



European Association of Urology



Neuro-urology

Differential Effects of the Antimuscarinic Agents Darifenacin and Oxybutynin ER on Memory in Older Subjects

Gary Kay^{a,*}, Thomas Crook^b, Ludmyla Rekeda^c, Raul Lima^c,
 Ursula Ebinger^c, Miguel Arguinzoniz^d, Michael Steel^d

^a Washington Neuropsychological Institute, Washington, DC, USA

^b Psychologix, Inc, Fort Lauderdale, FL, USA

^c Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

^d Novartis Pharma AG, Basel, Switzerland

Article info

Article history:

Accepted March 13, 2006

Published online ahead of
 print on April 19, 2006

Keywords:

Cognitive function

Darifenacin

Antimuscarinic

Older subjects

Oxybutynin ER

Abstract

Objectives: To investigate the effects of darifenacin controlled-release (CR) and oxybutynin extended-release (ER) on cognitive function (particularly memory) in older subjects.

Methods: Healthy subjects ($n = 150$) ≥ 60 years were randomised to darifenacin, oxybutynin ER or placebo in a multicentre, double-blind, double-dummy, parallel-group, 3-week study. Doses were administered according to US labels: oxybutynin ER 10 mg once daily (od), increasing to 15 mg od then 20 mg od by week 3; darifenacin 7.5 mg od in weeks 1 and 2, then 15 mg od in week 3. The primary end point was accuracy on the Name–Face Association Test (delayed recall) at week 3.

Results: Results of the Name–Face Association Test at week 3 showed no significant difference between the darifenacin and placebo on delayed recall (mean difference, -0.06 , $p = 0.908$). In contrast, oxybutynin ER resulted in memory impairment, with significantly lower scores than placebo and darifenacin (mean differences, -1.30 , $p = 0.011$ and -1.24 , $p = 0.022$, respectively) for delayed recall on the Name–Face Association Test at week 3. Additional tests of delayed recall indicated significant memory impairment with oxybutynin ER versus placebo at certain time points, whereas darifenacin was similar to placebo. No between-treatment differences were detected in self-rated memory, demonstrating that subjects were unaware of memory deterioration.

Conclusions: While darifenacin had no significant effects on memory versus placebo, oxybutynin ER caused significant memory deterioration (magnitude of effect comparable to brain aging of 10 years). The results also demonstrate that subjects may not recognise/report memory deterioration.

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* Corresponding author. Washington Neuropsychological Institute, 4910 Massachusetts Ave NW #100, Washington, DC 20016, USA. Tel. +1 202 686 7520; Fax: +1 202 686 8802. E-mail address: gkay@tidalwave.net (G. Kay).

1. Introduction

Overactive bladder (OAB) is a widespread condition, the prevalence of which rises with increasing age [1]. As bladder contractions are mediated primarily by cholinergic activation of muscarinic M_3 receptors [2], antimuscarinics are used widely as first-line OAB treatments [3]. Some agents may, however, be associated with safety concerns, including effects on the central nervous system (CNS), e.g., memory impairment [3]. The potential for CNS safety issues is of particular concern in older patients, who are more vulnerable because of age-related memory decline [4], reduced brain muscarinic receptor density [5] and comorbidities [6]. Furthermore, clinical studies have demonstrated increased sensitivity of older subjects to antimuscarinics, including effects on memory [7,8]. Consequently, selecting an appropriate antimuscarinic for OAB requires balancing efficacy with possible effects on memory.

An important differentiator between antimuscarinics is activity at muscarinic receptor subtypes (M_1 – M_5). While oxybutynin binds preferentially to M_3 and M_1 receptors, darifenacin demonstrates 9.3-fold selectivity for M_3 over M_1 receptors in-vitro [9]. This observation may be important for effects on memory, as the muscarinic M_1 receptor plays a role in memory/cognition [10,11]. Indeed, it has been proposed that M_3 selectivity may confer benefits, as non- M_3 -receptor-mediated CNS side effects may be avoided (or reduced) [12]. Supporting evidence includes two studies of healthy subjects (one in subjects ≥ 65 years), in which darifenacin had no effect versus placebo on cognition [13,14]. In contrast, a small-scale clinical study showed that oxybutynin was associated with cognitive dysfunction [15].

To our knowledge, there are no reports of a single-controlled study investigating the effects of two separate antimuscarinics on memory. We report a comparison of the effects of darifenacin and extended-release (ER) oxybutynin on memory in older subjects.

