

# 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

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**OBJECTIVES:** Determine the cognitive effect, safety, and tolerability of oral extended-release oxybutynin in cognitively impaired older nursing home residents with urge urinary incontinence.

**DESIGN:** Randomized, double-blinded, placebo-controlled trial.

**SETTING:** Twelve skilled nursing homes.

**PARTICIPANTS:** Fifty women aged 65 and older with urge incontinence and cognitive impairment.

**INTERVENTION:** Four-week treatment with once-daily oral extended-release oxybutynin 5 mg or placebo.

**MEASUREMENTS:** Withdrawal rates and delirium or change in cognition from baseline at 1, 3, 7, 14, 21, and 28 days after starting treatment using the Confusion Assessment Method (CAM), Mini-Mental State Examination (MMSE), and Severe Impairment Battery (SIB). The Brief Agitation Rating Scale, adverse events, falls incidence, and serum anticholinergic activity change with treatment were also assessed.

**RESULTS:** Participants' mean age  $\pm$  standard deviation was  $88.6 \pm 6.2$ , and MMSE baseline score was  $14.5 \pm 4.3$ . Ninety-six percent of subjects receiving oxybutynin ( $n = 26$ ) and 92% receiving placebo ( $n = 24$ ) completed treatment ( $P = .50$ ). The differences in mean change in CAM score from baseline to all time points were equivalent between the oxybutynin and placebo groups. Delirium did not occur in either group. One participant receiving

oxybutynin was withdrawn because of urinary retention, which resolved without treatment. Mild adverse events occurred in 38.5% of participants receiving oxybutynin and 37.5% receiving placebo ( $P = .94$ ).

**CONCLUSION:** Short-term treatment using oral extended-release oxybutynin 5 mg once daily was safe and well tolerated, with no delirium, in older female nursing home participants with mild to severe dementia. Future research should investigate different dosages and long-term treatment. *J Am Geriatr Soc* 2008.

**Key words:** aged; anticholinergics; cognition; safety; urinary incontinence

Urge urinary incontinence (UUI) and cognitive impairment are prevalent and frequently coexist in older nursing home residents.<sup>1</sup> Despite being preferred by nursing home residents for managing their incontinence,<sup>2</sup> antimuscarinic medications are underused in this population.<sup>3</sup> Barriers to using antimuscarinics include little information regarding their safety and efficacy, particularly in frail elderly people and those with cognitive impairment, in whom concern exists that antimuscarinics may further impair cognition.<sup>4,5</sup> Previous trials have showed that antimuscarinic therapy is modestly effective in treating UUI in cognitively impaired nursing home residents.<sup>6</sup> The purpose of this trial was to evaluate the effect of antimuscarinic therapy for overactive bladder on cognition, safety, and tolerability in older female nursing home residents with UUI and impaired cognition.

## METHODS

### Design

A randomized, double-blinded, placebo-controlled trial design was used. Selection criteria are listed in Table 1.<sup>7-11</sup>

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**Table 1. Eligibility Criteria**

Inclusion criteria
Female
Aged $\geq 65$
Resident for $\geq 3$ months in long-stay nursing home unit
Mini-Mental State Examination score of 5–23 <sup>7</sup>
Global Deterioration Scale score of 3–6 <sup>8</sup>
Urinary incontinence
$\geq 1$ symptom or sign of urge urinary incontinence ( $\geq 4$ micturitions or wet checks or requests to toilet within an 8-hour period of prompted voiding schedule on 2 consecutive days (8:00 a.m. to 4:00 p.m.); <sup>9,10</sup> nocturia or nocturnal enuresis $> 2$ times per night; staff observation that incontinence occurs on way to toilet or resident reports urgency; or medical record documentation of detrusor overactivity or urgency)
Ability to swallow medication intact
Medication adherence rate $\geq 80\%$ during the week before screening
Exclusion criteria
Terminal illness
Bed-bound
Noncommunicative
Delirium (Confusion Assessment Method feature 1 (acute onset) and 2 (inattention) plus feature 3 (disorganized thinking) or 4 (altered level of consciousness)) <sup>11</sup>
Lewy body dementia
History of $\geq 3$ urinary tract infections in previous year or current infection
Postvoid residual urine volume $\geq 150$ mL (bladder ultrasound)
Urethral diverticulum
Bladder tumor or stone
Severe pelvic organ prolapse or vaginitis
Genitourinary surgery within past 6 months
Hepatic disease
Severe cardiovascular disease
Myasthenia gravis
Spinal cord injury
Bowel movement $<$ every 3 days
History of gastrointestinal obstruction or decreased motility
Current drug therapy for urinary incontinence
Current use of acetylcholinesterase inhibitor or bisphosphonate
Investigational drug, systemic or ophthalmic cholinomimetic drug, diphenhydramine, or gastrointestinal antispasmodic within 2 weeks before trial

Participants were stratified according to cognition using Mini-Mental State Examination (MMSE) scores 5 to 10 and 11 to 23<sup>7</sup> and randomized by the investigational pharmacy using a computer-generated randomization program to 4 weeks of treatment with oral extended-release oxybutynin chloride 5 mg tablets or placebo (identical-appearing sham tablet) once daily. Using an intention-to-treat analysis, the same experienced research nurse practitioner (NP; MM) collected data at baseline and 1, 3, 7, 14, 21, and 28 days after starting treatment. All study personnel were blinded to group assignment until data collection was complete. The University of Minnesota institutional review board approved the trial protocol.

