were to be enrolled in the study. Subjects who withdrew from the study before completing all 4 study periods could be replaced with a mirror replacement. To show a clinically meaningful difference in the Detection task endpoint (change from baseline to end of treatment) of 0.06 ($\log^{10}$ ms) between active treatment and placebo, a sample size of 17 subjects was needed for the statistical test to have a power of 90% to detect a difference between

Table 1. Cognitive Function Outcomes Measures

	Cognitive Domain
Detection task (primary endpoint)	• Psychomotor function or processing speed • Measures subject's speed of response to a card being turned over on the computer screen • Data are presented as mean log10 with a lower score corresponding to better performance
Identification task	• Visual attention or vigilance • Measures subject's speed of deciding if a card turned over on the screen is red or not • Data are presented as mean log10 with a lower score corresponding to better performance
One-card learning task	• Visual learning and memory • Measures subject's accuracy of remembering which cards have been shown before in the task • Data are presented as an arcsine transformation of proportion of correct responses with a higher score corresponding to a better performance
CPAL task	• Visual kearning and memory • Measures subject's error rate in learning and remembering pictures hidden beneath different locations on the computer screen • Lower scores correspond to better performance
GMLT	• Executive function/spatial problem solving • Measures subject's error rate in finding a hidden pathway across a grid • Lower scores correspond to better performance
RAVLT	• Verbal learning and memory • Measures subject's ability to recall words • Higher scores correspond to better performance

Abbreviations: CPAL, Continuous Paired Associate Learning task; GMLT, Groton Maze Learning Task; RAVLT, Rey Auditory Verbal Learning Test.

treatment means, at a significance level of 0.05 (2-sided). This was rounded up to the nearest multiple of 4 to ensure an equal number of subjects in each sequence, giving a total sample size of 20. This calculation assumes an estimate of the within-subject standard deviation (SD) to be 0.05 for change in the Detection task endpoint at the end of treatment observed in previous studies.

Analysis of primary and secondary endpoints was based on the Per Protocol Analysis Set (PPAS), which includes all subjects who completed the study, and who did not violate any of the inclusion/exclusion criteria or deviate from the protocol in a way that could affect the outcome of the study. The Safety Analysis Set consists of all subjects who received study drug, regardless of whether they completed the study.

Change from baseline to day 6 for all endpoints was analyzed using an analysis of covariance (ANCOVA) model with period and treatment as fixed effects, subject as a random effect, and between and within subject baseline values as covariates. The least squares (LS) mean change in scores from baseline to day 6 and corresponding standard errors for active treatments and placebo are presented, along with the 95% CIs and *P* values for the differences in LS means for active treatments versus placebo. Statistical significance was tested based on $P < 0.05$.

Results

A total of 20 healthy volunteers were randomized and treated, among whom 1 discontinued for personal reasons and 1 was excluded from the PPAS for a violation of the study protocol (receiving a prohibited medication). The 2 subjects who were not included in the PPAS were not from the same treatment sequence group. No subjects were excluded for lack of compliance with the dosing regimen. The safety set (all subjects who received study drug) consisted of 12 men and 8 women with a mean (SD, range) age of 72.2 (5.2, 65–84) years, who had a mean (SD, range) 15.4 (2.4, 12–20) years of education, and a mean (SD, range) MMSE score of 29.05 (1.15, 26–30).

Least-square mean changes in all endpoints are shown in Figure 1. Differences in LS mean changes in Detection task scores from baseline to day 6 (primary endpoint) for fesoterodine 4 or 8 mg versus placebo were not statistically significant ($P > 0.05$); the 95% CIs for the differences versus placebo included zero (Figure 2). In contrast, in a secondary comparison, alprazolam demonstrated statistically significant changes in Detection task scores from baseline to day 6 compared with placebo ($P = 0.0013$); the 95% CIs for the difference versus placebo did not include zero (Figure 2).

Similarly, baseline to day 6 changes in the Identification task, One Card Learning task, CPAL task, GMLT, and RAVLT with fesoterodine 4 and 8 mg were not statistically significant compared with placebo, (all $P > 0.05$); the 95% CIs associated with the differences versus placebo included zero (Figure 2). In contrast, in the alprazolam treatment period, baseline to day 6 changes in all the secondary endpoints were statistically significantly different when compared with placebo (all $P < 0.05$); the 95% CIs associated with the differences versus placebo did not include zero (Figure 2).