2. Methods

2.1. Subjects and study design

Healthy male and female subjects aged ≥ 60 years with English as a first language ($n = 150$) were entered into a multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group, 3-week study. Subjects had to be able to follow instructions and complete the computerised cognitive tests with valid responses. Medications prohibited for 2 weeks prior to screening included drugs with anticholinergic properties, drugs with known effects on cognition (e.g.,

opioids, benzodiazepines or sedating antihistamines), or drugs that are substrates or inhibitors of cytochrome P450 (CYP) 2D6 or CYP 3A4. Subjects were excluded if they suffered from conditions for which anticholinergic use is contraindicated (e.g., uncontrolled narrow angle glaucoma, urinary retention), if they suffered from dementia or scored ≤ 27 on the Mini-Mental State Exam (MMSE) or if they displayed evidence of depression (score ≥ 9 on Geriatric Depression Scale).

Subjects entered a 2-week screening period, during which eligibility was assessed, and cognitive tests were administered for familiarisation with procedures. Subjects were randomised (1:1:1 ratio) to receive once-daily (od) treatment with oxybutynin ER, darifenacin or placebo (Fig. 1). The 3-week duration allowed titration of oxybutynin ER in accordance with US prescribing information [16]; treatment for 1 week at each dose allowed steady-state cerebrospinal fluid concentrations to be reached. Thus, the oxybutynin ER group received 10 mg od in week 1, 15 mg od in week 2, and 20 mg od in week 3. The darifenacin group received 7.5 mg od in weeks 1 and 2 (with a sham dose increase after 1 week), then 15 mg od during week 3 (in line with US prescribing information) [17]. The third group received placebo throughout, with sham dose increases after 1 and 2 weeks. Blinding was maintained by using the double-dummy technique. Dosing was supervised during week 3 to ensure compliance.

Written informed consent was obtained, and the study was performed in accordance with good clinical practice guidelines following ethical approval by a local review board according to the ethical principles laid down in the Declaration of Helsinki.

2.2. Assessment of cognitive function

Cognitive function was assessed through the Psychogix/CogScreen (Psychogix Inc, Fort Lauderdale, FL, USA; CogScreen, LLC, Washington, DC, USA) battery of computerised cognitive function tests (CFTs) performed during clinic visits at baseline and following each week (prior to dose or sham dose increase) (Fig. 1). Table 1 shows the tests that were employed (which have been demonstrated to be reliable and valid in numerous studies) [18,19], tasks performed in each test and the sequence in which the tests were performed.

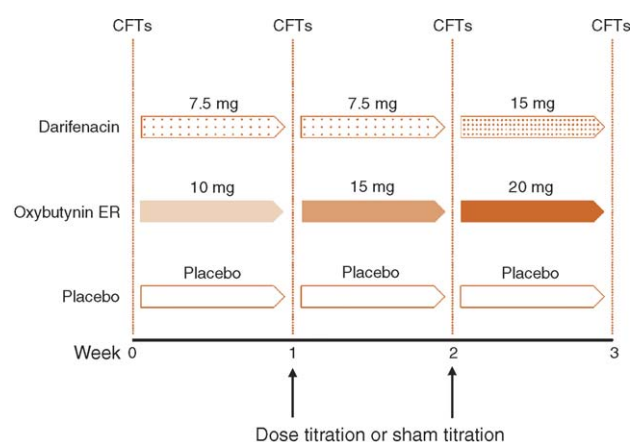


Fig. 1 – Study design. CFT = cognitive function test; ER = extended release.