### Procedures

After 12 nursing facilities agreed to participate in the trial, designated nursing staff were provided with a standard

screening checklist for trial inclusion (nursing home resident for at least 3 months; aged  $\geq 65$ ; not residing in a subacute, transitional care, or rehabilitation unit of the nursing home; not enrolled in hospice; bladder incontinence (Minimum Data Set 2.0 score of 1–4);<sup>12</sup> no indwelling catheter; able to swallow medication intact) and obtained permission from potential participants or their designated proxies for chart review by the NP. For eligible individuals, primary care providers were contacted to obtain approval for their trial participation. Informed consent was obtained from the individual or their proxies. Participant assent was verified implicitly by cooperation with trial procedures; refusal of venipuncture and other procedures that resulted in withdrawal.

The NP determined final eligibility after a history, physical examination, mental status evaluation, postvoid residual (PVR) determination, and urine culture. Individuals with a urinary tract infection (UTI) who achieved urine culture–documented resolution after antibiotic therapy and remained incontinent were included. A research nursing assistant conducted wet pad checks (hourly for 8 hours on 2 consecutive days) using an adapted protocol;<sup>9,10</sup> those with all dry checks were excluded.

Serum anticholinergic activity (SAA) was measured at baseline and at the end of week 1 (estimated SAA steady-state).<sup>13</sup> Serum assays were performed at the Geriatric Psychopharmacology Research Laboratory, University of Pittsburgh Medical Center/Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania, following an established protocol used in prior trials.<sup>14</sup>

Both treatments were administered with water with the administration of the first morning medications. Nursing staff maintained a medication administration record and documented medication omissions or other aberrations with an explanation for such occurrences.

Participants were monitored weekly for medication errors, adverse events, UTIs, and urinary retention according to bladder ultrasound. Treatment was discontinued if the PVR was 250 mL or greater; if a UTI was present (positive urine dipstick test for leukocyte esterase, nitrite, and bacteria); or at participant, surrogate, or primary care provider request. When treatment was discontinued because of an adverse event, cognitive function tests were administered at 1, 3, and 7 days after treatment discontinuation.

### Outcome Measures

#### *Cognitive Effects*

The Confusion Assessment Method (CAM), a standard diagnostic algorithm based on four of the nine key features from the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*, criteria,<sup>11</sup> was used to measure cognitive effects. Cognitive decline as measured according to mean change in CAM scores from baseline to the different time periods was the primary outcome.

The presence or absence of delirium as determined according to the CAM was used as a secondary outcome measure. The CAM has been validated in elderly outpatients<sup>11</sup> and used in previous research involving nursing home residents.<sup>15</sup>

Other secondary endpoints were measures of cognition using the MMSE<sup>7</sup> and Severe Impairment Battery (SIB)<sup>16</sup>

and agitation using the Brief Agitation Rating Scale (BARS),<sup>17</sup> all of which have been validated in nursing home residents. Secondary measures of cognitive decline were any clinically meaningful (i.e., exceeding measurement error) decrease in MMSE (> 3 points)<sup>18</sup> or SIB (> 14 points)<sup>19</sup> scores. A clinically meaningful increase in the BARS score indicated worsening agitation (> 7 points).<sup>20</sup>

### *Tolerability and Safety*

Tolerability was measured by comparing withdrawal rates between treatment groups. Adverse events were identified according to participant self-report, solicited reports from primary care providers and nursing staff, progress notes, NP-administered checklist of established adverse effects, and PVR measurement on days 1, 3, 7, 14, 21, and 28 after treatment initiation. Adverse events were rated mild (resolved with little or no long-term effect), moderate (not immediately life-threatening or resulting in death or hospitalization but may jeopardize well-being or require intervention to prevent hospitalization or death), or severe (hospitalization, life-threatening, or persistent or significant disability). The NP categorized adverse events as possibly, probably, or very likely treatment-related in consultation with a physician co-investigator (TCM). The frequency of falls 3 months before, during, and 3 months after treatment were collected using incident reports and progress notes.