Among the safety set, 7 (35%), 6 (30%), 11 (58%), and 18 (95%), subjects receiving placebo, fesoterodine 4 mg, fesoterodine 8 mg, and alprazolam, respectively, reported any AEs, among whom 4 (20%), 5 (25%), 8 (42%), and 17 (89%) subjects reported AEs related to treatment. No serious AEs were reported and no AEs were considered to be severe. As expected, the most common AEs were dry mouth for fesoterodine 4 mg (10%) and fesoterodine 8 mg (32%) and sedation for alprazolam (53%; Table 2). There was no reported sedation with fesoterodine.

Discussion

The current study examined the effects of fesoterodine 4 mg, fesoterodine 8 mg, and alprazolam versus placebo across a wide range of tests assessing different elements of cognitive function, including psychomotor function, visual attention, visual learning, visual associative learning, executive function, verbal learning, and memory. Both the CogState test battery and the RAVLT have demonstrated validity and sensitivity to cognitive change in clinical research settings and are known to be sensitive to antimuscarinic treatment.[35,36] In the current study, there was no observed improvement in performance for any of the cognitive tests during administration of placebo. This finding suggests that repeated administration of the tests does not give rise to practice effects and is consistent with the results of previous studies in which the CogState battery has also been given repeatedly without inducing practice effects.[34]

The results show that at steady state, fesoterodine 4 or 8 mg were not associated with impairment of cognitive functioning in healthy older subjects versus placebo. In contrast, an acute 1-mg dose of alprazolam gave rise to statistically significant worsening in all cognitive function scores. The magnitude and consistency of the decline in cognitive function observed following alprazolam in the current sample of healthy older adults indicates that the current experimental design had sufficient sensitivity and power to detect impairing