Table 1 – Battery of tests used to assess memory and cognitive function

Test	Description	Test sequence*
Immediate memory recall		
Name–Face Association	Subjects are presented with a series of 14 people (displayed on a video monitor) who introduce themselves individually by common first names. Subjects are then asked to recall names when the 14 people reappear in a different sequence. Two separate tests performed (first and second acquisition).	1
First–Last Name Association	Subjects are presented with four pairs of first and last names. Subjects are then asked to recall corresponding first names as each last name is presented. Two separate tests performed (first and second acquisition).	2
Facial Recognition	Subjects are presented with a single facial photograph and are required to touch the face on the screen. In each of 24 subsequent trials, subjects are required to identify a new face added to the set (8-second delay between each trial). Results are analysed as ‘correct before first miss’ and ‘total correct’.	4
Delayed memory recall		
Name–Face Association	30 minutes after completion of the immediate recall Name–Face Association Test (as described above), subjects are re-presented with each face and asked for the corresponding name.	8
First–Last Name Association	30 minutes after completion of the immediate recall First–Last Name Association Test (as described above), subjects are asked to recall corresponding first names as each last name is re-presented.	9
Misplaced Objects	Subjects are presented with a 12-room house on a monitor and asked to place 20 objects within the house using a touchscreen (no more than 2 objects per room). After a 30-minute delay subjects are asked to recall object placement. Correct recall at first attempt is assessed.	3 (presentation) 10 (delayed recall)
Visual attention and memory		
Matching to Sample	Subjects are presented with a checkerboard pattern (4 × 4) made up of purple and yellow squares. The pattern disappears and is replaced by one identical and one similar pattern. Subjects are asked to identify the identical pattern. Response speed, accuracy and efficiency are measured.	5
Visual Sequence Comparison	Subjects are presented with two random strings of numbers and letters (4–8 items) simultaneously (shown on left and right hand sides of a monitor) and are asked to identify whether they are the same or different. For each pair of strings, differences of up to two items are allowed. Speed, accuracy and efficiency (the number of problems correctly completed per minute) are measured.	6
Psychomotor/reaction time and information processing		
Divided Attention (Visual Monitoring Alone)	Subjects watch a cursor (indicator) move vertically within a circle divided into central, upper and lower sections. When the cursor crosses into upper or lower sections, subjects are required to press a box marked ‘CENTRE’ with a light pen. Indicator speed is measured as the median time the cursor spent outside the central section of the circle before the subject presses ‘CENTRE’. Premature responses also are assessed.	7
Divided Attention (Visual Sequence Comparison and Visual Monitoring, Dual Condition)	In the second component of the Divided Attention Test, the Visual Sequence Comparison task (as described above) is performed simultaneously with the Divided Attention Indicator Alone Task (as described above). Response speed is measured for both tasks and accuracy and efficiency (number of items completed) are measured for the Visual Sequence Comparison Task in the Dual Condition (i.e., when performed with the Divided Attention Visual Monitoring Task). When the two tasks are presented simultaneously, the test assesses divided attention, working memory, and visual-motor and visual-perceptual speed. In addition, comparison of performance under single and dual task conditions yields information regarding the subject’s capacity for multitasking.	7

* Order in which tests were performed.

The primary end point was the effect of each antimuscarinic at week 3, versus placebo, on recent (delayed) memory as measured by accuracy on the delayed recall Name-Face Association Test [20]. This test measures an ability that declines markedly with advancing age [4] and has shown some limited changes in response to drugs [21]. Name-recall is the most frequent memory complaint at all ages across multiple cultures [18,22]. This parameter is therefore relevant to the daily activities of older patients with OAB, making it appropriate for analysis. The most important secondary end points were delayed recall on the First-Last Name Association Test [19] and the Misplaced Objects Test [23], both of which measure memory abilities relevant to daily life, and on which performance declines with advancing age. Also included as secondary measures were delayed recall scores at weeks 1 and 2, and effects on immediate memory, visual attention, information processing and psychomotor/reaction time.

Subjective memory loss was assessed as a tertiary end point, using a validated self-reporting instrument, the Memory Assessment Clinics Self-Rating Scale (MAC-S) [18]. The MAC-S is a test in pencil/paper format, in which each subject is asked to rate their abilities on 10 specific memory tasks and two global items. Subjects were asked to rate how their memory had changed since the beginning of the study.

2.3. Assessment of safety and tolerability

Adverse events (AEs) (graded by severity and relationship to study drug as assessed by investigators), including serious AEs (SAEs), were documented. Results of laboratory tests and vital signs were recorded.

2.4. Statistical analyses

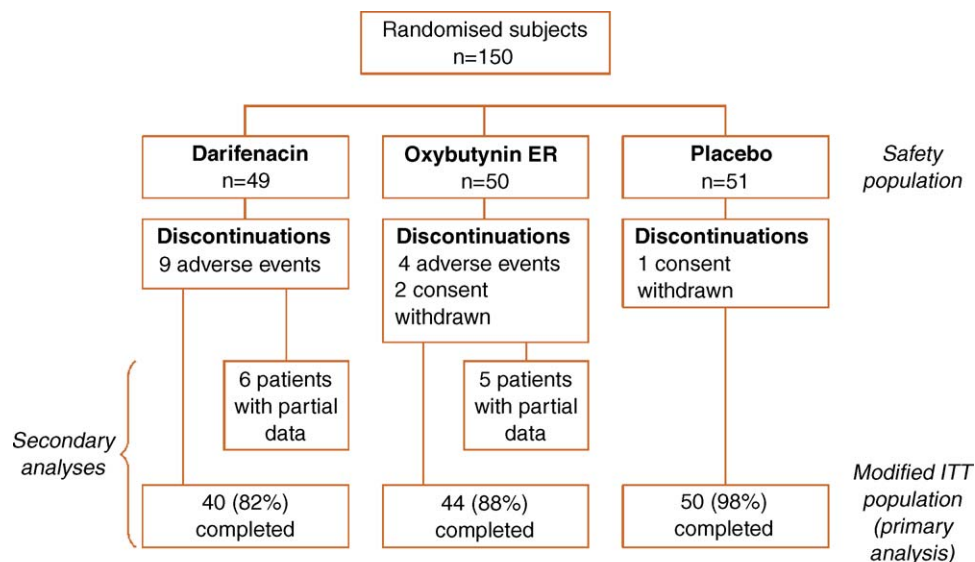
A sample size of 35 subjects per group was considered sufficient to detect an effect size of 0.867 for active treatment versus placebo at week 3. This decision was based on