### *Statistical Analysis*

The primary hypothesis of equivalence between treatment groups was tested by evaluating the 95% confidence intervals of the mean change in CAM score from baseline at each time point. Sample size calculations assuming an alpha significance level of .05 indicated that 21 participants per group would provide adequate power (80%) to conclude equivalence between treatment groups in mean change in CAM score from baseline. A 95% confidence interval contained within the range of clinical equivalence provided evidence of statistical equivalence. Clinical equivalence (i.e., non-clinically meaningful change), not a trial outcome, was defined as a 2-point or less difference in mean change in CAM score (S. Inouye, personal communication, March 31, 2002). Differences between groups in baseline characteristics and secondary outcomes (delirium, MMSE, SIB, BARS) were evaluated using Wilcoxon rank-sum tests and chi-square tests as appropriate. Any changes from baseline to beyond the time of participant withdrawal from the trial were not included in the analysis (i.e., the method of last observation carried forward was not employed) in order to most reliably reflect change at the time point of participant withdrawal. Within-group changes from baseline were evaluated using Wilcoxon signed-rank tests. Multiple regression analysis was used to test between-group differences in mean change in MMSE score from baseline to Week 4, adjusted for age, SAA, and number of anticholinergic medications. Tolerability was evaluated according to comparison of treatment withdrawal using the chi-square test. Safety was evaluated using chi-square tests for falls and adverse events. In addition, a generalized estimating equation (GEE) repeated-measures Poisson regression model was used to evaluate change in falls per month over the 3 months before, during, and 3 months after the trial. Correlation analysis was used to evaluate associations between

changes in SAA and changes in CAM, MMSE, SIB, and BARS scores from baseline to Day 7. An alpha significance level of .05 was used to establish significance.

## **RESULTS**

### *Participants*

Figure 1 presents participant flow. Fifty participants (mean age  $\pm$  standard deviation  $88.6 \pm 6.2$ ) were enrolled between August 2003 and May 2005. Except for one white Hispanic participant randomized to placebo, all participants were white non-Hispanic. Thirty-seven participants had a MMSE score between 11 and 23 (18 receiving placebo, 19 receiving oxybutynin), and 13 had MMSE scores between 5 and 10 (6 receiving placebo, 7 receiving oxybutynin). Overall, 26 participants were randomized to oxybutynin and 24 to placebo. Participants' mean baseline MMSE score was  $14.5 \pm 4.3$ . There were no group differences in baseline demographic, functional, or neuropsychiatric characteristics or clinical factors predisposing to delirium, participants' ability to make themselves understood by nursing staff, or SAA (Table 2).

### *Treatment Adherence*

Treatment adherence (e.g., proportion of total doses received) was similar between groups—97% receiving oxybutynin and 97.4% receiving placebo. There was no difference between groups in the proportion of participants with missed doses ( $P = .54$ ). An individual participant receiving drug and placebo missed no more than three doses and two doses, respectively. No doses were withheld for a suspected adverse drug event in either group.

### *Cognitive Effects*

The differences in mean CAM scores between groups were statistically and clinically equivalent at each time point, and no participant experienced delirium (Figure 2A).<sup>11</sup>

To evaluate the possible effect of dementia severity, an analysis was conducted with participants in the two baseline MMSE strata. For participants with baseline MMSE scores between 11 and 23, mean change in CAM score between groups was equivalent at all time points. For participants with baseline MMSE scores between 5 and 10, equivalence could not be definitively concluded because of small sample sizes for the drug ( $n = 7$ ) and placebo ( $n = 6$ ) groups. None of the estimated differences in mean change in CAM score from baseline were greater than  $\pm 2$  points, but upper and lower confidence interval limits extended beyond the range of conclusive clinical equivalence (Figure 2B).

### *Other Cognitive Changes*

Within both groups, median changes in MMSE and SIB scores from baseline to each time point were positive (i.e., cognitive improvement). Although there were several significant increases in median MMSE and SIB scores from baseline within each group, the increase for those receiving the drug was not different from those who received placebo at any time point ( $P = .24-.93$  (MMSE) and  $.38-.85$  (SIB)) or on day 28 ( $P = .98$  (MMSE) and  $.62$  (SIB)). Even after adjusting for potential confounders (age, number of medications known to have SAA, measured SAA after 7 days of