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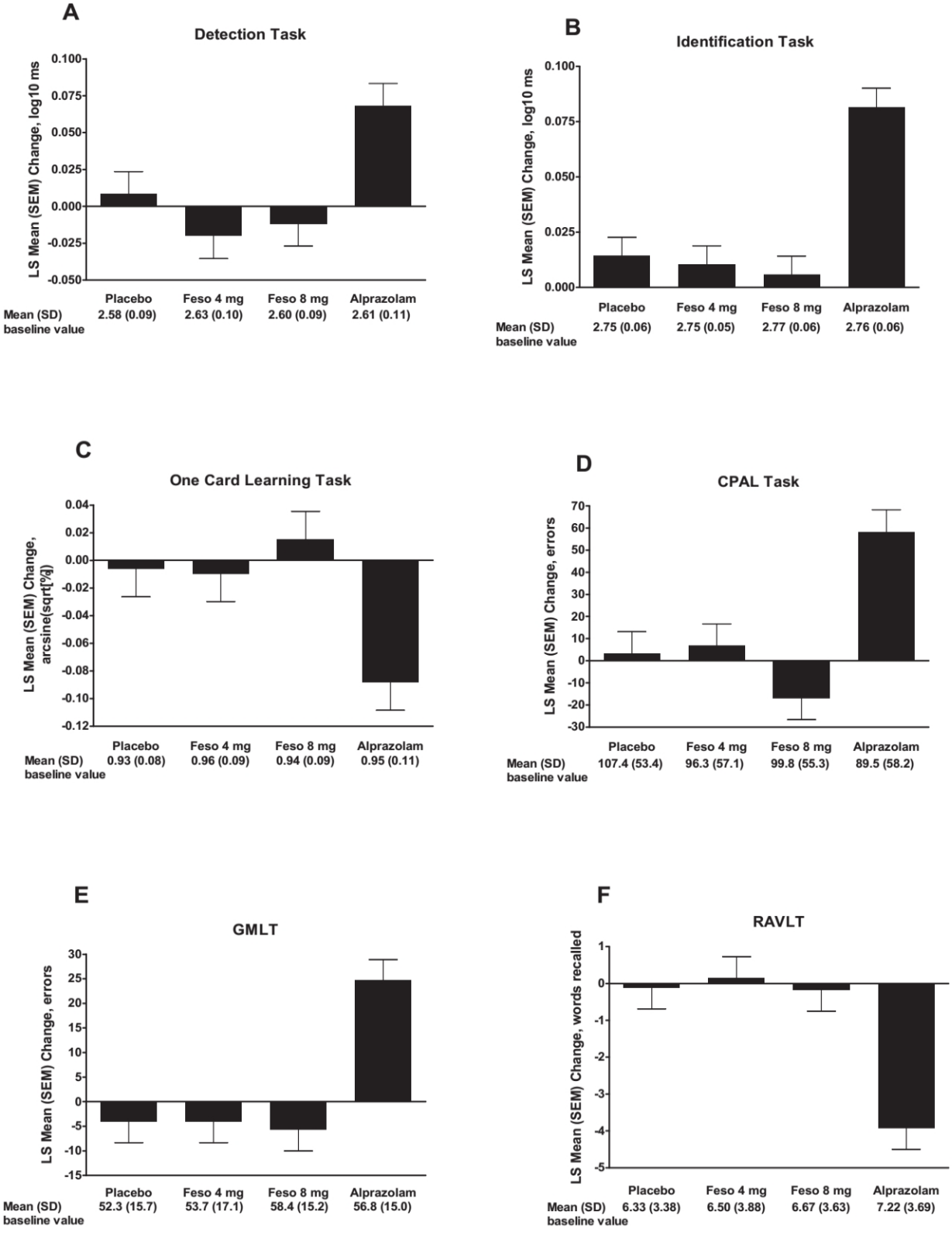
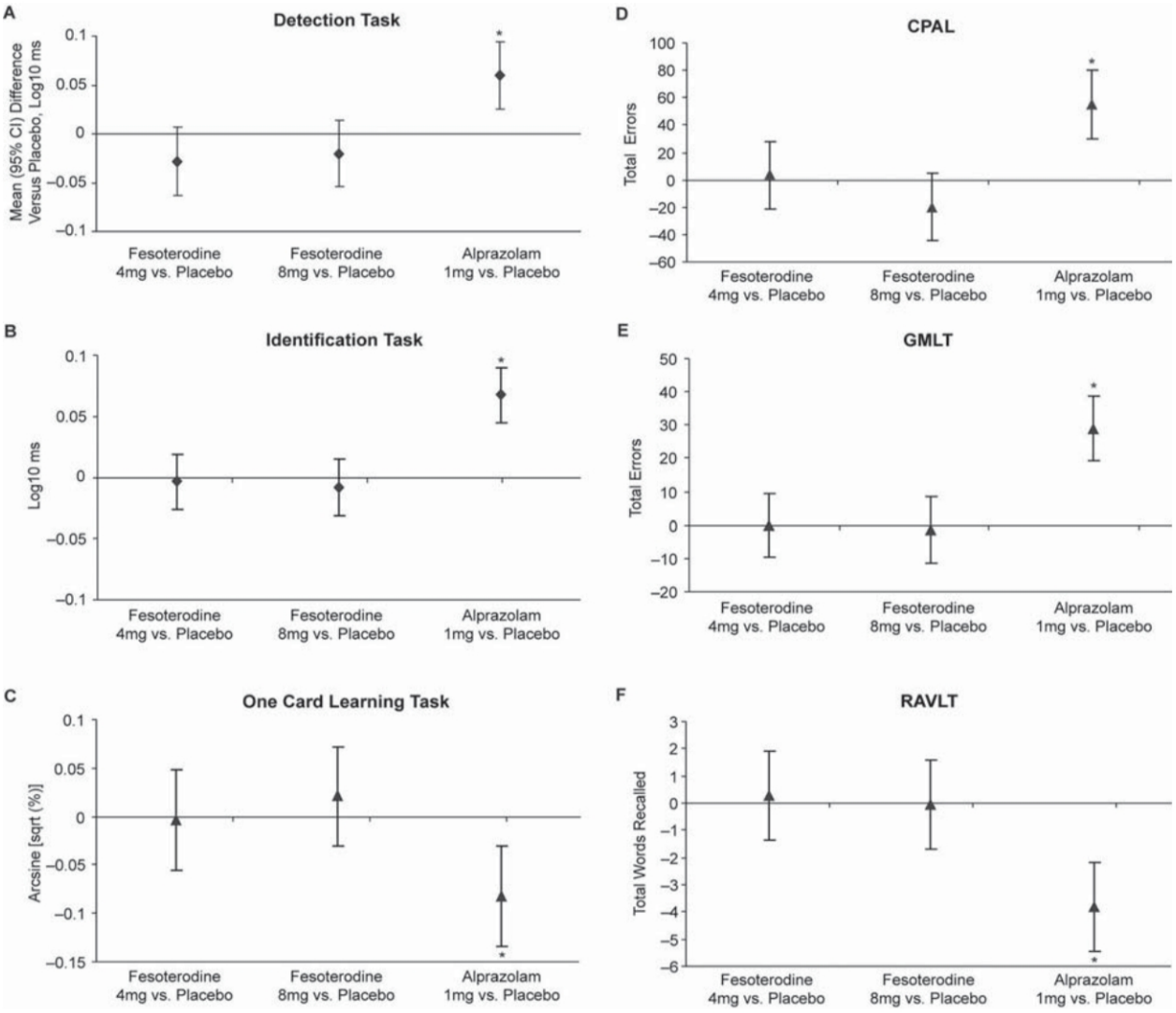
Figure 1. Least-squares mean (SEM) change from baseline to day 6 in Cogstate Subtest [Detection Task (**A**), Identification Task (**B**), One-card Learning Task (**C**), CPAL (**D**), GMLT (**E**)] and RAVLT (**F**) scores. Data represent the PPAS (n = 18).