oxybutynin ER having an effect size, versus placebo, approximately one third of that seen with scopolamine in older patients [7]. Allowing for a dropout rate of 30%, enrollment continued until at least 150 subjects ($\geq 50\%$ female) were recruited. Thus, a 1:1:1 randomisation schedule gave approximately 50 subjects per group. Analysis of the primary end point was based on a modified intent-to-treat (ITT) population (subjects taking at least one dose of study medication with complete baseline and week 3 scores for the primary end point). For secondary end points, the modified ITT population comprised subjects with scores for at least one test at baseline and any post-baseline time point. Scores for active treatments were compared with placebo using an analysis of covariance (ANCOVA) model with baseline score, age and gender as covariates. This was a two-sided test at the 5% significance level. For exploratory purposes, comparisons between darifenacin and oxybutynin ER were derived from an identical ANCOVA model.

3. Results

3.1. Subjects

One hundred and fifty subjects (darifenacin $n = 49$, oxybutynin ER $n = 50$, placebo $n = 51$) were randomised and comprised the safety population. Of these, 134 completed the study and formed the modified ITT population for the primary analysis (Fig. 2). Of the nine subjects who discontinued in the darifenacin group, six had partial data and were included in secondary analyses. There were six discontinuations in the oxybutynin ER group, of which partial data available for five subjects were included in secondary analyses. One subject in the placebo group discontinued, for whom partial data were not available for



ER: extended release; ITT: intent-to-treat.

Fig. 2 – Patient flow through the 3-week study.

Table 2 – Subject demographics and baseline characteristics

	Darifenacin (n = 49)	Oxybutynin ER (n = 50)	Placebo (n = 51)
Mean age (yr) (range)	66.4 (60–82)	68.0 (60–81)	67.4 (61–83)
Female (n [%])	29 (59.2)	31 (62.0)	33 (64.7)
Mean BMI (kg/m ²) (range)	25.9 (19–30)	26.7 (21–30)	25.7 (19–30)
Race (%)			
Caucasian	93.9	94.0	94.1
Black	4.1	6.0	3.9
Pacific Islander	2.0	0	0
Other	0	0	2.0
Mean baseline score for delayed recall on:			
Name–Face Association Test [*]	5.2	5.8	5.4
First–Last Name Association Test [†]	1.7	1.8	1.6

BMI = body mass index.
^{*} Modified intent-to-treat population (primary): darifenacin n = 40, oxybutynin ER n = 44, placebo n = 50.
[†] Modified intent-to-treat population (secondary): darifenacin n = 46, oxybutynin ER n = 49, placebo n = 50.

inclusion in secondary analyses (Fig. 2). Demographics and baseline characteristics were similar across treatment groups (Table 2).

3.2. Assessment of memory – delayed recall

There was no significant difference between the darifenacin and placebo groups with respect to the primary end point, delayed recall on the Name–Face Association Test at week 3 (mean difference, -0.06 , $p = 0.908$). In contrast, scores for delayed recall on the Name–Face Association Test were significantly lower in the oxybutynin ER group than the placebo group (mean difference, -1.30 , $p = 0.011$) or darifenacin group (mean difference, -1.24 , $p = 0.022$), indicating memory deterioration (Fig. 3).