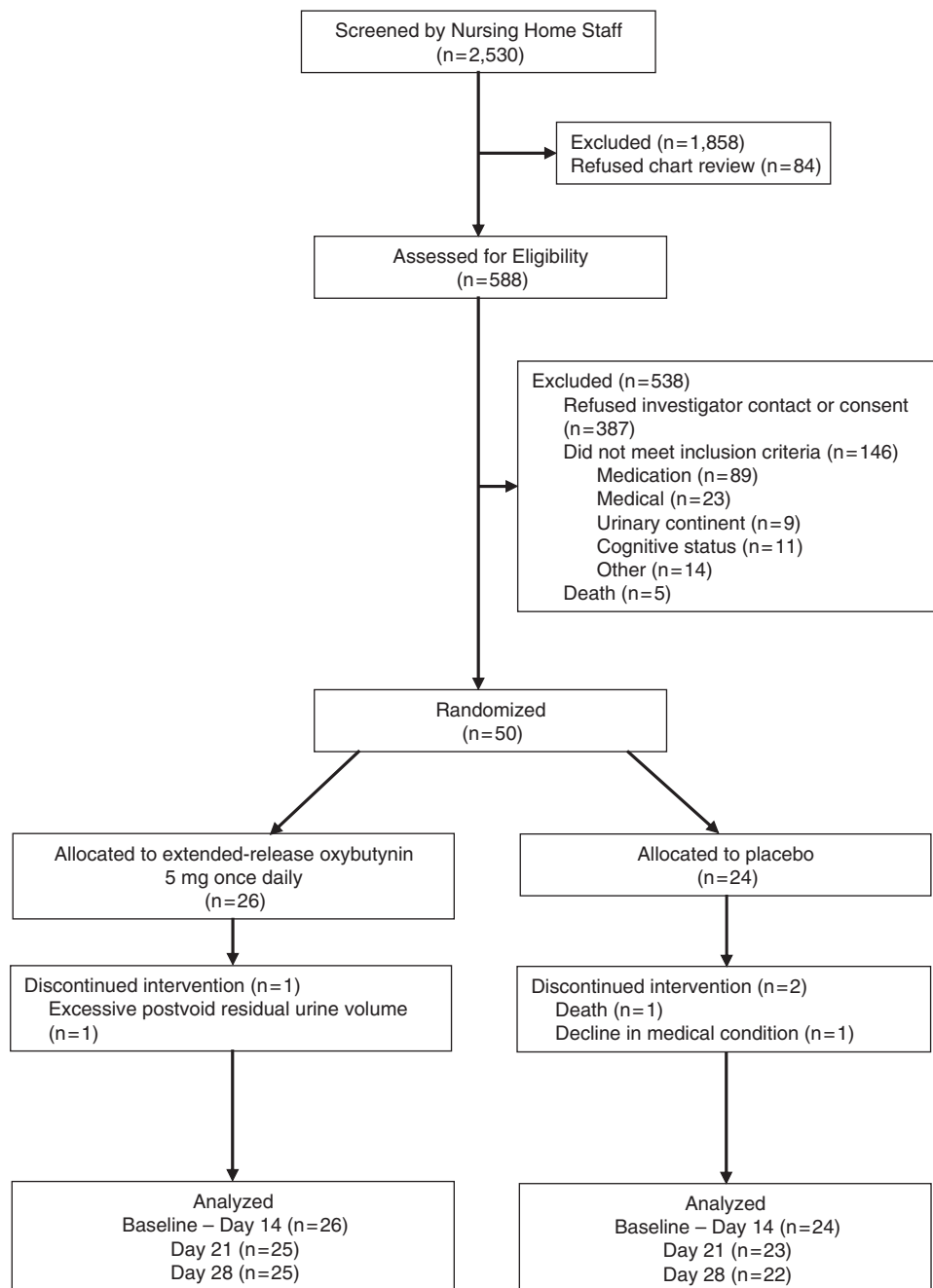


Figure 1. Participant flow.

treatment), there was no difference in mean MMSE score change from baseline to day 28 between groups.

### Agitation

There were no significant within-group changes in BARS scores from baseline to any time point for the drug ( $P = .48$ – $1.00$ ) or placebo ( $P = .15$ – $1.00$ ) groups. In addition, there were no group differences in the mean BARS score change at any time point ( $P = .50$ – $.94$ ).

### Serum Anticholinergic Levels and Cognitive Function

No participant received new medication with known anticholinergic activity from the first day of the trial through

Day 7, when the follow-up SAA was measured. There were no significant correlations between baseline SAA and baseline CAM or BARS scores within or between groups. Nor were there any correlations between change from baseline SAA and change in CAM, SIB, and BARS scores at Day 7 within or between groups.

### Tolerability and Safety

#### Tolerability

Forty-seven participants (94%) completed the trial: 25 participants (96%) receiving drug and 22 participants (92%) receiving placebo ( $P = .55$ ). Three participants were withdrawn before trial completion: one participant on Day 14