Abbreviations: CPAL, Continuous Paired Associate Learning task; Feso, fesoterodine; GMLT, Groton Maze Learning Task; LS, least-squares; PPAS, per-protocol analysis set; RAVLT, Rey Auditory Verbal Learning Test.

Figure 2. Least-squares mean (95%CI) difference between placebo and active treatments for changes from baseline to Day 6 in Cogstate Subtest [Detection Task (**A**), Identification Task (**B**), One-card Learning Task (**C**), CPAL (**D**), GMLT (**E**)] and RAVLT (**F**) scores. Data represent the PPAS (n = 18).



*$P < 0.05$.

Abbreviations: CPAL, Continuous Paired Associate Learning task; Feso, fesoterodine; GMLT, Groton Maze Learning Task; LS, least-squares; PPAS, per-protocol analysis set; RAVLT, Rey Auditory Verbal Learning Test.

drug effects, particularly given that the statistically significant difference in the primary endpoint between alprazolam and placebo was identical to the clinically meaningful difference the study was powered on. Figure 1 shows the magnitude of decline associated with alprazolam and the absence of any decline associated with fesoterodine or placebo for each of the cognitive tasks. The magnitude of effect sizes, when expressed as Cohen's d with a negative value representing deterioration in performance, were generally close to zero with placebo, fesoterodine 4 mg, and fesoterodine 8 mg, but this was not the case for alprazolam, demonstrating a true lack of effect between placebo and fesoterodine 4 and 8 mg, and the converse for alprazolam. The small and equivalent effect sizes observed for change from baseline under the fesoterodine and placebo conditions also indicate that the absence of any statistical significance between these conditions reflected true non-differences rather than lack of power.

Although concern has been expressed regarding potential CNS effects of antimuscarinic agents in older individuals, the likelihood of these effects occurring may differ widely across the medications in this class.[9] The propensity for an antimuscarinic agent to cause CNS effects depends on its physicochemical properties, including molecular size, charge, structure, and lipophilicity, which determine its potential to cross the BBB and its muscarinic receptor subtype selectivity.[7] Agents that have higher lipophilicity,

Table 2. Most Frequently Reported TEAEs[a]

TEAE, n (%)	Placebo (N = 20)	Fesoterodine 4 mg (N = 20)	Fesoterodine 8 mg (N = 19)	Alprazolam 1 mg (N = 19)
Dry mouth	0 (0)	2 (10)	6 (32)	0 (0)
Ataxia	0 (0)	0 (0)	0 (0)	2 (11)
Dizziness	1 (5)	2 (10)	1 (5)	4 (21)
Headache	3 (15)	1 (5)	2 (11)	2 (11)
Sedation	1 (5)	0 (0)	0 (0)	10 (53)
Somnolence	0 (0)	0 (0)	0 (0)	2 (11)