Results from the Name–Face Association Test at week 2 were consistent with those at week 3, when there also was no significant difference between the darifenacin and placebo groups for delayed recall

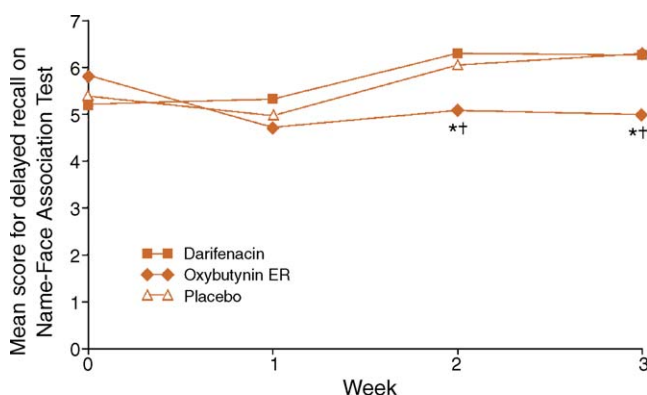


Fig. 3 – Effects of darifenacin, oxybutynin ER and placebo on accuracy of delayed recall on the Name–Face Association Test at each time point. ER = extended release; ANCOVA = analysis of covariance.

(Fig. 3, Table 3). For oxybutynin ER, scores at week 2 were significantly lower than for placebo or darifenacin (mean differences, -0.99 , $p = 0.022$ and -1.23 , $p = 0.007$, respectively), showing that the memory impairment at week 3 also was evident at week 2 (Table 3). There were no significant between-treatment differences at week 1, when lowest doses were administered.

For darifenacin and placebo, there was a trend for improvement during the study (Fig. 3), reflecting a learning effect whereby subjects improve through practise. Thus, by week 3, mean scores for delayed recall on the Name–Face Association Test had increased by 0.9 and 1.0 in the placebo and darifenacin groups, respectively. In the oxybutynin ER group, in whom a similar learning effect was expected, a decrease in performance by -0.8 was observed.

In delayed recall on the First–Last Name Association Test, oxybutynin ER resulted in significant impairment versus placebo ($p < 0.05$) at weeks 1 and 2 (Fig. 4; Table 4). In contrast, no significant differences were observed between darifenacin and placebo at any time point (Fig. 4; Table 4).

In the Misplaced Objects Test, oxybutynin ER resulted in significantly lower scores than placebo at weeks 2 and 3 for correct recall at first attempt (Table 4), suggesting a decline in performance, whereas darifenacin was not significantly different from placebo at any time point.

3.3. Assessment of memory – immediate recall

Oxybutynin ER reduced accuracy scores for immediate recall on the First–Last Name Association Test at second acquisition (attempt) versus placebo (mean differences, -0.28 , -0.55 and -0.32 at weeks 1, 2 and 3, respectively), with significant effect at week

Table 3 – Accuracy of delayed recall on the Name–Face Association Test over time*

Treatment	n	Comparator	Estimated LSM difference	95% CI	p value
Week 1					
Darifenacin 7.5 mg	45	Oxybutynin ER 10 mg	0.61	–0.26, 1.49	0.170
		Placebo	0.32	–0.54, 1.19	0.463
Oxybutynin ER 10 mg	49	Placebo	–0.29	–1.13, 0.55	0.497
Placebo	50	–	–	–	–
Week 2					
Darifenacin 7.5 mg	42	Oxybutynin ER 15 mg	1.23	0.35, 2.12	0.007
		Placebo	0.25	–0.62, 1.12	0.576
Oxybutynin ER 15 mg	47	Placebo	–0.99	–1.83, –0.15	0.022
Placebo	49	–	–	–	–
Week 3					
Darifenacin 15 mg	40	Oxybutynin ER 20 mg	1.24	0.18, 2.29	0.022
		Placebo	–0.06	–1.08, 0.96	0.908
Oxybutynin ER 20 mg	44	Placebo	–1.30	–2.28, –0.31	0.011
Placebo	50	–	–	–	–

ER = extended release; LSM = least square mean.

* Analysis of covariance model adjusted for baseline score, age and gender. Negative differences indicate relatively worse scores.

2 ($p = 0.029$; Table 4). No significant difference was detected between darifenacin and placebo on this test (Table 4). No significant between-treatment differences were noted for this test at first acquisition (data not shown).

No significant difference was observed among treatment groups for other assessments of immediate recall: accuracy on Name–Face Association Test (first or second acquisition) or accuracy on Facial Recognition Test (correct before first miss and total correct) (Table 4).

3.4. Visual attention

No significant differences were observed between treatment groups at any time point in the Matching to Sample Test for efficiency (Table 4), speed or or

accuracy. Similarly, in the Visual Sequence Comparison Test, there was no significant difference in scores over time among treatment groups for efficiency (Table 4), speed or accuracy.