**Table 2. Baseline Sample Characteristics**

Characteristic	Oxybutynin (n = 26)	Placebo (n = 24)	P-Value*
<b>Demographics, mean ± SD</b>			
Age	89.2 ± 1.0	88 ± 1.5	.76
Body mass index <sup>†</sup>	27.2 ± 1.4	25.2 ± 1.2	.24
<b>Neuropsychiatric measures</b>			
Confusion Assessment Method score, mean ± SD <sup>‡</sup>	2.0 ± 0.3	1.8 ± 0.3	.72
MMSE score, mean ± SD <sup>§</sup>	15.2 ± 0.8	13.7 ± 0.9	.25
MMSE score 5–10 (26% of trial population), n (%)	7 (26.9)	6 (25.0)	.88
Severe Impairment Battery score, mean ± SD <sup>  </sup>	87.1 ± 1.6	87.0 ± 1.6	.96
Brief Agitation Rating Scale score, mean ± SD <sup>#</sup>	16.9 ± 1.9	16.1 ± 1.8	.75
<b>Predisposing or precipitating factors for delirium</b>			
Depression, n (%)	17 (65.4)	15 (62.5)	.83
Ambulatory without assistance, n (%)	9 (34.6)	11 (45.8)	.42
Able to transfer without assistance, n (%)	7 (26.9)	7 (29.2)	.86
Fall in past 30 days, n (%)	3 (11.5)	4 (16.7)	.60
Vision disturbance, n (%)	11 (42.3)	10 (41.7)	.96
Hearing disturbance, n (%)	4 (15.4)	3 (12.5)	.77
Number of medications, mean ± SD	10.9 ± 3.8	10.1 ± 4.5	.32
Opioids, n (%)	7 (26.9)	8 (33.3)	.62
Psychoactive medications, n (%)	22 (84.6)	20 (83.3)	.90
> 2 medications, n (%)	9 (34.6)	4 (16.7)	.15
Antipsychotics, n (%)	7 (26.9)	5 (20.8)	.61
Benzodiazepines, n (%)	2 (7.7)	2 (8.3)	.93
Antidepressants, n (%)	15 (57.7)	16 (66.7)	.51
Hypnotics (trazodone), n (%)	6 (23.1)	2 (8.3)	.16
Barbiturates, n (%)	2 (7.7)	1 (4.2)	.60
Antiepileptics, n (%)	2 (7.7)	4 (16.7)	.33
Number of medications with anticholinergic activity, mean ± SD	2.9 ± 0.3	2.5 ± 0.4	.37
Serum anticholinergic activity, median (range) (pmol/mL atropine equivalents)	0.95 (0.00–6.20)	1.15 (0.00–5.05)	.96
Number of chronic diseases, mean ± SD	9.1 ± 0.49	9.7 ± 0.42	.54
Chronic renal impairment, n (%)	3 (11.5)	1 (4.2)	.34
History of stroke, n (%)	8 (30.8)	8 (33.3)	.85
Parkinson's disease, n (%)	3 (11.5)	1 (4.2)	.34
Psychiatric disorder, n (%)	3 (11.5)	4 (16.7)	.60
Chronic anxiety, n (%)	6 (23.1)	3 (12.5)	.33
Anemia diagnosis, n (%)	8 (30.8)	12 (50)	.17
Current treatment, n (%)	8 (30.8)	5 (20.8)	.42
Painful condition, n (%)	17 (65.4)	20 (83.3)	.15
Insomnia ≤5 days/week, n (%)	0 (0.0)	2 (8.3)	.11
Sleep apnea, n (%)	0 (0.0)	1 (4.2)	.27
<b>Urological parameter</b>			
Postvoid residual volume, mL, mean ± SD	45.2 ± 9.8	67.5 ± 10.2	.05
Number of attempts to toilet per day, median (range)**	9 (1.5–12)	7.5 (0–16.5)	.67
Urinary incontinence episodes per day, median (range)**	9 (3.0–18)	6.8 (4.5–15)	.16

\* P-values are for chi-square test of proportions or Wilcoxon rank-sum test.

<sup>†</sup> Body mass index is weight in kilograms divided by the square of the height in meters.

<sup>‡</sup> Range 0–7, with scores ≥2 indicating delirium.

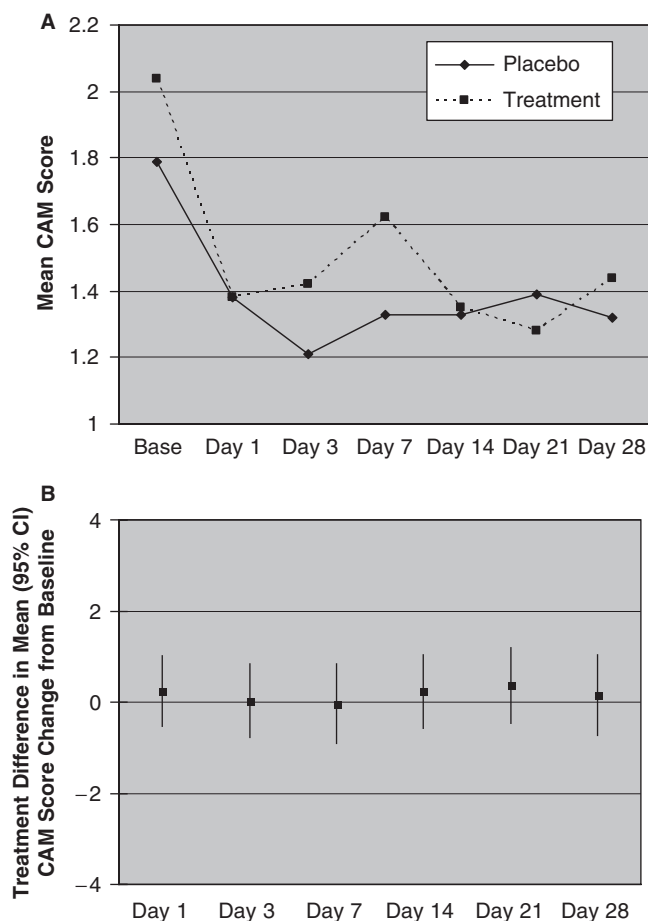
<sup>§</sup> Mini-Mental State Examination (MMSE) score range 0–30, with lower scores indicating greater cognitive impairment.