[a]Data represent TEAEs occurring in ≥ 2 subjects in a treatment condition in the safety set (all subjects who received study drug).
Abbreviation: TEAE, treatment-emergent adverse event.

smaller size, neutral polarity, and are not substrates of the P-gp efflux transporter are most likely to penetrate and remain within the CNS.[25,37] Agents that have high affinity for muscarinic Ml and M2 receptors, which are abundant in hippocampus and prefrontal cortex and known to be important for memory, may also be more likely to produce cognitive effects.[8,9]

The present results, showing an apparent lack of effect of fesoterodine 4 and 8 mg on cognitive function, are consistent with data suggesting that 5-HMT, the active metabolite of fesoterodine, has a relatively low lipophilicity at physiologic pH and a low potential for penetration into the CNS.[7] After oral dosing, fesoterodine is rapidly and extensively converted by ubiquitous esterases to 5-HMT, and fesoterodine, the parent compound, is not detectable. Thus, antimuscarinic activity after oral fesoterodine administration is primarily attributable to 5-HMT.[7] Tolterodine is also converted to 5-HMT; however, in contrast to fesoterodine, this occurs primarily in the liver via cytochrome P450 (CYP) 2D6. For this compound a significant fraction of unconverted tolterodine is found in plasma.[38] Tolterodine is relatively lipophilic compared with 5-HMT and has a relatively increased potential for crossing the BBB.[7] Although tolterodine has not been associated with significant CNS adverse events in clinical trials,[9] the potential for such effects is increased in the approximately 7% of white and 2% of black individuals in the population who are referred to as CYP 2D6 poor metabolizers. Among other antimuscarinics, oxybutynin is relatively lipophilic[7] and is associated with significant cognitive effects. Additionally, antimuscarinics that are substrates of the P-gp efflux transporter, such as 5-HMT, darifenacin, and trospium, have been shown to exhibit lower levels of brain penetration than agents that are not P-gp substrates, such as oxybutynin, solifenacin, and tolterodine.[25] In clinical studies, oxybutynin has been associated with deterioration in cognitive function in older individuals.[8,39–41] In fact, oxybutynin has been used as an active-comparator in studies investigating the CNS effects of darifenacin, solifenacin, tolterodine extended release, and trospium.[8,39,40] Currently, the evidence suggests lack of effect on cognitive function with darifenacin, solifenacin, tolterodine, and trospium.[39,41–45] It has been reported that the quarternary amine trospium is undetectable in the cerebrospinal fluid of older individuals after oral administration.[45]

Inclusion in this study required that the older adults have no cognitive impairment; therefore, the current results do not extend to circumstances where antimuscarinic drugs are used to treat OAB in older adults with cognitive impairment (eg, in Alzheimer's disease or after stroke). In addition, this study population had a relatively high level of education compared with the general population of the United States.[46] It is possible that older adults with higher levels of education are less prone to cognitive impairment with antimuscarinics, perhaps due to higher brain reserve. Lastly, the number of concomitant medications, and thus the potential for cumulative anticholinergic effects, may have been lower in this population of healthy older adults than in the general population of older adults. These limitations should be considered when interpreting the observed treatment effects in the context of the overall population.

Conclusion

In these healthy older adults, fesoterodine 4 and 8 mg had no statistically significant effects compared with placebo on any of the cognitive functions assessed, including memory. In contrast, in the same adults, alprazolam resulted in a large, generalized, and statistically significant deterioration in cognitive functioning compared with placebo.

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Conflict of Interest Statement

Gary G. Kay, PhD discloses a conflict of interest with Allergan, Novartis, Pfizer Inc, and Watson. Paul Maruff, PhD discloses a conflict of interest with Cogstate Ltd. David Scholfield, MBBS discloses a conflict of interest with Pfizer Inc. Bimal Malhotra, PhD discloses a conflict of interest with Pfizer Inc. Laurence Whelan, PhD discloses a conflict of interest with Pfizer Inc. Amanda Darekar, MSc a conflict of interest with Pfizer Inc. Diane L. Martire, MD discloses a conflict of interest with Pfizer Inc.

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