3.5. Information processing speed

Darifenacin was associated with significantly slower response times than placebo at week 3 for sequence comparison speed in the Divided Attention Test (mean difference, 0.3 seconds, $p = 0.012$; Table 4). There was no significant difference among treatments in scores over time for sequence comparison efficiency or accuracy, and median reaction to correct response in the Visual Sequence Comparison Test (Table 4).

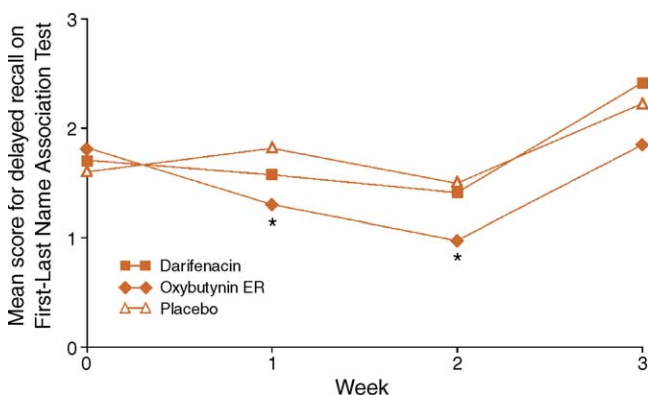
At week 2, darifenacin had a significantly higher score than oxybutynin ER for Single Task Premature Hits (mean difference, 0.56, $p = 0.046$; Table 4), but was not significantly different from placebo. No significant difference was observed among treatment groups over time for Dual Task Reaction Time or Dual Task Premature Hits.

3.6. Psychomotor/reaction time

No significant difference was observed among treatment groups in response speed to the Visual Monitoring Task alone.

3.7. Memory Assessment Clinics Self-Rating Scale

In contrast with objective memory tests, there was no significant difference between groups in self-rated memory, as assessed by MAC-S scores at any



* $p < 0.05$ vs placebo (ANCOVA, adjusted for baseline score, age and gender).

Fig. 4 – Effects of darifenacin, oxybutynin ER and placebo on accuracy of delayed recall on the First–Last Name Association Test at each time point. ER = extended release; ANCOVA = analysis of covariance.

Table 4 – Scores in additional tests of memory and cognitive function over time

Test	Treatment	Comparator	Estimated LSM difference		
			Week 1	Week 2	Week 3
Immediate memory recall					
Name–Face Association (accuracy, second acquisition)	Darifenacin	Placebo	0.10	0.48	–0.30
		Oxybutynin ER	–0.13	0.91	0.44
	Oxybutynin ER	Placebo	0.23	–0.43	–0.74
First–Last Name Association (accuracy, second acquisition)	Darifenacin	Placebo	–0.13	–0.26	–0.00
		Oxybutynin ER	0.15	0.29	0.32
	Oxybutynin ER	Placebo	–0.28	–0.55 [†]	–0.32
Facial Recognition (accuracy, correct before first miss)	Darifenacin	Placebo	0.36	0.28	0.29
		Oxybutynin ER	1.22	–0.09	1.66
	Oxybutynin ER	Placebo	–0.87	0.37	–1.37
Delayed memory recall					
First–Last Name Association (accuracy)	Darifenacin	Placebo	–0.26	–0.11	0.18
		Oxybutynin ER	0.27	0.43	0.57
	Oxybutynin ER	Placebo	–0.53 [†]	–0.53 [†]	–0.39
Misplaced Objects (correct recall at first attempt)	Darifenacin	Placebo	–0.73	–1.13	–0.73
		Oxybutynin ER	–0.42	0.38	0.30
	Oxybutynin ER	Placebo	–0.31	–1.51 [†]	–1.03 [*]
Visual attention					
Matching to Sample (efficiency)	Darifenacin	Placebo	–0.61	–0.27	–1.94
		Oxybutynin ER	–2.05	–1.04	–1.83
	Oxybutynin ER	Placebo	1.44	0.77	–0.11
Visual Sequence Comparison (efficiency)	Darifenacin	Placebo	–0.15	–1.06	–2.33
		Oxybutynin ER	–0.81	–1.89	–1.24
	Oxybutynin ER	Placebo	0.65	0.83	–1.09
Information-processing speed					
Divided Attention (Sequence Comparison Speed, Dual Condition) (s)	Darifenacin	Placebo	0.03	0.06	0.30 [*]
		Oxybutynin ER	–0.07	0.08	0.24
	Oxybutynin ER	Placebo	0.10	–0.02	0.06
Divided Attention (Sequence Comparison Efficiency) (s)	Darifenacin	Placebo	0.42	0.31	–2.19
		Oxybutynin ER	–0.20	0.19	–1.98
	Oxybutynin ER	Placebo	0.61	0.12	–0.21
Divided Attention (Sequence Comparison Accuracy) (s)	Darifenacin	Placebo	–1.47	2.21	2.21
		Oxybutynin ER	–0.88	2.38	2.38
	Oxybutynin ER	Placebo	–0.59	–0.17	–0.17
Visual Sequence Comparison (median reaction to correct response)	Darifenacin	Placebo	0.04	0.07	0.12
		Oxybutynin ER	0.00	0.11	0.10
	Oxybutynin ER	Placebo	0.03	–0.03	0.01
Divided Attention (Single Task Premature Hits) (s)	Darifenacin	Placebo	0.21	0.50	0.12
		Oxybutynin ER	0.10	0.56 [*]	0.38
	Oxybutynin ER	Placebo	0.11	–0.06	–0.27
Divided Attention (Task Reaction Time, Dual Condition) (s)	Darifenacin	Placebo	0.05	0.10	0.02
		Oxybutynin ER	–0.01	0.04	–0.04
	Oxybutynin ER	Placebo	0.06	0.06	0.06
Divided Attention (Premature Hits, Dual Condition) (s)	Darifenacin	Placebo	0.40	–0.20	0.12
		Oxybutynin ER	0.25	0.22	0.39
	Oxybutynin ER	Placebo	0.15	–0.42	–0.27
Psychomotor/reaction time					
Divided Attention (Response Speed to Visual Monitoring Task Alone) (s)	Darifenacin	Placebo	–0.01	0.00	–0.03
		Oxybutynin ER	–0.01	–0.01	–0.03
	Oxybutynin ER	Placebo	–0.00	0.01	0.01