<sup>||</sup> Range 0–100, with lower scores indicating greater cognitive impairment.

<sup>#</sup> Range 10–70, with higher scores indicating more agitation.

\*\* Median number of toileting attempts during two 8-hour assessments periods (8:00 a.m. to 4:00 p.m.) over 2 consecutive days.

SD = standard deviation.



**Figure 2.** (A) Mean CAM scores for placebo and extended-release oral oxybutynin. (B) 95% confidence intervals for difference in the mean Confusion Assessment Method (CAM) score change from baseline between placebo and extended-release oxybutynin groups. Upper and lower limits of each confidence interval are within the range of clinical equivalence of a  $\pm 2$  point change in CAM score (area between the two outer lines).

(reversible excessive PVR volume of 353 mL, drug group) one on Day 16 (fatal stroke, placebo group), and one on Day 24 (family request because of a continuing decline in medical condition that predated trial enrollment, placebo group). Their data are included in the safety analysis. Of these three withdrawals, only the elevated PVR finding was considered very likely to be treatment related.

### Adverse Events

There was no difference in overall adverse events between groups ( $P = .53$ ). Drug and placebo treatments were associated with generally mild, transient adverse events, the majority of which were anticholinergic in nature (Table 3). Eight (31%) participants receiving drug experienced at least one of 14 treatment-related adverse events, and nine (37.5%) participants receiving placebo experienced at least one of 15 treatment-related adverse events ( $P = .76$ ). One participant receiving drug experienced six of 14 treatment-related adverse events, and one participant receiving placebo experienced five of 15 treatment-related adverse events.

The most common treatment-related adverse events were cough, constipation, falls, and dry mouth in both

**Table 3. Treatment-Related Adverse Events According to Treatment Group**

Adverse Event	Oxybutynin (n = 26)	Placebo (n = 24)
	n (%)	
Total adverse events	8 (30.8)	9 (37.5)
Withdrawal due to adverse treatment event	1 (3.8)	0 (0.0)
Cough	3 (11.5)	3 (12.5)
Constipation	2 (7.7)	0 (0.0)
Abdominal pain	1 (3.8)	0 (0.0)
Nausea	1 (3.8)	0 (0.0)
Vomiting	1 (3.8)	0 (0.0)
Fall*	1 (3.8)	2 (8.3)
Dry mouth	1 (3.8)	1 (4.2)
Urine retention	1 (3.8)	0 (0.0)
Dry nasal or sinus membranes	1 (3.8)	0 (0.0)
Headache	1 (3.8)	0 (0.0)
Skin rash	1 (3.8)	0 (0.0)
Dyspepsia	0 (0.0)	1 (4.2)
Dizziness	0 (0.0)	1 (4.2)
Somnolence	0 (0.0)	1 (4.2)
Fatigue	0 (0.0)	1 (4.2)
Confusion	0 (0.0)	1 (4.2)
Paranoia	0 (0.0)	1 (4.2)
Anorexia	0 (0.0)	1 (4.2)
Facial droop	0 (0.0)	1 (4.2)
Dysuria	0 (0.0)	1 (4.2)
Vision disorder	0 (0.0)	0 (0.0)

*Note:* Some participants experienced more than one adverse event.

Adverse treatment-related events were events probably or possibly related to treatment.

\* Falls during 4-week treatment.

groups. Although one participant discontinued drug treatment because of an elevated PVR, there was no difference in mean change in the PVR volume at Week 4 from baseline between the drug group (8.7 mL) and the placebo group ( $-0.86$  mL) ( $P = .57$ ).

Except for one participant experiencing moderate constipation, all treatment-related adverse events in the drug group were mild (92.3%). All treatment-related adverse events in the placebo group were mild (90%) with the exception of a stroke in one participant that was considered to be possibly treatment related. Except for persisting nervousness in one participant receiving oxybutynin and a cough in two participants receiving placebo, all adverse events resolved without treatment interruption or remedial treatment.

### Falls

Approximately 54% of participants in both groups experienced at least one fall during the 3 months before, during, or during the 3 months after the trial. There were no differences between the proportion of participants receiving oxybutynin and those receiving placebo who had falls for the 3 months immediately before trial initiation (27%,

33%;  $P = .62$ ), during treatment (19.2%, 16.7%;  $P = .81$ ), or during the 3 months after treatment (30.8%, 41.7%;  $P = .42$ ). Moreover, there was no difference between groups in the median change in the number of falls per month at these same time points ( $P = .24-.66$ ). A GEE repeated-measures Poisson regression analysis revealed no treatment or period effect for the number of falls per month over time of observation (treatment effect,  $P = .24$ ; period effect,  $P = .51$ ).