Modified intent-to-treat population. ER = extended release; LSM = least square mean.

^{*} $p < 0.05$.[†] $p < 0.01$ (analysis of covariance [adjusted for baseline score, age and gender]).

Table 5 – Adverse event incidence (safety population)

	Darifenacin (n = 49)	Oxybutynin ER (n = 50)	Placebo (n = 51)
Subjects with any adverse event (n)	27	26	23
Treatment-related	26	22	16
Severe adverse events	4	7	1
Serious adverse events	0	1	0
Most common all-causality adverse events (n)			
Dry mouth	13	20	6
Constipation	10	2	1
Dyspepsia	3	2	1
All-causality nervous system events (n)	5	4	3
Severe	0	2	0

time point. At week 3, the mean MAC-S scores were 40.2, 41.8 and 40.2 for darifenacin, oxybutynin ER and placebo, respectively, which were similar to baseline (40.7, 40.0 and 39.1, respectively).

3.8. Adverse events

The incidence of all-causality AEs is shown in Table 5. The most frequently reported AEs, as expected for this class, were dry mouth and constipation. Dry mouth occurred more frequently during oxybutynin ER than darifenacin treatment (40.0% vs 26.5%). One patient in each of the oxybutynin ER and darifenacin groups discontinued because of dry mouth. The incidence of constipation was higher in the darifenacin than oxybutynin ER group (Table 5). Only one patient (in the darifenacin group) discontinued because of constipation. The total incidence of all-causality nervous system events was similarly low in all groups, with only two severe cases, both in the oxybutynin ER group (Table 5). There was one serious AE (hip fracture following an accident at home in a subject given oxybutynin ER), which was not considered to be related to the study drug. There were no clinically significant findings from assessments of laboratory values or vital signs.

4. Discussion

This study demonstrated that the M₃ selective receptor antagonist darifenacin had no significant effect on memory in older subjects. In contrast, oxybutynin ER resulted in significant memory deterioration, as measured by delayed recall on the Name–Face Association Test at week 3. Comparing these results with normative data for this test [4] indicates that the degree of memory change seen with oxybutynin ER (baseline to week 3) was comparable to a decline that occurs over the course of 10 years in the normal aging process. Additional

tests of delayed recall indicated significant memory impairment with oxybutynin ER versus placebo (Name–Face Association at week 2, First–Last Name Association at weeks 1 and 2, and Misplaced Objects at weeks 2 and 3), while darifenacin was not significantly different from placebo in delayed recall at any time point.

The delayed recall tests were selected on the basis of their relevance to daily activities. Recalling the name of someone to whom one is introduced is the most problematic memory task faced on a daily basis in many cultures, and performance declines markedly over the adult life-span [4,22]. For example, performance on the Name–Face Association Test [20] declines by >65% between age 25 and 75 years [4]. This ‘normal’ decline may be exaggerated by drugs [24], and the combined effect would be expected to be of clear clinical significance. In a similar manner, performance declines with age on the First–Last Name Association [19] and Misplaced Objects Tests [23]; this effect also can be exaggerated by drugs [24]. Thus, the deleterious effects of oxybutynin ER on these tests suggests that this agent, at the dosage tested, may be associated with diminished performance on important tasks of daily life that depend on delayed recall.

Differential outcomes between darifenacin and oxybutynin ER may arise from differences in either CNS penetration or muscarinic receptor-binding profiles. Darifenacin exhibits limited CNS penetration in preclinical studies, which may result from its moderate lipophilicity, relatively large molecular size, polarity and active efflux across the blood-brain barrier via the P-glycoprotein pump [25]. Once in the CNS, muscarinic-binding profiles play a role. Whereas darifenacin shows marked M₃ selectivity, oxybutynin demonstrates high affinity for M₃ and M₁ subtypes [9]. The latter subtype is abundant in the neocortex, hippocampus and neostriatum, in contrast with low levels of M₃ receptors in the brain [26], and M₁ receptors are known to be particularly important for memory/cognition [10,11]. This

hypothesis is supported by the low incidence of nervous system AEs with darifenacin, both here and in longer-term clinical trials. A pooled analysis of three 12-week, fixed-dose studies with darifenacin showed a profile of nervous system events that was comparable with placebo, both overall and in patients ≥ 65 years [27,28]. In contrast, results from four clinical studies of ≤ 4 months showed that the incidence of somnolence and dizziness with oxybutynin ER 5–30 mg/day was 12% and 6%, respectively [16].

This study also measured immediate recall, for which oxybutynin ER showed some impairment versus placebo, while darifenacin and placebo were not significantly different. Major changes were not expected here, as muscarinic receptor activation is thought to be involved primarily in memory consolidation [29] (i.e., how recent recollections are crystallised into memory). Similarly, significant effects were not expected in attention tests, and no effects were observed across multiple tests. Within the Divided Attention Test, however, darifenacin was significantly worse than placebo for sequence comparison speed (mean difference, 0.3 s) but did not differ from placebo in accuracy. Darifenacin scored worse than oxybutynin ER in the number of premature hits on a reaction time measure at week 2 (but not week 3) and did not differ significantly from placebo. Given that subjects receiving darifenacin performed no differently than those on placebo/on multiple other tests of attention, these isolated findings are not considered clinically relevant. In contrast, findings with oxybutynin ER on memory were replicated across multiple tests at different time points, and are supported by earlier studies and an identifiable mechanism of action.

Interestingly, there were no reported differences in self-rated memory between treatments. This finding is particularly important as it indicates that memory changes may go unnoticed. This low level of awareness may account for the low rate of reporting of memory impairment with antimuscarinic therapies in clinical practice. In addition, disease- or treatment-related memory/cognitive impairment may be difficult to recognise, and memory decline may be attributed wrongly to aging.

Although relevant for all patients, these findings are particularly important for older patients, since this population may have risk factors for memory/cognitive impairment [30]. Important differences between this study and clinical practice are that frail elderly patients may have been under-represented (since ability to complete computerised cognitive tests and normal MMSE scores were required), and

use of multiple medications with anticholinergic activity will be common in older patients in clinical practice [30]. In the study reported here, where patients were not receiving anticholinergic co-medication and had no cognitive impairment at baseline, the lowest oxybutynin ER dose (10 mg od) did not cause memory impairment. In clinical practice, however, when patients may be receiving concomitant anticholinergics or have existing memory impairment, it is possible that this dose of oxybutynin ER may have a greater impact.

5. Conclusions

The results of this study add considerably to our knowledge regarding the differential effects of two antimuscarinics, darifenacin and oxybutynin ER, on memory. The finding that darifenacin does not impair memory is consistent with earlier studies [13,14], and the observation assumes clinical significance in light of the clear demonstration of memory impairment during oxybutynin ER treatment. These findings highlight a need for further studies to fully establish the effects of all OAB antimuscarinics on memory/cognition.

Conflicts of interest

Preparation of this manuscript was supported by Novartis Pharma AG, and editorial and project management services were provided by ACUMED®.

Acknowledgements

We are grateful for the support of our co-investigators, J. Diaz, FL, USA; L. Gilderman, FL, USA; J. Miller, FL, USA; J. Nardandrea, FL, USA; B. Rankin, FL, USA; M. Sabbagh, AZ, USA; L. Schmidt, AZ, USA, and to the staff of Network Neurometrics, Inc, and Advanced Research Corporation who conducted the study.

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