## DISCUSSION

This trial provides evidence that a 4-week treatment with oral extended-release oxybutynin at a dose (5 mg daily) commonly used in elderly patients is well tolerated, with little risk for delirium or short-term decline in cognition in older female nursing home residents with UUI and mild to severe cognitive impairment. This study is the first to document the absence of negative cognitive effects of an antimuscarinic, extended-release oxybutynin, for UUI in this population. Strengths of this trial include the standardized measurement of delirium and other cognitive effects using validated instruments, the measurement of serum anticholinergic activity, and the detailed adverse event surveillance. In addition, a post hoc analysis verified that there was adequate power to conclude equivalence in mean change in CAM score between treatment groups.

Although the potential for delirium may have been smaller because of the conservative criteria used for enrollment (in accordance with the manufacturer's prescribing information), it was important to eliminate avoidable confounding factors in order to determine the independent risk of delirium associated with oral extended-release oxybutynin. Additional explanations for the absence of delirium are unlikely. Compared with diagnosis by trained geropsychiatrists, the CAM test used to identify delirium has been shown to have a sensitivity and specificity of more than 90% in elderly participants, 21.4% of whom had dementia.<sup>15</sup> In addition, although not specific for delirium, there was no significant decline in MMSE or SIB scores; the SIB is the most sensitive to cognitive changes in individuals with severe cognitive impairment.<sup>21</sup> Finally, although delirium onset can be delayed after treatment initiation and can fluctuate in severity over a 24-hour time period, it is unlikely that delirium was undetected, because cognitive testing was repeated over the time period during which delirium generally arises,<sup>22-25</sup> together with resident and nursing staff interviews and review of daily progress notes and medication records.

A trend for a change in CAM scores between the groups was most pronounced in the MMSE score 5 to 10 strata, in which the proportion of participants with no change or improvement was smaller with oxybutynin than placebo. Although the small size of this stratum limits this finding, it suggests that older adults with more severe cognitive impairment may be most likely to experience poorer cognition with oxybutynin, but because of the smaller potential decrement in cognition at this level of impairment, the clinical implication may be minimal.

The initial significant positive changes in MMSE and SIB scores within both groups could be due to a "learning" effect with repeated measurement or possibly an intrinsic

ability of the participants to compensate for initial negative cognitive effects of oxybutynin.<sup>26</sup> Conversely, natural disease progression could falsely implicate drug treatment in worsening cognition. However, based on this short trial period, the absolute changes in test scores did not exceed average measurement error (i.e., clinically meaningful change in MMSE and SIB of 3 points and 14 points, respectively), and there is no learning effect with the SIB,<sup>19</sup> no known effect with the BARS,<sup>27</sup> and disparate but generally no reported effect with the MMSE.<sup>18,26</sup>

This study's findings differ from several case reports that had indicated that antimuscarinics for UUI in older adults are associated with the development of delirium.<sup>23,24,28,29</sup> These reports included a variety of medications and dose levels and did not include formal testing for cognitive function. Because of the small number of patients and the different dosage levels used in these cases, meaningful comparisons with this study's findings are not possible.

Although previous antimuscarinic therapy trials have documented adverse events, including central nervous system events, none have conducted specific testing for cognitive effects in older nursing home residents with mild to severe cognitive impairment.<sup>4</sup> One short-term (2 week) placebo-controlled crossover study of darifenacin in outpatient volunteers aged 65 and older that included an unknown number of individuals with mild cognitive impairment but without clinical dementia found that it had no effect on cognition,<sup>30</sup> although the method of assessing cognition at baseline was not specified, and the cognitive effect of the treatments in subjects with impaired cognition was not distinguished from the overall study population. A 3-week, single-blind, crossover study of unspecified formulations and doses of oxybutynin and tolterodine in nine older outpatients with mild to moderate cognitive impairment found that, although the change in MMSE score was significantly inversely related to antimuscarinic use, there was no difference in Alzheimer's Disease Assessment Scale—Cognitive Subscale scores in subjects receiving and not receiving antimuscarinic medication.<sup>31</sup>

A few trials in healthy older adults have found that short-term use of immediate-release oxybutynin (5 mg, 10 mg/d),<sup>22</sup> oral extended-release oxybutynin (15 mg, 20 mg/d),<sup>32</sup> and trospium chloride (40 mg/d)<sup>33</sup> decreased cognition. Cognition was not found to be impaired during short-term therapy with darifenacin (7.5 mg, 15 mg/d)<sup>32</sup> and oral extended-release oxybutynin (10 mg/d).<sup>32</sup> Although it appears from the direct comparison trial that darifenacin 7.5 mg/d and 15 mg/d poses less risk of cognitive impairment than oral extended-release oxybutynin at doses of 15 mg/d and 20 mg/d, a bias toward darifenacin cannot be discounted, considering that oxybutynin was increased weekly up to a dosage (20 mg/day) uncommon in clinical practice, whereas darifenacin was uptitrated only at Week 3 to a usual clinical dose.<sup>32</sup> The lack of memory impairment with oral extended-release oxybutynin 10 mg/d is consistent with the results of this trial, which used a lower dose,<sup>32</sup> although differences in study populations, treatment duration, and cognitive tests preclude a direct comparison. Different findings from those from a previous study of immediate-release oxybutynin may be due to the current

trial's use of an extended-release form of oxybutynin that is associated with fewer adverse anticholinergic effects, participants with preexisting cognitive impairment, multiple-dosage regimen, longer treatment duration, different tests of cognition, and repeated testing.<sup>22</sup>

The risk of falls with antimuscarinics is considered to be greater because of their effect of causing dizziness, blurred vision, diplopia, and delayed ocular refocusing between near and distant objects. Although this sample was at greater risk of falling by virtue of the inclusion criteria (advanced age, female, cognitive impairment, and incontinence),<sup>34-37</sup> the results did not show a greater rate of falling for the oxybutynin group. This is consistent with community-based trials of oral extended-release oxybutynin (5-30 mg) in healthy older patients.<sup>38-40</sup>

The low incidence of drug-related discontinuations was similar to rates found in previous trials using a variety of dosing regimens in participants with unknown cognitive function.<sup>41</sup> Cough and constipation were the most common treatment-related adverse events in this trial, with a similar incidence in each group. The incidence of dry mouth was lower, but moderate to severe dry mouth was similar to the rates reported in other trials using the same dose and formulation of oxybutynin but involving generally middle-aged adults without impaired cognition.<sup>38,40,42</sup> Despite the adverse event assessment, it is possible that dry mouth was underrecognized because of the subjective nature of this sensation, especially in individuals with dementia.

The incidence of other treatment-related adverse events in this study was similar to or lower than those reported in other trials in adults, including older adults with unknown cognitive function.<sup>38-40,43</sup> Although adverse events may have been undetected or underreported because of their mild severity, excluding those with the most severe degree of cognitive impairment (MMSE score <5) minimized this possibility. Also, the weekly monitoring of adverse events using multiple strategies made it less likely that an adverse event would be missed.

Although there is no established threshold level of SAA for delirium or other cognitive decline, one trial of surgery patients (mean age 55) reported an absolute level of 7.5 pmol/mL or greater in seven of eight patients experiencing delirium, compared with less than 7.5 pmol/mL in 13 of 17 patients who were not delirious.<sup>44</sup> Although the low mean SAA of 2.2 pmol/mL after 7 days' treatment in the oxybutynin group, compared with the mean SAA related to delirium in other trials (range 1.8-23.0 pmol/mL),<sup>44</sup> may explain, at least in part, the absence of delirium or other cognitive decline in this trial, there is great disparity in the magnitude of SAA at which delirium or other cognitive decline has been reported in other trials.<sup>44</sup>

Several study limitations should be noted. This was a short-term trial designed to collect data during the time period when delirium is most likely. Although delirium was not detected at any time point, there is some evidence that long-term therapy with antimuscarinic medications in general may worsen cognitive function in persons with dementia.<sup>45,46</sup> In addition, it is possible that the concomitant assessment of adverse events together with other outcomes could have resulted in detection bias, although this risk was minimized by keeping the NP blinded to treatment assignment until all data were collected. Another limitation was

the choice of the lowest available daily dose of extended-release oxybutynin (5 mg). This dosage was selected because, until this trial, there have been no existing safety data for this particular patient population at any dosage level. In addition, this dose has been shown to have similar efficacy as a 10-mg/d dose in young adults<sup>38-40</sup> and was the most commonly prescribed dose for nursing home residents.<sup>47</sup> The exclusion of men, which was done because of their higher risk of urinary retention associated with benign prostatic hyperplasia, also limited the results. Consequently, the potential for delirium may have been lower because older men appear to be at a somewhat higher risk for delirium than older women.<sup>48</sup> Therefore, results cannot be generalized to older men. Because the sample was almost entirely white, results can also not be generalized to other races, although race has not been shown to affect the occurrence of delirium.<sup>49</sup> The exclusion of residents receiving acetylcholinesterase inhibitors or with known contraindications or precautions for oxybutynin use also may have affected findings. Although some residents may have been excluded with detrusor hyperactivity with impaired contractility (DHIC), which is common in nursing home residents and for which antimuscarinics may be safely prescribed, 44% of the sample had a PVR volume of 50 mL or greater at baseline, a common criterion for DHIC.

In conclusion, this trial demonstrates that short-term therapy with oral extended-release oxybutynin 5 mg/d was safe and well tolerated and did not impair cognition or cause delirium in older female nursing home residents with UUI and cognitive impairment. Future research is needed to determine the safety and tolerability of long-term therapy, as well as of larger doses of oral extended-release oxybutynin that may be necessary for managing incontinence in older patients with impaired cognition.

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